CHAPTER 4: MAMMALIAN TOXICOLOGY

Adverse health effects from exposure to CDD and CDF compounds have been the subject of intense study in recent years. The 2,3,7,8-tetraCDD congener has been the most extensively studied CDD or CDF compound and, being the most toxic of either class, is the standard for comparison of toxic effect. The principal effects include high acute toxicity, immunotoxicity, teratogenicity, adverse effects on reproduction, enzyme induction, chloracne, carcinogenicity, and possibly mutagenicity. Adverse health effects related to CDDs and CDFs have been recently reviewed by CARB and CDHS (1986), U.S. EPA (1985b), NRCC (1981, 1984), and Huff et al. (1980).

ABSORPTION AND TISSUE DISTRIBUTION

Gastrointestinal absorption and tissue distribution studies have been done on a limited number of CDD and CDF compounds, mostly on 2,3,7,8-tetraCDD and 2,3,7,8-tetraCDF. From 50 to 86 percent of the administered dose of 2,3,7,8-tetraCDD is absorbed from the rat gastrointestinal tract. The carrier used to administer the dose also affects the extent of absorption, with organic solvent mixtures, such as a combination of corn oil and acetone, producing the greatest effect. When 2,3,7,8-tetraCDD was administered to rats in combination with activated charcoal, very little of the dose was absorbed. A decrease in the absorbed dose was seen when 2,3,7,8-tetraCDD was given in combination with soil; the dose absorbed decreased as the length of time the 2,3,7,8-tetraCDD was in contact with the soil increased (U.S. EPA, 1985b).

Umbreit et al. (1986) used guinea pigs to study the bioavailability of 2,3,7,8-tetraCDD from contaminated soil obtained from a site where the herbicides 2,4,5-T and 2,4-D were manufactured (Newark, N.J.), and from a second site where the chemical stills from this plant were dismantled for salvage. Animals of both sexes were dosed by gavage with a soil suspension at levels of 6 ug/kg and 12 ug/kg of 2,3,7,8-tetraCDD. No toxicity was produced by soils from either site. The bioavailability of 2,3,7,8-tetraCDD from the manufacturing site soil was less than 0.5 percent, and from the salvage site soil was 21.3 percent.

McConnell et al. (1984) administered a soil suspension from two sites contaminated with 2,3,7,8-tetraCDD along with other CDDs and CDFs to both rats and guinea pigs by gavage at levels of 1, 3, or 10 ug/kg of 2,3,7,8-tetraCDD. This soil was obtained from the Times Beach, Missouri area and was contaminated when waste oil containing CDDs and CDFs was applied to roads to

pancreas, with lower levels in the liver. The effect of the neoplasms on the (normal) distribution of 2,3,7,8-tetraCDD is not known, but the pattern was similar to that seen in the guinea pig and non-human primates (NRCC, 1981; U.S. EPA, 1985b).

Movement across the placenta occurs with 2,3,7,8-tetraCDD. The placenta affects distribution to the fetus in mice, with higher levels found in the embryo before the placenta is in place compared to after. Levels in the placenta itself were found to be greater than those in the fetus by an order of magnitude. The fetal liver concentrated 2,3,7,8-tetraCDD to a lesser extent than did the maternal liver, with studies indicating distribution to other organs being similar to that seen in maternal tissues (U.S. EPA, 1985b).

In Japan, analysis of tissues from humans ingesting rice oil contaminated with various CDF isomer groups (Yusho poisoning) has provided some data on human tissue distribution in man. Of the total CDFs reported to be in the contaminated oil, approximately 2 percent were triCDFs, 22 percent tetraCDFs, 46 percent pentaCDFs, and 30 percent hexaCDFs, with at least 40 congeners of these isomer groups determined to be present. In human tissues analyzed, higher concentrations were found in adipose tissue compared to liver. The pentaCDFs and hexaCDFs were most persistent, in some cases being detected up to nine years after exposure. An inverse relationship appeared to exist between tissue concentrations and length of survival after exposure (NRCC, 1984).

In animals, retention of isomer groups may vary between species, and there are also differences between species in the organs where isomer groups are retained. The rat retained a greater proportion of the dose of the hexaCDF group in the liver compared to the monkey in a study by Kuroki et al. (1980). In this same study, the monkey retained the 2,3,4,7,8-pentaCDF isomer to a greater extent than the 1,2,4,7,8-pentaCDF or the 1,2,3,7,8-pentaCDF isomers in the liver, indicating the differential retention of isomers in the same organ for a given species.

The NRCC (1984) reported that CDFs crossed the placenta in small amounts relative to the maternal dose, with the mouse fetus accumulating the various isomer groups to different degrees when a mixture of CDFs was fed to female mice during gestation. This same study also found CDFs transferred to offspring in the milk to a greater extent than across the placenta when the same CDF mixture was fed to female mice during lactation.

control dust. Signs of acute toxicity, induction of aryl hydrocarbon hydroxylase activity and measurable levels of 2,3,7,8-tetraCDD in various tissues were seen. The bioavailability of 2,3,7,8-tetraCDD from these soils was estimated at about 85 percent by Umbreit et al. (1986), and at about 25 to 50 percent by Lucier et al. (1986).

Absorption of 2,3,7,8-tetraCDF occurs readily from the GI tract in guinea pigs, rats and mice. In mice 70 to 90 percent of the dose is absorbed depending on the strain used. In guinea pigs absorption has been about 90 percent of the dose given by gavage (NRCC, 1984). Skin absorption of 2,3,7,8-tetraCDD has been estimated at about 40 percent of an equivalent oral dose in rats. This estimate assumes that levels in the liver can be used to estimate the amount absorbed by both oral and dermal routes (U.S. EPA, 1985b).

Tissue distribution studies using 2,3,7,8-tetraCDD have shown that it has an affinity for tissues with high lipid content, which is not surprising due to its lipophilic nature. In the rat, the liver accounted for 38 to 52 percent of a single dose seven days after dosing by both oral and intraperitoneal routes (U.S. EPA, 1985b). The rat, mouse, and hamster have similar distribution patterns, with the liver, then adipose tissue, having the largest percentage of the dose. Levels in other tissues are generally much lower. For non-human primates and guinea pigs, adipose tissue levels are higher than levels in the liver, with high levels also present in the skin (CARB and CDHS, 1986).

With 2,3,7,8-tetraCDF the route of administration did have some effect on distribution initially, but after 3 days it was similar for both the intravenous and oral routes. Greater than 95 percent of the tissue levels in the rat and guinea pig were believed to be unmetabolized 2,3,7,8-tetraCDF (NRCC, 1981). The greater amount of adipose tissue present in the female mouse relative to the male is thought to have produced a difference in the tissue distribution of 2,3,7,8-tetraCDD fed in the diet. Male mice stored approximately 15 percent more of the total body residue in the liver compared to females (U.S. EPA, 1985b).

Tissue distribution of CDDs in humans has been estimated from accidental exposures caused by industrial releases or contamination of food. One report describes a 55 year-old woman exposed to 2,3,7,8-tetraCDD as a result of an industrial accident in Seveso, Italy. This woman, who died seven months after exposure, also had a carcinoma not believed related to the accidental exposure which involved the pancreas, liver, and lungs. Levels were highest in the adipose tissue and the

sensitive species, excrete equal amounts of label in urine and feces, but at a much slower rate than the monkey or rat. About 90 percent of the urine excretion is in metabolite form in the guinea pig, with the radioactivity in feces showing little evidence of being metabolized in one study (NRCC, 1984).

Elimination in most species is predominantly via the feces (80 to 100 percent) with small amounts in the urine. An exception is the hamster, with excretion in the urine and feces being 41 percent and 59 percent respectively (NRCC, 1981; U.S. EPA, 1985b). The biological half-life for 2,3,7,8-tetraCDD in all species tested is about 10 to 40 days, and is nearly three times greater in the guinea pig than in the hamster. Within a species the half-life for three strains of mice was seen to vary by a factor of two, with the two strains having the shorter half-life also having about half the amount of adipose tissue as the strain with the longer half-life. A study in the monkey indicated a half-life for 2,3,7,8-tetraCDD in adipose tissue of about one year (U.S. EPA, 1985b).

For most species tested elimination seems to follow first-order kinetics, with the guinea pig possibly having a zero-order rate. In several studies with the mouse, rat, guinea pig, and hamster all radioactivity associated with administration of labeled 2,3,7,8-tetraCDD appeared in the urine and bile as metabolites. Such metabolites have not been found in the liver and fat tissues themselves, possibly because they are readily excreted as they are formed. Unmetabolized 2,3,7,8-tetraCDD has been found in feces from the hamster and rat, implying another route in addition to the bile for fecal elimination (U.S. EPA, 1985b).

2,3,7,8-TetraCDD has been found in rats during lactation. The milk is also a route of excretion in humans, with 2,3,7,8-tetraCDD, 1,2,3,7,8-pentaCDD, 1,2,3,4,7,8-hexaCDD, 1,2,3,6,7,8-hexaCDD, 1,2,3,7,8,9-hexaCDD, 1,2,3,4,6,7,8-heptaCDD, and octaCDD having been detected (U.S. EPA, 1985b).

In various species CDFs also have different rates of elimination, with the half-life ranging from less than two days in the rat to 20 days in the guinea pig. Morita and Oishi (1977) administered a mixture of CDF isomer groups to mice which produced an estimated half-life of about two weeks, with the different groups eliminated at different rates. Variations in the amount of adipose tissue between two strains of mice was thought to have produced a two-fold difference in the biological half-life of 2,3,7,8-tetraCDF, with the strain with more adipose tissue having the longer half-life (NRCC, 1984).

METABOLISM AND ELIMINATION

Studies with labeled 2,3,7,8-tetraCDD in various animal species have demonstrated biotransformation of CDDs. In rats, hamsters, and guinea pigs, ^{14}C labeled 2,3,7,8-tetraCDD produced labeled glucuronide conjugates in the bile and sulfate conjugates in the urine (U.S. EPA, 1985b). In rats, 90 to 100 percent of the recovered radioactivity in the bile appeared to be metabolites of 2,3,7,8-tetraCDD. In hamsters and guinea pigs there was no unmetabolized ^{14}C labeled 2,3,7,8-tetraCDD found in either urine or bile (NRCC, 1981).

CDDs and other halogenated hydrocarbons appear to be metabolized in the liver by mixed function oxidases (MFO). The MFO system is a multi-enzyme group located in the endoplasmic reticulum of the cell. It metabolizes a wide range of substances from many different chemical classes. The MFOs are present in liver in high amounts. Animal studies have indicated metabolism of CDDs and CDFs in the liver by either cytochrome P-450, or more likely by cytochrome P_1-450, which are components of this enzyme system.

In rats, studies incorporating age and sex related differences in MFO activity, along with differences produced through the use of both inhibitors and inducers of MFO activity, have helped to define an inverse relationship between MFO activity and toxicity (Beatty et al., 1978). Studies in dogs have detected metabolites consistent with biotransformation to an epoxide intermediate resulting from MFO activity (U.S. EPA, 1985b).

The 2,3,7,8-tetraCDD isomer is a potent inducer of MFO activity, causing an increase in smooth endoplasmic reticulum. Like 3-methylcholanthrene (3-MC), administration of 2,3,7,8-tetraCDD apparently results in the induction of cytochrome P-448 (P_1-450) (Doull et al., 1980). Associated aryl hydrocarbon hydroxylase oxidative activity is also induced by polycyclic hydrocarbons such as 2,3,7,8-tetraCDD (Hodgson and Guthrie, 1980). The role metabolism plays in the toxicity of CDDs is not known. Although an epoxide intermediate has been suggested (CARB and CDHS, 1986), metabolism in the case of 2,3,7,8-tetraCDD seems to be mostly a detoxification process producing metabolites less toxic than the parent compound (U.S. EPA, 1985b).

When a mixture of CDF isomer groups was administered to mice, the groups were metabolized at different rates. Metabolism in the liver was rapid relative to adipose tissue in a study done by Morita and Oishi (1977) and summarized by NRCC (1984). The monkey metabolized 2,3,7,8-tetraCDF slower than the rat, with about four times as much label (consisting mostly of metabolites) in the feces as in the urine (NRCC, 1984). Guinea pigs, the most

TABLE 4.1

COMPARATIVE SINGLE ORAL DOSE LD_{50} VALUES FOR CDD CONGENERS

(CARB AND CDHS, 1986)

Oral LD50 Values (ug/kg)

Chlorodibenzodioxin	Guinea Pig	Mouse	Rat	Monkey	Hamster	Rabbit	Dog
2,3,7,8-Tetra	0.6-2	14-284	22-45	70	1157-5051	115	>300,<3,000
Unsub		>50,000	>1,000,000				
2,3-Di			>1,000,000				
2,7-Di		>2,000,000	>1,000,000				
2,6-Di	>300,000	847,000,000	>5,000,000				
1,3,7-Tri		>15,000,000	>5,000,000				
2,3,7-Tri	29,444	>3,000	>1,000,000				
1,2,3,4-Tetra			>1,000,000				
1,3,6,8-Tetra	>15,000,000	>2,987,000	>10,000,000				
1,2,3,7,8-Penta	3.1	337.5					
1,2,4,7,8-Penta	1,125	>5,000					
1,2,3,4,7,8-Hexa	72.5	825					
1,2,3,6,7,8-Hexa	70-100	1,250					
1,2,3,7,8,9-Hexa	60-100	>1,440					
1,2,3,4,6,7,8-Hepta	>600						
Octa		>4,000,000	>1,000,000				

Blood samples taken at one and two year intervals from persons in Taiwan who had ingested rice oil contaminated with CDFs (Yusho poisoning) demonstrated an estimated half-life of greater than a year for the 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF isomers. Analysis of blood samples eleven years after a similar human exposure in Japan could still detect the 2,3,4,7,8-pentaCDF isomer (NRCC, 1984).

Poiger and Schlatter (1986) studied the pharmacokinetics of tritium labeled 2,3,7,8-tetraCDD in a 42 year old, 92 kg adult human volunteer. After fasting overnight, 105 ng of [1,6-^{3}H] 2,3,7,8-tetraCDD dissolved in corn oil was given orally, corresponding to a dose of 1.14 ng/kg. During the first three days after dosing 11.5 percent of the radioactivity was eliminated in the feces, with another 1.5 percent eliminated by the same route over the next four days. From days 7 to 125 an additional 3.5 percent of the dose was found in the feces. No label was detected in urine during the 125 days following dosing, with the exception of the first few urine samples which contained small amounts of radioactivity.

Samples of subcutaneous adipose tissue were taken two weeks before, and again at 13 and 69 days after exposure. These latter two samples contained 2,3,7,8-tetraCDD at levels of 3.09 $\pm$ 0.05 and 2.85 $\pm$ 0.28 ppt, respectively. The authors estimated that approximately 90 percent of the dose was sequestered in the adipose tissue. Low levels were detectable in the blood, with 0.13 pg/ml measured 2 hours after dosing, 0.03 pg/ml after 5 days, which fell to <0.02 pg/ml after 12 days. Based on elimination in the feces, a half-life of 2120 days (5.8 years) was calculated, with the data supporting elimination by first-order kinetics (Poiger and Schlatter, 1986).

ACUTE, SUBCHRONIC, AND CHRONIC EFFECTS

Animal Data

Most data on the toxicity of CDDs has been obtained using 2,3,7,8-tetraCDD, which is considered the most toxic CDD or CDF. There is wide variability in sensitivity between species to the toxic effects of CDDs and CDFs, as Tables 4.1 and 4.2 demonstrate. For 2,3,7,8-tetraCDD the guinea pig is the most sensitive species tested, with an LD_{50} for the male of 0.6 ug/kg, and the hamster the least sensitive, with an LD_{50} for the male of up to 5,051 ug/kg.

Toxic effect after exposure to 2,3,7,8-tetraCDD is apparently more related to the total dose received than to whether the total dose is given all at once, or is distributed over time. Even

with acutely toxic exposures, death is delayed, and may take from 5 to 45 days (U.S. EPA, 1985b). Weight loss occurs during this time, and is often described as "wasting away", with the animal apparently not able to utilize nutrients from the diet (CARB and CDHS, 1986).

2,3,7,8-TetraCDD-induced liver damage is seen in most species as necrosis, lipid accumulation, bile duct hyperplasia and an increase in liver to body weight ratio. Also in the liver, mixed function oxidase (MFO) activity is increased. In the rat a single dose of 200 ug/kg will produce liver necrosis, with 5 to 25 ug/kg causing fatty changes and an increase in both hepatic endoplasmic reticulum and MFO activity. In the mouse porphyria may also be seen (U.S. EPA, 1985b). This liver damage is generally not seen in the guinea pig, the most sensitive species tested (CARB and CDHS, 1986).

The immune system is affected in all species tested, with thymic atrophy caused by loss of cortical lymphocytes being the principal change (McConnell, 1980). The spleen, lymph nodes, and bone marrow may also be affected. Cell-mediated immunity is suppressed, with decreased resistance to bacterial infection demonstrated in animals exposed to 2,3,7,8-tetraCDD. It is thought that 2,3,7,8-tetraCDD may bind to the T-lymphocyte cell membrane, interfering with antigen and cell-cell recognition (U.S. EPA, 1985b).

Humoral immune response has also been reduced by 2,3,7,8-tetraCDD, with a decrease in antibody production and altered serum immunoglobulin levels detected in mice. These effects have been seen with a dose of 2,3,7,8-tetraCDD as low as 0.04 ug/kg/wk (Table 4.3). There is some indication that this immuno-suppression may be reversible with time (Poiger and Schlatter, 1983).

Kerkvliet et al. (1985) used C57B1/6 mice dosed by gavage in a study of humoral immune response using technical grade PCP and its commonly occurring contaminants, which include polychlor-inated diphenyl ethers, phenoxyphenols, dibenzodioxins and dibenzofurans. Several purified CDD and CDF congeners were also tested. A single oral dose was given two days before a challenge by sheep red blood cells, and five days later the peak splenic IgM antibody reponse was measured. Where technical grade PCP (86 percent PCP) produced a dose-related decrease in antibody response, analytical grade PCP (>99 percent PCP) had no effect. A chlorinated phenoxyphenol fraction and a chlorinated diphenyl ether fraction produced no immunosuppression when given at levels likely to be found in technical PCP, while the CDD and CDF fraction produced significant immunosuppression. OctaCDD and

TABLE 4.2

COMPARATIVE SINGLE ORAL DOSE LD_{50} VALUES FOR CDFs COMPARED TO 2,3,7,8-TetraCDD
(CARB AND CDHS, 1986)

Oral LD_{50} Values (ug/kg)

Chlorodibenzodioxin/ furan	Guinea Pig	Mouse	Rat	Monkey	Hamster	Rabbit	Dog
2,3,7,8-TetraCDD	0.6-2	114-284	22-45	70	1157-5051	115	>300,<3,000
Chlorodibenzofuran							
2,8-DiCDF		>15,000,000	>15,000,000				
2,4,8-TriCDF		>15,000,000	>5,000,000				
2,3,7,8-TetraCDF	5-10	>6,000	>1,000	1,000			
2,3,4,7,8-PentaCDF	<10						
2,3,4,6,7,8-HexaCDF	120						

several purified phenoxyphenol isomers also had no effect on immune response. The ID_{50} dose (that dose producing a 50 percent suppression in humoral immune response compared to controls) was 83 ug/kg for technical PCP, 7.1 ug/kg for 1,2,3,6,7,8-hexaCDD, 85 ug/kg for 1,2,3,4,6,7,8-heptaCDD, and 208 ug/kg for 1,2,3,4,6,7,8-heptaCDF. For comparison, the authors calculated an ID_{50} for 2,3,7,8-tetraCDD of 0.65 ug/kg from data produced by Vecchi et al. (1980) in a similiar study.

When 10 ppm technical PCP was fed to both Ah-responsive C57B1/6 and non-Ah-responsive DBA/2 mice for six weeks, immunosuppression and Ah-induced P_1-450 related enzyme activity were seen only in C57B1/6 mice. At a level of 250 ppm both strains showed signs of immunosuppression and enzyme induction, with the response significantly greater in C57B1/6 strain compared to the DBA/2. The authors suggest that these results support the conclusion that the immunosuppression produced by technical PCP is mediated by the CDD and CDF contaminants interacting with the Ah-receptor. Immunosuppression appeared to be additive in nature when 1,2,3,6,7,8-hexaCDD and 1,2,3,4,6,7,8-heptaCDD were given concurrently. When the linear dose-response curves for the congeners tested are compared they are parallel, which suggests a common mechanism of action for immunosuppression (Kerkvliet et al., 1985).

In subchronic studies with 2,3,7,8-tetraCDD using the mouse and rat, the liver was again the organ most affected. Rats dosed at 1 ug/kg/wk showed fatty changes of the liver, first seen 28 weeks into the study and persisting 12 weeks after dosing had ended. Elevated porphyrin levels in the liver have also been produced in rats dosed for 16 weeks, and remained high for up to six months after the exposure had ceased (U.S. EPA, 1985b).

In mice, subchronic exposure to 2,3,7,8-tetraCDD produced toxic hepatitis as the only effect. In female mice a NOEL of 2 ug/kg/wk was established for 2,3,7,8-tetraCDD. In male mice dosed at 1 ug/kg/wk, the lowest dose tested, toxic hepatitis was still apparent (U.S. EPA, 1985b). Chronic studies in mice and rats have also shown the liver to be the major target organ. In the rat, fatty infiltration of the liver is seen first, progressing to liver necrosis as the dose increases. A NOEL for the rat was established at 0.001 ug/kg/wk (U.S. EPA, 1985b). Chronic studies in the mouse and monkey have not established a NOEL for either species. Liver damage in mice has been seen at doses as low as 0.001 ug/kg/day. In the monkey, alopecia, edema, and pancytopenia has been produced at levels of 50 to 500 ppt in the diet (NRCC, 1981).

TABLE 4.3

SUMMARY OF THE COMPARATIVE TOXICITY OF 2,3,7,8-TetraCDD IN GUINEA PIGS, RATS, AND MICE (U.S. EPA 1985b)

SPECIES	Immunotoxicity (ug/kg/week)		Teratogenicity (ug/kg/day)		Reproduction (ug/kg/day)	
	LOEL	NOEL	LOEL	NOEL	LOEL	NOEL
RAT	5.0	1.0	0.125	0.03	0.01	0.001
MOUSE	1.0	0.5	1.0	0.1	INSUFFICIENT DATA	
GUINEA PIG	0.04	0.008	ND	ND	ND	ND

ROUTE OF ADMINISTRATION FOR ALL DOSES IS EITHER ORAL OR GAVAGE.

LOEL = LOWEST OBSERVABLE EFFECT LEVEL

NOEL = NO OBSERVABLE EFFECT LEVEL

ND = NO DATA

A recent study by Hoffman et al. (1986) examined persons living in an area of Missouri where waste oil contaminated with 2,3,7,8-tetraCDD was applied to roads to control dust. The exposed group had a mean residence time of 2.8 ± 1.9 years in an area where 2,3,7,8-tetraCDD levels in the contaminated soil ranged from 39 to 2200 ppb. Alterations of liver function, considered subclinical, consisted of a lower mean serum bilirubin level and an elevated mean urinary uroporphyrin level in the exposed group. A statistically significant increase in the serum levels of enzymes possibly associated with liver function was also seen as suggestive of a compound-related effect. An indication of depressed cell-mediated immunity, considered subclinical, was seen in the exposed group, but was not supported by a history of any increase in lengthy or recurring infections, or accompanied by clinical signs of immune suppression.

Defoliation efforts during the Vietnam War involved the use of about 19 million gallons of herbicides, of which 11 million gallons consisted of Agent Orange, a mixture of 2,4,5-T and 2,4-D (Wolfe et al., 1985). Application of the Agent Orange alone resulted in approximately 368 pounds of the 2,3,7,8-tetraCDD contaminant also being released. An epidemiological study by the United States Air Force utilizing a matched cohort design has examined the occurrence of adverse effects in Air Force personnel involved in the spraying operations.

Results indicate no relationship between herbicide exposure and any long-term health effects. However, the study did report many minor or indeterminate effects for which a cause-and-effect relationship could not be defined. The study design allows for annual mortality and other updates for an additional 20 year period for detection of any developing trends in mortality or disease (Wolfe et al., 1985).

In humans, a cumulative toxic dose is estimated at 0.1 ug/kg. Epidemiological studies, and data from persons exposed to chemical products contaminated with CDDs, indicate that adverse effects are variable in duration, and either may persist for years or subside (U.S. EPA, 1985b).

STRUCTURE-ACTIVITY RELATIONSHIPS

While most available data are related to 2,3,7,8-tetraCDD, enough work has been done on related compounds to indicate that certain biological activity associated with CDDs and CDFs appears to be related to molecular structure; the number and location of the chlorine atoms is particularly important. CDDs, CDFs and related halogenated aromatics seem to have a common mechanism of action for some effects, and are believed to be mediated by a common receptor. There are species differences in susceptibility to effects produced by CDDs and CDFs, and even though each species

Human Data

Most observations on the toxicity of 2,3,7,8-tetraCDD to man indicate that the most common effects from exposure are chloracne, liver abnormalities, hematologic disorders, porphyria, and hyperpigmentation disorders (U.S. EPA, 1985b). Peripheral and central neurological disorders, seen as peripheral neuropathy, lethargy, and sensory impairment have also been reported (CARB and CDHS, 1986; NRCC, 1981). Most human exposures to CDDs and CDFs have occurred either occupationally or accidentally, and concurrently with exposure to other chemicals. In these situations the actual dose received could not be determined. It should be noted that in earlier literature, there were reports of severe liver disease and human fatalities associated with synthesis of 2,3,7,8-tetraCDD (May, 1973; Esposito et al., 1980). However, these brief observations have not been included in recent reviews.

Chloracne is the most common adverse effect seen in man after exposure to CDDs, and may occur anytime from a few days to weeks after exposure (U.S. EPA, 1985b). This dermal lesion is characterized by comedones and cysts, which may progress to pustules as the dose increases. It may subside within a few months or persist for years, with some cases lasting up to 15 years after exposure. 2,3,7,8-TetraCDD has produced chloracne in the monkey and rabbit, although it is usually not seen in other species (U.S. EPA, 1985b).

Human consumption of rice oil contaminated with polychlorinated biphenyls (PCBs) and CDFs in Japan (1968) and Taiwan (1979) produced a number of toxic effects known collectively as Yusho. In the Japan incident the contaminated oil was found to contain PCBs at levels of 1000 ppm and CDFs at levels of 5 ppm, with 2,3,7,8-tetraCDF detected at 0.45 ppm (Huff et al., 1980).

Adverse effects related to Yusho poisoning include:

- pigmentation disorders
- chloracne
- eye discharge
- swelling of upper eyelids
- distinctive hair follicles
- neurological disturbances

These effects are similar to those seen in experimental animals exposed to CDFs, and are generally attributed to the CDF contaminants in the oil. However, the presence of PCBs and polychlorinated quaterphenyls as contaminants in addition to the CDFs must also be considered (NRCC, 1984).

Certain toxic effects of 2,3,7,8-tetraCDD and other CDDs and CDFs are believed to be at least partially mediated by binding to the Ah receptor, a soluble protein in the cytoplasm of the cell (Figure 4.1). According to this theory, after binding with the Ah receptor in the cell cytoplasm, the 2,3,7,8-tetraCDD-receptor complex moves into the cell nucleus in a manner believed similar to that suggested for steroid hormones (U.S. EPA, 1985a). In the nucleus this complex interacts with the Ah locus producing mRNAs during transcription. These mRNAs are used as templates by ribosomes during translation in the cytoplasm to produce the gene products of the Ah locus, which leads to increased levels of these products in the cell and any activity associated with them. Cytochrome P_1-450 levels along with aryl hydrocarbon hydroxylase (AHH) activity are increased, as is the level of Ah receptor in the cell. Examples of other increased enzyme activity apparently linked to the Ah locus (pleiotropy) include glutathione-s-transferase, choline kinase and ornithine decarboxylase (Roberts et al., 1985; Vickers et al., 1985; McKinney and McConnell, 1982).

The significance of this enzyme activity is to increase the biotransformation of not only CDDs and CDFs, but also that of other drugs and chemicals that are substrates for these enzymes. For many such chemicals, biotransformation may either increase toxicity through formation of a reactive intermediate, or decrease toxicity by formation of a less reactive product. Although as Figure 4.1 indicates, there is some uncertainty as to how CDDs and CDFs produce various biochemical effects (steps 9 to 11), the toxicity of 2,3,7,8-tetraCDD and other CDDs and CDFs appears to be unrelated to cytochrome P_1-450 or other metabolic activity in general (U.S. EPA, 1985b).

The tissue distribution of the Ah receptor has been determined in rodents, non-human primates and to a limited extent in humans. In these animal species, high concentrations of the receptor have been found in the liver, thymus, spleen, gastrointestinal tract, skin and pancreas. Although the Ah receptor has been determined to be present in human tissues such as the lung of a human fetus, in lung cells from adults, and in other cultured human cells, it is not known how widely distributed it is in the human population (Roberts et al., 1985).

2,3,7,8-TetraCDD is a very potent inducer of AHH activity, and is similar to, although more potent, than 3-methylcholanthrene and other halogenated aromatic compounds in this respect. Increased AHH activity has been seen not only in the hepatic endoplasmic reticulum, but also in other organelles such as the outer mitochondrial membrane and the nuclear membrane, in addition to other organs (Parkinson and Safe, 1981). Chemicals inducing AHH activity are usually competitive inhibitors of the binding of 2,3,7,8-tetraCDD to the receptor. The toxicity of such

tested does not exhibit exactly the same clinical signs, there are a number of effects that are commonly seen, including (U.S. EPA, 1985b; Goldstein, 1980):

1) progressive weight loss (wasting)
2) skin disorders
3) thymic atrophy
4) porphyria
5) enzyme induction
6) liver disorders
7) teratogenicity

2,3,7,8-TetraCDD is the most potent CDD or CDF producing these effects, with 2,3,7,8-tetraCDF the most potent among the CDFs.

CDD and CDF structures with chlorine atoms at the 2,3,7, and 8 positions are associated with the highest biological activity. Increasing or decreasing the number of chlorine atoms results in a decrease in activity. For example, octaCDD, chlorinated in all available positions, is considered to be essentially biologically inactive (U.S. EPA, 1985b). CARB and CDHS (1986) consider those CDDs and CDFs having four, five, six, or seven chlorine atoms, four of which are in the 2,3,7, and 8 positions to have potentially significant toxicity associated with them (Table 4.4).

TABLE 4.4
(CARB and CDHS, 1986)
CDDs AND CDFs OF TOXICOLOGICAL CONCERN

	Dibenzodioxins	Dibenzofurans
Tetrachloro	2,3,7,8	2,3,7,8
Pentachloro	1,2,3,7,8,	1,2,3,7,8 2,3,4,7,8
Hexachloro	1,2,3,4,7,8 1,2,3,6,7,8 1,2,3,7,8,9	1,2,3,4,7,8 1,2,3,6,7,8 1,2,3,7,8,9 2,3,4,6,7,8
Heptachloro	1,2,3,4,6,7,8	1,2,3,4,6,7,8 1,2,3,4,7,8,9

NOTE: The numbers indicate the position of chlorine atoms on the dibenzodioxin or dibenzofuran molecule.

compounds, and also that of 2,3,7,8-tetraCDD does not always correlate with affinity for the receptor, or with the concentration of the receptor in the tissue (U.S. EPA, 1985b).

TERATOGENICITY AND REPRODUCTION

Studies with 2,3,7,8-tetraCDD have demonstrated teratogenic and fetotoxic effects in rats, mice, and rabbits, and fetoxicity in the monkey (CARB and CDHS, 1986). In mice the most common malformation seen is cleft palate, which has been produced with a dose of 1 ug/kg/day during gestation. Kidney defects are also common in the mouse, with embryotoxicity occurring as the dose is increased. The results of studies using strains of mice which are responsive and unresponsive to enzyme induction by 2,3,7,8-tetraCDD suggest that the occurrence of cleft palate may be controlled by the Ah gene locus. Responsive mice having high tissue concentrations of Ah receptor are more susceptible to this defect relative to unresponsive mice (U.S. EPA, 1985b).

In rats, teratogenicity produced by 2,3,7,8-tetraCDD is usually seen as subcutaneous edema, hemorrhage in the GI tract, and kidney malformation, which have been produced in animals dosed at levels greater than 0.1 ug/kg/day during gestation. There is evidence of enzyme induction in newborn rats after in utero exposure and through exposure during nursing (U.S. EPA, 1985b).

A three-generation reproduction study in the rat found adverse effects at doses greater than 0.001 ug/kg/day, which was considered a NOAEL. Doses of 0.01 and 0.1 ug/kg/day in the diet adversely affected reproduction. The use of this data for human risk assessment has been questioned due to differences in the dose a human infant would receive in milk relative to a rat (CARB and CDHS, 1986).

Studies in monkeys have been limited; typically few animals have been used. Fetotoxicity has been demonstrated, but there are insufficient data to clearly define a teratogenic response (U.S. EPA, 1985b). Fetotoxicity was produced in the monkey with an oral dose of 1 ug/kg administered either as a single dose or in multiple doses between days 20 and 40 of gestation (McNulty, 1985). The estimated NOAEL for the monkey is 0.002 ug/kg/day (CARB and CDHS, 1986).

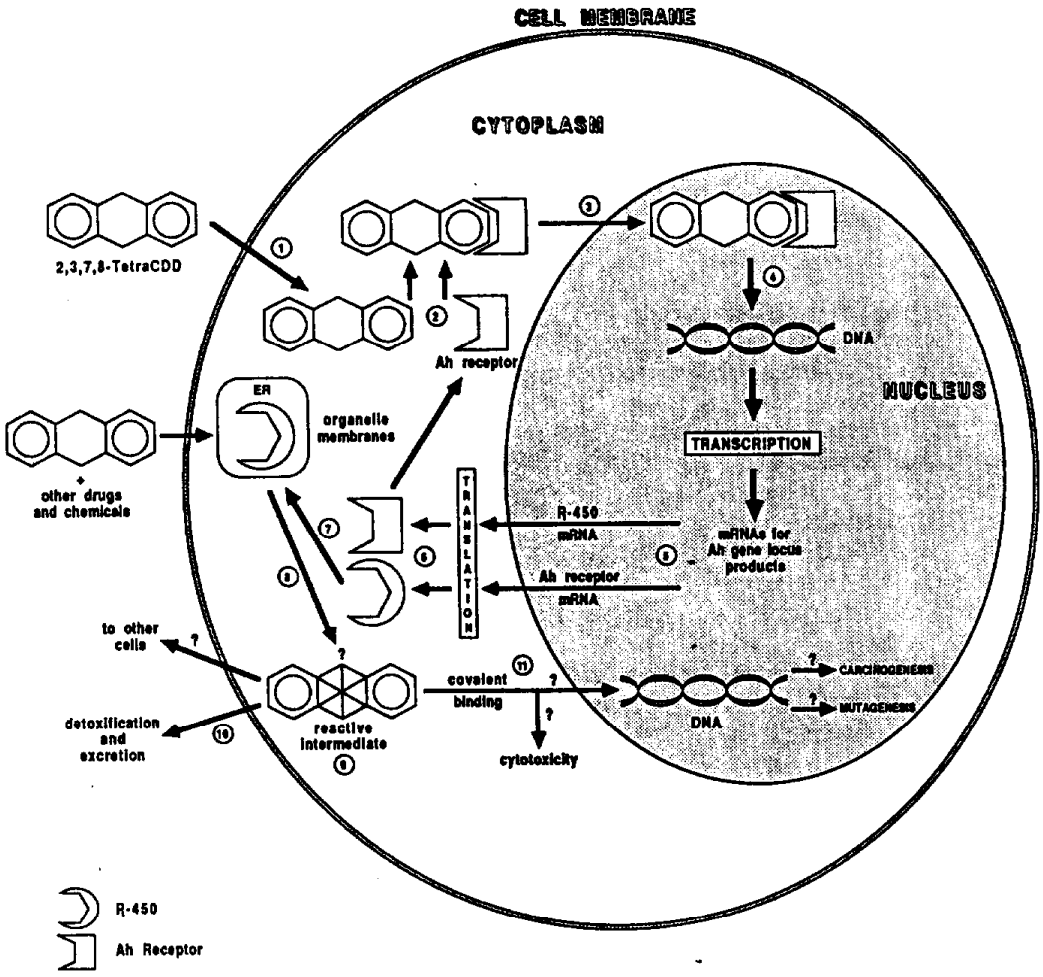
Rats treated with mixed isomers of hexaCDD during gestation showed an increase in the occurrence of cleft palate, edema and vertebral defects at 100 ug/kg/day. Fetotoxicity was produced at levels greater than 10 ug/kg/day, with a dose of 0.1 ug/kg/day producing no increase in fetal malformation (U.S. EPA, 1985b).

Human studies have mostly centered around the herbicides 2,4,5-T and chlorophenols containing 2,3,7,8-tetraCDD as a contaminant. Evidence from studies done to date is not sufficient to

FIGURE 4.1

MODEL FOR AH RECEPTOR MEDIATED MECHANISM OF ACTION

(Adapted from Roberts et al., 1985)



1. 2,3,7,8-TetraCDD passes through cell membrane
2. binds with Ah receptor in cytoplasm and is "activated"
3. activated 2,3,7,8-TetraCDD-receptor complex is transported to nucleus
4. complex interacts with DNA causing messenger RNAs (mRNAs) to be synthesized
5. mRNAs which code for gene products of the Ah locus eg. cytochrome P_1-450 and the Ah receptor, move into cytoplasm
6. the gene products coded for by the mRNAs are assembled by ribosomes
7. cytochrome P_1-450 is incorporated into organelle membranes, such as the endoplasmic reticulum, increasing the metabolizing capacity of the cell
8. the biotransformation of 2,3,7,8-TetraCDD and other substrate drugs and chemicals is increased
9. biotransformation products (metabolites) are formed which may be either more or less toxic than the original molecule
10. metabolites of many drugs and chemicals are detoxified and excreted, which appears to be the case with 2,3,7,8-TetraCDD
11. hypothesized actions of reactive intermediates in cytoplasm and nucleus

and CARB and CDHS (1986) are all in agreement that there is not sufficient evidence to determine the genotoxicity of 2,3,7,8-tetraCDD to man.

CARCINOGENICITY

Animal Studies

Chronic studies in rats and mice have demonstrated the carcinogenicity of 2,3,7,8-tetraCDD. Table 4.5 summarizes the major studies available on the carcinogenicity of various CDDs.

A two year 2,3,7,8-tetraCDD feeding study using Sprague-Dawley rats was conducted by Kociba et al. (1978) at levels of 0.001, 0.01, and 0.1 ug/kg/day in the diet (U.S. EPA, 1985b). At the 0.01 and 0.1 ug/kg/day levels, a significant increase in hepatocellular carcinoma and hepatocellular neoplastic nodules was seen in both sexes. The 0.1 ug/kg/day level produced carcinoma of the hard palate and carcinoma of the nasal turbinates in both sexes, carcinoma of the lung in females, and carcinoma of the tongue in males. This study, determined by the U.S. EPA (1985b) to have been properly carried out, reported a significant increase in tumor response at the 0.01 and 0.1 ug/kg/day levels. The International Agency for Research on Cancer (IARC, 1982) and CARB and CDHS (1986) also consider this study adequate as a bioassay for carcinogenicity.

In a two year gavage study by NTP (1982a) using B6C3F1 mice, males were dosed with 2,3,7,8-tetraCDD at 0.01, 0.05, and 0.5 ug/kg/week and females at 0.04, 0.2, and 2.0 ug/kg/week. Males in the high dose group had a statistically significant increase in hepatocellular carcinoma. Females in the high dose group had a significant increase in hepatocellular adenoma and carcinoma, subcutaneous fibrosarcoma, thyroid follicular-cell adenoma and adrenal cortical adenoma. Where NTP considered an increase in histiocytic lymphoma to be dose-related, CARB and CDHS (1986) did not, based on the incidence of lymphoma in all control groups in the study.

A study, done by Toth et al. (1979) and summarized by U.S. EPA (1985b), used Swiss mice in a gavage study with 2,3,7,8-tetraCDD given weekly at 0.007, 0.7, and 7.0 ug/kg for a year. The mice were then followed over the course of a lifetime with pathology emphasizing liver neoplasm incidence. A significant increase in liver tumors was seen only in the 0.7 ug/kg/week treatment group. Although an increase in liver tumors was seen in the high dose group, it was not statistically significant but did appear to be dose related. Survival in the high dose group was poor, and may explain the lack of a significant tumor response. This study is considered by U.S. EPA (1985b) to provide only suggestive evidence of carcinogenicity.

characterize adverse effects on human reproduction (U.S. EPA, 1985b). Human exposure in the chemical industry, during the Vietnam War from Agent Orange, and in forestry operations has not been able to define a teratogenic or other adverse effect on reproduction related to 2,3,7,8-tetraCDD. The animal data conclusively demonstrate that 2,3,7,8-tetraCDD is teratogenic and fetotoxic at low levels of exposure, and indicate a need to better define the potential for adverse reproductive effects in humans (U.S. EPA, 1985b).

MUTAGENICITY

Early in vitro studies with 2,3,7,8-tetraCDD produced positive results in test systems without mammalian metabolic activation in Salmonella typhimurium strain TA 1532, which is useful for detecting mutagens causing frameshift mutations. In these studies there was no indication of mutagenicity in strains used for detecting point mutations, such as strain TA 1530 (CARB and CDHS, 1986).

Later in vitro studies using the same or similar strains of S. typhimurium with or without mammalian metabolic activation have produced negative results. A positive mutagenic response has been seen in vitro with test cells such as E. coli SD-4, S. cervisiae and cultured mouse lymphoma cells (CARB and CDHS, 1986). Many of these studies are difficult to interpret due to solubility problems with 2,3,7,8-tetraCDD, poor cell survival or solvent related effects on the test cells. The capacity for 2,3,7,8-tetraCDD to produce mutation seems to be low, but remains questionable (Kociba, 1984).

In vivo studies in mice and rats designed to detect chromosome abnormalities have produced conflicting results. Studies in humans exposed to 2,3,7,8-tetraCDD either occupationally or accidentally have also produced questionable data and are insufficient to evaluate the capacity of 2,3,7,8-tetraCDD to produce chromosome aberrations in man (U.S. EPA, 1985b).

Of the CDFs, 2,9-diCDF, 2,6-diCDF, 2,3,7,8-tetraCDF and octaCDF produced no evidence of mutagenicity in S. typhimurium strains TA 98 and TA 100. 2,3,7,8-TetraCDF also produced negative results in strains TA 1535, TA 1537 and TA 1978. A mixture of CDFs did produce a dose-related response for increasing sister chromatid exchange (SCE) in cultured chinese hamster lung cells (NRCC, 1984).

Evaluation of the mutagenicity of CDDs and CDFs, particularly 2,3,7,8-tetraCDD, is difficult due to conflicting results from existing studies. While 2,3,7,8-tetraCDD does show some indication of being weakly mutagenic, its high toxicity may provide only a small range of doses for a mutagenic response to be seen (U.S. EPA, 1985b). The U.S. EPA (1985b), IARC (1982),

TABLE 4.5 (continued)

COMPARATIVE CARCINOGENICITY OF ORALLY ADMINISTERED CDDs

Dibenzo-p-dioxin	Strain/species	Dose	Response
	B6C3F1 Mice	0.01, 0.05 & 0.5 ug/kg/week in males and 2.0, 0.2 & 0.04 for females	Statistically significant increase of hepatocellular carcinomas in the high-dose males and females, and thyroid tumors, subcutaneous fibrosarcomas and histiocytic lymphomas in females.
1,2,3,6,7,8 HexaCDD (31%) + 1,2,3,7,8,9 HexaCDD (67%) mixture	Osborne Mendel Rats	1.25, 2.5 & 5 ug/kg/week	In male rats, the liver tumor incidence was significantly increased over control values only in the high-dose groups, while in female rats the incidence was significantly greater at both the medium and high dose groups.
	B6C3F1 Mice	1.25, 2.5 & 5 ug/kg/week for males and 2.5, 5.0 & 10 ug/kg/week for females	Liver tumor incidence was significantly increased in both male and female mice in the high-dose groups compared to control values.

Table compiled from U. S. EPA, 1985b; NRCC, 1981; Poiger and Schlatter, 1983.

TABLE 4.5

COMPARATIVE CARCINOGENICITY OF ORALLY ADMINISTERED CDDs

Dibenzo-p-dioxin	Strain/species	Dose	Response
Unsubstituted	Osborne-Mendel Rats	5,000 or 10,000 ppm	No carcinogenic response.
	B6C3F1 Mice	5,000 or 10,000 ppm	No carcinogenic response.
2,7-DiCDD	Osborne-Mendel Rats	5,000 or 10,000 ppm	No carcinogenic response.
	B6C3F1 Mice	5,000 or 10,000 ppm	No carcinogenic response in females, suggestive evidence in males.
2,3,7,8-TetraCDD	Sprague-Dawley Rats	0.1, 0.01 & 0.001 ug/kg/day	Significant increase in hepatocellular carcinomas and hyperplastic nodules in female rats at both the intermediate and high-dose levels. At the high-dose, there was a significant increase in carcinomas of the hard palate/nasal turbinates in both sexes, of the tongue in males and of the lungs in females.
	Osborne-Mendel Rats	0.5, 0.05 & 0.01 ug/kg/week	Statistically significant increase in hepatocellular carcinomas, subcutaneous fibrosarcomas and adrenal cortical adenomas in high-dose females. Significant increase of thyroid tumors in male rats at all dose levels.

Human Case Studies and Epidemiology

Human exposure to CDDs and CDFs has usually been associated with the manufacture or use of chemical products which contain them as contaminants. CDDs and CDFs have been found in the low parts per million (ppm) level in phenoxyacid herbicides such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), in PCBs (Bowes et al., 1975), and in chlorinated phenols such as the wood preservative pentachlorophenol (PCP).

During the Vietnam War, Agent Orange, a mixture of the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-T was used extensively as a defolient. 2,3,7,8-TetraCDD was found as a contaminant at low ppm levels. U.S. military personnel involved in the spraying and persons exposed on the ground have been the subject of epidemiological studies (Wolfe et al., 1985).

Industrial accidents in chemical manufacturing plants have exposed large numbers of people to chemical products containing CDDs and CDFs as contaminants. Exposed persons have included plant workers and people living in nearby neighborhoods. The incident in Seveso, Italy in 1976, resulting in the release of 2,4,5-trichlorophenol contaminated with 2,3,7,8-tetraCDD, is one of the better known accidents producing data on human exposure to CDD containing materials. Other accidents have also provided a basis for other epidemiological investigations.

Human consumption of rice oil contaminated with polychlorinated biphenyls (PCBs) and CDFs (Yusho poisoning) has provided data for epidemiological studies. In one case 1200 people in Japan during 1968 ingested this contaminated oil, which contained PCBs at levels of 1000 ppm. The PCBs contained CDFs at levels of 5 ppm, mostly tetra- and pentaCDFs, with 2,3,7,8-tetraCDF present at a relatively high level of 0.45 ppm (Huff et al., 1980; Bowes et al., 1978).

These studies of human exposures have been reviewed by the U.S. EPA (1985b), IARC (1982), and CARB and CDHS (1986) and evaluated for their statistical power to determine carcinogenicity to humans. Most of these studies are of case/control and cohort study types, and have several deficiencies which limit their usefulness (CARB and CDHS, 1986):

- Amounts of CDDs/CDFs can only be estimated, and the dose received cannot be defined quantitatively.

- All exposures have involved CDDs and CDFs in combination with other chemicals, if they were present at all. Human exposure to only CDDs and CDFs has not been studied.

As discussed by U.S. EPA (1985b), Van Miller (1977a,b) administered 2,3,7,8-tetraCDD in the diet to Sprague-Dawley rats at levels ranging from 0.0003 to 500 ug/kg/week for a period of 78 weeks. Survival was decreased in groups treated at levels greater than 24 ug/kg/week. Tumors of the lung and neoplastic nodules in the liver were significantly increased in the 2 ug/kg/week treatment group. Tumors were not seen in either control or low dose animals, which is unexpected for this strain of rat. Both U.S. EPA (1985b) and CARB and CDHS (1986) consider this study to provide suggestive evidence only, and is inadequate to determine a carcinogenic effect.

A 2,3,7,8-tetraCDD dermal study in Swiss-Webster mice of both sexes by NTP (1982b) produced significant increase in integumentary system fibrosarcomas in female mice, but not in males.

A gavage study by NTP (1980a), as discussed by U.S. EPA (1985b), used Osborne-Mendel rats and B6C3F1 mice administered a mixture containing 31 percent 1,2,3,6,7,8-hexaCDD, 67 percent 1,2,3,7,8,9-hexaCDD, and other CDDs including 2,3,7,8-tetraCDD as impurities. Rats of both sexes and male mice received 1.25, 2.5, and 5 ug/kg/week, and female mice 2.5, 5.0, and 10 ug/kg/week. Female rats had statistically significant increases in liver neoplastic nodules at all dose levels. Mice of both sexes in the high dose groups had a significant increase in hepatocellular adenoma or carcinoma.

There has been some controversy with regard to certain aspects of this latter study, with questions being raised about both the histologic preparation, and the pathologic interpretation of tissues. The female rat liver tissue slides have been reevaluated by several independent pathologists, and in all cases fewer neoplastic nodules and carcinomas were determined than in the original NTP interpretation (EPA, 1985b). Even though fewer such lesions were actually present than originally reported, the incidence in the high-dose female group was still statistically significant, and a dose-related response was seen when all groups were considered (CARB and DHS, 1986). The contribution of 0.09 percent tetraCDD present in the test mixture was also determined to be of no significance to the observed liver tumor incidence attributed to this hexaCDD mixture (EPA, 1985b).

A dermal study in Swiss mice of both sexes, conducted by NTP, (1980b) with the same hexaCDD mixture produced no significant increase in tumors, as reported by U.S. EPA (1985b). A small increase in fibrosarcomas of the integumentary system was seen, but was not considered significant.

TABLE 4.6

SUMMARY OF MAJOR CASE/CONTROL STUDIES OF CDD EXPOSURE
(CARB and CDHS, 1986)

NATURE OF EXPOSURE	NO. OF CASES	POTENTIAL LATENCY	RESULTS	IF NEGATIVE, POWER TO DETECT A 50% INCREASE IN RISK (ONE-SIDED 95% TEST)	REFERENCES
Self-reported history of using herbicides 1 day	52 Male cases of soft tissue sarcoma	≥ 5 yrs	Significant odds ratio for exposure to phenoxy acids and chlorophenols		Hardell and Sandstrom, 1979
Self-reported history of using herbicides > 1 day	110 Male cases of soft tissue sarcoma	≥ 5 yrs	Significant odds ratio for exposure to phenoxy acids and chlorophenols		Erickson et al., 1981
Self-reported history of using chemicals > 1 day	71 Male cases of naso-pharyngeal cancer	≥ 5 yrs	Significant odds ratio for exposure to chlorophenols (adjusting for wood working)		Hardell et al., 1982

- Persons have generally been exposed for only short periods of time relative to a human life time.

- Sample sizes under study have been small. The small numbers of subjects involved do not allow the detection of small increases in tumor occurrence.

The studies resulting from exposure situations such as these have produced both positive and non-positive results. The positive associations of carcinogenicity in humans have provided only what is considered limited, suggestive evidence that phenoxyacetic acid herbicides, chlorophenols, and their CDD and CDF contaminants are capable of causing cancer in man.

CARB and CDHS (1986) have summarized the major epidemiological studies in Tables 4.6 and 4.7, and have calculated the statistical power of each. Only a non-positive human study (no effect seen) which has the statistical power to detect a 50 percent increase in risk should be used as evidence of "no effect". A statistical power of 0.80 or greater is usually considered adequate to detect a small increase in risk. Such statistical power is achieved by studies with larger sample sizes which are followed over a longer period of time (CARB and CDHS, 1986). CARB and CDHS (1986) prefer that a study should be able to detect the increase in cases that would be predicted to occur using exposure values and risk estimates obtained from animal studies.

Carcinogenicity Summary

Both U.S. EPA (1985b) and CARB and CDHS (1986) agree with IARC (1982) that the evidence from studies using rats and mice is sufficient to classify 2,3,7,8-tetraCDD as a carcinogen in these species. While evidence from human exposures has provided some suggestive evidence of carcinogenicity, it is considered inadequate by U.S. EPA (1985b) and CARB and CDHS (1986) to determine the carcinogenicity of 2,3,7,8-tetraCDD to man. The U.S. EPA (1985b) considers mixtures of phenoxyacetic acid herbicides or chlorophenols and their 2,3,7,8-tetraCDD contaminant "probably" carcinogenic to man.

The mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexaCDDs is considered an animal carcinogen by both U.S. EPA (1985b) and CARB and CDHS (1986), based on data obtained from the rat and the mouse. This mixture is also considered a potential human carcinogen. There are presently insufficient data to definitively assess the carcinogenicity of other CDDs or CDFs.

TABLE 4.7

SUMMARY OF MAJOR COHORT STUDIES OF CDD EXPOSURE
(FROM CARB AND CDHS, 1986)

NATURE OF EXPOSURE	NO. OF SUBJECTS	POTENTIAL LATENCY	RESULTS	IF NEGATIVE, POWER TO DETECT A 50% INCREASE IN RISK (ONE-SIDED 95% TEST)	REFERENCES
Trichlorophenol process accident	121 Males	29 yrs	No excess total cancer *SMR for lung cancer = 1.8 (not significant)	For Total Cancer = 0.38 For Lung Cancer = 0.14	Zack and Suskind, 1980
Employment in a trichlorophenol process	39 Males with "high exposure potential" 22 Males with "low exposure potential"	15 yrs	SMR for total cancer = 1.9 (not significant)	For Total Cancer = 0.10	Cook et al., 1980
Employment in a 2,4,5,-T plant	204 Males, but only 47 exposed > 1 yr	20 yrs	No excess total cancer	For Total Cancer = 0.18	Ott et al., 1980

* SMR = Standardized Mortality Ratio: Observed Deaths vs Expected Deaths

TABLE 4.6 (continued)

SUMMARY OF MAJOR CASE/CONTROL STUDIES OF CDD EXPOSURE
(CARB and CDHS, 1986)

NATURE OF EXPOSURE	NO. OF CASES	POTENTIAL LATENCY	RESULTS	IF NEGATIVE, POWER TO DETECT A 50% INCREASE IN RISK (ONE-SIDED 95% TEST)	REFERENCES
Occupational data from cancer registry	834 Male cases of nasal, sinus, and naso-pharyngeal cancer	Not Given	No association with chlorophenol exposure	0.48	Olsen and Jensen, 1984
Self-reported history of using herbicides ≥ 5 days	82 Male cases of soft tissue sarcoma	≥ 10 yrs	No significant association with phenoxy herbicides	0.25	Smith et al., 1984
Self-reported history of Vietnam service or using herbicides	281 Male cases of soft tissue sarcoma	4-14 yrs	No association with exposure to Agent Orange, or 2,4,5-T	0.26	Greenwald et al., 1984

Mechanism of Carcinogenicity

The mechanism by which the carcinogenic CDDs and CDFs induce a tumor response is presently not understood (see Figure 4.1). In addition to the known capacity of 2,3,7,8-tetraCDD to produce tumors in animals, studies have provided an indication of tumor initiation, promotion, co-carcinogenicity, and also inhibition of tumors initiated by other carcinogens.

Dermal studies in mice have produced both positive and negative results for tumor promotion by 2,3,7,8-tetraCDD of tumors initiated by 7,12-dimethylbenz(a)anthracene (DMBA). In the rat, 2,3,7,8-tetraCDD was a promoter of liver carcinogenesis initiated by diethylnitrosamine. The mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexaCDD was not a promoter of tumors initiated by DMBA in a dermal study with mice (U.S. EPA, 1985b).

A response suggestive of tumor initiation was seen when 2,3,7,8-tetraCDD was applied to the skin of mice as an initiator, with the tumor promoter 12-0-tetradecanoylphorbol-13-acetate (TPA) applied later. Co-carcinogenicity through enzyme induction is also suggested as a possibility (CARB and CDHS, 1986).

In mice, 2,3,7,8-tetraCDD has also inhibited the tumor response produced by DMBA when both are applied to the skin. In this study, the time of application of 2,3,7,8-tetraCDD relative to DMBA was important to the outcome. The tumor response was inhibited to the greatest extent if 2,3,7,8-tetraCDD was applied 1 to 5 days before the DMBA, with less inhibition produced if 2,3,7,8-tetraCDD was applied 10 days before the DMBA. No decrease in tumor response was seen if 2,3,7,8-tetraCDD was applied just before or five days after initiation with DMBA. Similar results were obtained when 3-MC and benzo(a)pyrene (BaP) were used as initiators. In contrast, BaP-diol-epoxide tumor response was decreased to a greater extent when the 2,3,7,8-tetraCDD was applied either three days or five minutes before, or one day after BaP-diol-epoxide, implying that different mechanisms of tumor inhibition may be involved (U.S. EPA, 1985b).

SUMMARY AND DISCUSSION

The importance of molecular structure, specifically the number and location of the chlorine atoms on the CDD or CDF molecule, has proved to be an essential consideration when comparing the toxicity of individual congeners of both classes. Those congeners chlorinated in the 2,3,7 and 8 positions having a total of four, five, six or seven chlorine atoms possess the greatest toxicity, with 2,3,7,8-tetraCDD the most toxic of any CDD or CDF, and 2,3,7,8-tetraCDF the most toxic CDF. This relationship between molecular structure and toxicity is apparent for a number

TABLE 4.7 (continued)

SUMMARY OF MAJOR COHORT STUDIES OF CDD EXPOSURE

NATURE OF EXPOSURE	NO. OF SUBJECTS	POTENTIAL LATENCY	RESULTS	IF NEGATIVE, POWER TO DETECT A 50% INCREASE IN RISK (ONE-SIDED 95% TEST)	REFERENCES
2,4,5-T process accident	74 Males	Mean = 23 yrs	*SMR for total cancer = 1.7 (not significant) SMR for stomach cancer = 4.3 (significant at at 95% one-sided level)	For Total Cancer = 0.17	Theiss et al., 1982
Herbicide process accident	141 Males	20 yrs	SMR for total cancers = 1.2 (not significant)	For Total Cancer = 0.34	Dalderup and Zellenrath, 1983
Herbicide applicators	1926 Males	≥ 10 yrs	No excess total cancer	For Total Cancer = 0.68	Riithimaki et al., 1983
Employment in a 2,4,5-T plant	884 Males, but number actually exposed to 2,4,5-T much less	Median Approx. 30 yrs	SMR for lung cancer = 1.4 SMR for bladder cancer = 9.9 (significant at 95% level)	For Total Cancer = 0.80 For Lung Cancer = 0.42	Zack and Gaffey, 1983

*SMR = Standardized Mortality Ratio: Observed Deaths vs Expected Deaths

1,125 ug/kg for the 1,2,4,7,8-pentaCDD isomer. Even after acute exposures death is prolonged, with a decrease in bodyweight known as "wasting" occurring over time in most animals tested. In man chloracne is the most common effect after exposure. Other adverse effects seen after human exposure include liver abnormalities, hematologic disorders, hyperpigmentation and neurological changes. Such effects may be of short duration or may persist for years.

A number of toxic effects produced by 2,3,7,8-tetraCDD and related compounds are believed to be mediated through binding to a receptor protein designated as the Ah receptor, which has been found in cells of a number of tissues in animals, and to some extent in humans. For certain effects including P_1-450 enzyme induction and aryl hydrocarbon hydroxylase (AHH) activity, there is a correlation between binding of the CDD or CDF molecule to this receptor and biochemical effect in a number of species. The potency of a CDD or CDF congener for producing such receptor-mediated effects is related to the number and location of the chlorine atoms on the molecule, and is a structure-activity related phenomenon. 2,3,7,8-TetraCDD is the most potent CDD or CDF, and 2,3,7,8-tetraCDF the most potent CDF producing these effects. For other effects there is some correlation between the presence of this receptor and toxicity for a few species, which is not seen in most species tested. What role, if any, the Ah receptor has in the carcinogenicity of CDDs and CDFs has not been determined.

Tetratogenicity and other adverse effects on reproduction, including fetotoxicity, have been produced in several animal species at very low levels of exposure. Cleft palate is characteristic in the mouse, with kidney defects also frequent after exposure to 2,3,7,8-tetraCDD. There is some evidence which indicates that the cleft palate defect may be genetically related to the Ah locus and induction of AHH activity, which is mediated by 2,3,7,8-tetraCDD binding to the Ah receptor. Fetotoxicity has been seen in the monkey and in the rat. Studies in humans resulting from environmental or occupational exposures have not provided sufficient data to determine either teratogenicity or other adverse effects on reproduction. Such data are also inadequate to eliminate the possibility that such effects would occur in humans.

Studies on the genotoxicity of CDDs and CDFs have produced conflicting or otherwise questionable results in most *in vitro* and *in vivo* test systems, and are considered inadequate to determine the genotoxicity of 2,3,7,8-tetraCDD. 2,3,7,8-TetraCDD and a mixture of two hexaCDD isomers have been determined to be carcinogens in the mouse and the rat. Neoplasms of the liver are most commonly seen, with tumors of the lung and thyroid gland also occurring. Other CDD or CDF congeners chlorinated in the 2,3,7, and 8 positions and having a total of four, five, six or

of compound-related effects, and becomes important when evaluating the potential toxicity of mixtures containing multiple CDD and CDF congeners. The occurrence of various congeners in combination with one another is more the rule than the exception when dealing with environmental contamination.

Absorption from the GI tract and distribution to tissues also varies between species. The vehicle used to administer the dose affects absorption, and in cases where 2,3,7,8-tetraCDD is administered in combination with soil particles, bioavailability is decreased and less of the dose is absorbed. The effect soil (or other matrices) has on altering the bioavailability of CDDs and CDFs must be considered in any risk assessment, especially if a site-specific approach is to be used. In general, the liver and tissues with high lipid content sequester a greater part of the dose.

After metabolism, which occurs primarily in liver by cytochrome P_1-450, most 2,3,7,8-tetraCDD is excreted in urine or bile, with the biological half-life varying between species. The number and location of chlorine atoms on the CDD or CDF molecule produces differences in the half-life, and isomers within an isomer group may be metabolized and excreted at different rates. CDDs and CDFs have rather long retention times in tissues such as adipose, with a half-life of about a year for the monkey and 5.8 years for man.

There are considerable qualitative and quantitative differences between species in sensitivity to the toxic effects of CDDs and CDFs. Some effects, such as adverse effects on the thymus gland and the liver, are seen in nearly all species tested, while others such as skin lesions are not. Acute toxicity is a good example of a quantitative difference in toxicity between species, with an LD_{50} of 0.6 ug/kg for the male guinea pig, and 5,051 ug/kg for the male hamster. As indicated below, this very low LD_{50} shows 2,3,7,8-tetraCDD to be one of the most acutely toxic substances known (Doull et al., 1980):

APPROXIMATE ACUTE LD_{50}s FOR SELECTED HIGHLY TOXIC SUBSTANCES

Agent	LD_{50} (ug/kg)
Botulinus Toxin	0.01
2,3,7,8-TetraCDD	0.6
Tetrodotoxin	100
Aldicarb	800
Strychnine sulfate	2000

Within a species there are also quantitative differences in toxicity between isomers of an isomer group, with LD_{50}s in the guinea pig of 3.1 ug/kg for the 1,2,3,7,8-pentaCDD isomer, and .e

RELATIVE CARCINOGENIC POTENCY

Chemical	Potency Relative to 2,3,7,8-TetraCDD
2,3,7,8-TetraCDD	1
1,2,3,6,7,8-/1,2,3,7,8,9-HexaCDD mixture (31%/67%)	1/20
Bis(chloromethyl) ether	1/50
Trichloroethylene (TCE)	1/50,000,000

Data are not available to assess the carcinogenicity of other CDDs or CDFs.

seven chlorine atoms are also of concern in the absence of valid carcinogenicity bioassays. There has been some controversy about whether 2,3,7,8-tetraCDD should be classified as a tumor initiator or as a tumor promotor. The CDHS (CARB and CDHS, 1986) considers any carcinogen to have a non-threshold mechanism of action, and unless evidence is sufficient to determine that the mechanism of action has a threshold, it does not distinguish between an initiator or a promoter. The CDHS also does not believe that toxic potency values derived from structure-activity relationships, along with acute, subchronic and in vitro studies are adequate to estimate carcinogenic potency (See Appendix E).

The U.S. EPA, in the Chlorinated Dioxins Workgroup Position Document of April 1985, has determined that as an interim measure, the toxic risks of complex mixtures can be reasonably estimated by considering the distribution of those CDDs and CDFs chlorinated in the 2,3,7, and 8 positions. The Scientific Advisory Board's Dioxin Toxic Equivalency Methodology Subcommittee evaluated the EPA method in a November 1986 report, and concluded that the method is a reasonable interim means of assessing the risk presented by exposure to complex mixtures of CDDs and CDFs, at least until the method has been validated by testing, or until better data become available on more congeners. Both the EPA and the CDHS approaches are discussed in greater detail in Chapter 6 of this report.

Human studies resulting from environmental or occupational exposure to phenoxyacetic acid herbicides, such as Agent Orange in Vietnam, and chlorophenol products containing CDDs or CDFs as contaminants have provided human epidemiological data. Ingestion of rice oil contaminated with CDFs (Yusho poisoning) in separate incidents in Taiwan and Japan have also formed the basis for additional human studies. Due to limitations involving uncertainty of the dose received, the presence of other agents, length of exposure, and generally small sample sizes, these studies are inadequate to determine the carcinogenicity of CDDs and CDFs to man.

Based on animal data, 2,3,7,8-tetraCDD and a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexaCDDs are considered potential human carcinogens. The U.S. EPA (1985b) Carcinogen Assessment Group has calculated a "relative potency index" for comparing the carcinogenic potency of 55 suspect human carcinogens. 2,3,7,8-TetraCDD was the most potent carcinogen ranked, and is compared below with the next two ranked chemicals and TCE, a common ground water contaminant in California:

CHAPTER 5. CRITERIA, STANDARDS, AND REGULATIONS

CRITERIA AND STANDARDS

Available criteria and standards for CDDs in water and other media are shown in Table 5.1. These only address 2,3,7,8-tetraCDD and the hexaCDDs: criteria have not been recommended for the CDFs and the other CDDs. The values listed in Table 5.1 are based upon different assumptions and have differing applications depending on their derivation. The CDD criteria and standards were developed based upon extrapolations from animal laboratory or human epidemiology studies of acute and chronic effects of CDDs. Where information was available, an explanation of the derivation of the concentration limit, as well as a description of how the limit should be applied is presented.

The criteria for 2,3,7,8-tetraCDD are generally based on dose-response data from animal studies. In many of the derived criteria, the linearized multi-stage model is used for low dose extrapolation. This model assumes that there is no threshold in the dose response curve. The model yields estimates of risk that are conservative, representing an upper limit (95 percent upper confidence limit) for the risk. In other words, it is unlikely that the actual risk is higher than the risk predicted by this model. The derived criterion is set equal to the upper 95 percent confidence limit for one excess lifetime cancer per one million people. This approach is used by the U. S. Environmental Protection Agency (U.S. EPA), California Department of Health Services (CDHS), Center for Disease Control (CDC), and the California Air Resources Board (CARB) in deriving their criteria for carcinogens.

Where adverse effects (other than cancer) are used to derive a criterion, uncertainty factors are applied. In these situations, the dose, expressed in milligrams of chemical per kilogram (mg/kg) of body weight, is divided by an uncertainty (or safety) factor to obtain an Acceptable Daily Intake (ADI) or a Suggested No Adverse Effect Level (SNARL). The uncertainty factor generally ranges from 10 to 1,000 and reflects the quality of the toxicological data, the degree of confidence in the data and the nature of the effects of concern (the more secure the data base, the lower the uncertainty factor). In contrast to the no-threshold approach used to determine risks of a carcinogen, the ADI and SNARL assume a threshold below which adverse effects do not occur. This approach was used by the U.S. Food and Drug Administration (FDA), the National Academy of Science (NAS), Ontario (Canada) Ministry of the Environment, National Research Council of Canada, and New York State in deriving criteria or setting standards for CDDs.

TABLE 5.1 (continued)
CRITERIA AND STANDARDS

COMPOUND	AGENCY/ APPLICATION	CRITERION[1/]	NOTES	REFERENCE
(continued)	"	2.2×10^{-7} ug/l ambient water (one in one million excess lifetime cancer risk)	This criterion is based upon drinking 2 liters of water per day.	"
2,3,7,8-tetraCDD	U.S. EPA (Carcinogen Assessment Group)	6.4×10^{-9} ug/kg/day total intake from all sources in humans	This criterion represents the intake which should not be exceeded in order to keep the excess cancer cases below one in one million people. It is based upon the upper limit incremental cancer risk of 1.56×10^{-1} per ng/kg/day of 2,3,7,8-tetraCDD, converted to a concentration as follows: $\frac{(1 \times 10^{-3} \text{ ug/kg/day}) \times (1 \times 10^{-6})}{1.56 \times 10^{-1}} =$ 6.4×10^{-9} ug/kg/day	U.S. EPA, 1985b
"	"	2.2×10^{-7} ug/l in drinking water	This criterion represents the concentration which should not be exceeded in order to keep the excess cancer cases below one in one million people. It is based upon the upper limit estimate of the incremental cancer risk of 4.5×10^{-3} for a continuous lifetime exposure to .001 ug/l of 2,3,7,8-tetraCDD in drinking water, converted to a concentration as follows: $\frac{.001 \text{ ug/l} \times (1 \times 10^{-6})}{4.5 \times 10^{-3}} =$ 2.2×10^{-7} ug/l	"

TABLE 5.1
CRITERIA AND STANDARDS

COMPOUND	AGENCY/ APPLICATION	CRITERION[1/]	NOTES	REFERENCE
2,3,7,8-tetraCDD	U. S. FDA (Advisory for Great Lakes States)	.025 ug/kg (25 ppt) in fish flesh	Fish flesh containing greater than or equal to .025 ug/kg, but less than .050 ug/kg should not be consumed more than twice a month.	U.S. FDA, 1983
"	"	.050 ug/kg (50 ppt) in fish flesh	Fish flesh containing greater than or equal to .050 ug/kg should not be consumed. FDA premises its exposure assessment on the assumption that only limited amounts of fish having 2,3,7,8-tetra CDD concentrations at or near the advisory level will actually be consumed. FDA's estimate of the carcinogenic potential of 2,3,7,8-tetraCDD is 1.75×10^{4} cancers per mg/kg/day. This is one ninth the potency calculated by U.S. EPA for determination of Ambient Water Quality Criteria.	"
2,3,7,8-tetraCDD	U.S. EPA (Ambient Water Quality Criteria)	1.3×10^{-8} ug/l in ambient water (one in one million excess lifetime cancer risk)	This criterion is based upon daily ingestion of 2 liters of drinking water and consumption of 6.5 grams of fish and shellfish. U.S. EPA assumes that approximately 94% of the 2,3,7,8-tetraCDD exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 5,000 fold.	U.S. EPA, 1984a
"	U.S. EPA (Carcinogen Assessment Group Level)	1.4×10^{-8} ug/l in ambient water (one in one million excess lifetime cancer risk)	This criterion is based upon ingestion of fish and shellfish only. U.S. EPA's estimate of the carcinogenic potential of 2,3,7,8-tetraCDD is 1.5×10^{5} cancers per mg/kg/day. This is nine times the potency calculated by FDA for determination of action levels.	"

TABLE 5.1 (continued)
CRITERIA AND STANDARDS

COMPOUND	AGENCY/ APPLICATION	CRITERION[1/]	NOTES	REFERENCE
2,3,7,8-tetraCDD	Ontario Ministry of the Environment (Ontario, Canada) (Criterion)	20 ng/kg (ppt) in fish flesh	This agency assumes that 2,3,7,8-tetraCDD is a threshold pollutant below which tumor production due to exposure of this compound would be unlikely. A NOAEL of .001 ug/kg/day and a safety factor of 100 yields the maximum ADI of 1×10^{-5} ug/kg/day for humans.	Ontario, Canada, 1986
2,3,7,8-tetraCDD	New York State (standard)	1×10^{-6} ug/l in ambient water	This standard is designed to prevent aquatic food tainting and is deemed to be protective of the health of human or wildlife consumers of fish and shellfish flesh for 2,3,7,8-tetraCDD.	New York, 1985
2,3,7,8-tetraCDD	New York State (standard)	3.5×10^{-5} ug/l in groundwater	This standard is designed to protect human health from 2,3,7,8-tetraCDD contaminated drinking water.	Zambrano, 1987
2,3,7,8-tetraCDD	New York State (criterion)	10 ng/kg (ppt) in fish flesh	This criterion is deemed to be protective of humans consuming fish.	Zambrano, 1987
2,3,7,8-tetraCDD	Michigan Department of Public Health (Advisory)	10 ppt in fish	This criterion is deemed to be protective of humans consuming fish. The tetraCDD dose is related to 1×10^{-5} risk for a 70 kg individual exposed for a lifetime.	Michigan, 1986
2,3,7,8-tetraCDD	Centers for Disease Control (Action Levels)	1 ppb in soil	This is an action level to protect against human exposure to contaminated soil. It was derived as a site specific value for a residential area in Missouri.	Kimbrough et al., 1984

TABLE 5.1 (continued)
CRITERIA AND STANDARDS

COMPOUND	AGENCY/ APPLICATION	CRITERION[1/]	NOTES	REFERENCE
2,3,7,8-tetraCDD	California Air Resources Board and Department of Health Servces (Toxic Air Contaminant Level)	3.0×10^{-8} ug/m^3 in ambient air	This proposed criterion is based upon the CDHS no-threshold, multi-stage model. It is a concentration in air which should not be exceeded in order to keep the excess cancer cases below one in one million people.	CARB and CDHS, 1986
2,3,7,8-tetraCDD	World Health Organization International Agency for Research on Cancer (Classification Status of 2,3,7,8-tetra CDD)	Level has not yet been developed.	This agency has classified 2,3,7,8-tetraCDD as a 2B chemical which means that there is sufficient animal evidence to indicate that it is a carcinogen; however, there is inadequate human evidence for carcinogenicity.	IARC, 1982
hexa-CDD	U.S. EPA (Carcinogen Assessment Group)	1.6×10^{-7} ug/kg/day from all sources in humans (ADI)	This criterion represents the concentration which should not be exceeded in order to keep the excess cancer cases below one in one million people. It is based upon the upper limit incremental cancer risk of 6.2×10^{-3} per ng/kg/day of hexaCDD converted to a concentration level as follows: $\frac{(1 \times 10^{-3} \text{ ug/kg/day}) \times (1 \times 10^{-6})}{6.2 \times 10^{-3}} = 1.6 \times 10^{-7}$ ug/kg/day	U.S. EPA, 1985b
"	"	5.5×10^{-6} ug/l in drinking water	This level represents the concentration which should not be exceeded in order to keep the excess cancer cases below one in one million people. It is based upon the upper limit estimate of the incremental cancer risk of 1.8×10^{-4} for a continuous lifetime exposure to .001 ug/l of hexa-CDD (isomer unspecified) in drinking water, converted to a concentration level as follows: $\frac{.001 \text{ ug/l} \times (1 \times 10^{-6})}{1.8 \times 10^{-4}} = 5.5 \times 10^{-6}$ ug/l	"

TABLE 5.1 (continued)
CRITERIA AND STANDARDS

COMPOUND	AGENCY/ APPLICATION	CRITERION[1/]	NOTES	REFERENCE
hexa-CDD	"	7.7×10^{-7} ug/m^3 in ambient air	This criterion represents the concentration which should not be exceeded in order to keep the excess cancer cases below one in one million people. It is based upon the upper limit of air inhalation risk estimate of 1.3×10^{-6} for a continuous lifetime exposure to 1×10^{-6} ug/m^3 of hexa-CDD in ambient air. $\frac{(1 \times 10^{-6} \text{ ug/m}^3) \times (1 \times 10^{-6})}{1.3 \times 10^{-6}} =$ 7.7×10^{-7} ug/m^3	U.S. EPA, 1985b
hexa-CDD	California Air Resources Board and Department of Health Services Toxic Air Contaminant Level	1.0×10^{-6} ug/m^3 in ambient air	This proposed level is based upon the CDHS no threshold, multi-stage model. It is a concentration level in air which should not be exceeded in order to keep the excess cancer cases below one in one million people.	CARB and CDHS, 1986
hexa-CDD	Southern California Edison Co. (Proposal for Guideline)	6.2×10^{-4} ug/l in drinking water	This proposed guideline is based upon the lowest dose tested by the National Cancer Institute and includes a safety factor of 10,000. It is a threshold guideline.	Jaegar, 1984
hexa-CDD	National Research Council of Canada (Criteria)	1.26×10^{-2} ug/l in ambient water for human consumption of fish	This criterion is based upon the Lowest Observed Effect Level (LOEL) of .36 ug/kg/day with a safety factor of 1,000.	NRCC, 1981
	"	2×10^{-2} ug/kg (ppb) in fish flesh	This criterion is the limit allowed in the flesh of Lake Ontario commercial fish exported to the United States.	"

1/ Or standard where noted.

Of the criteria and standards presented in Table 5.1, only the New York State standard is legally enforceable, while the remaining values are advisory. States and local agencies may adopt advisory levels as enforceable standards, or they may be used as the toxicological basis for considering control technology.

REGULATIONS

The regulations presented in Table 5.2 are generally related to waste disposal and effluent discharges of CDD and CDF impurities found in such products as pentachlorophenol and pesticides. Federal regulations have been promulgated under the Resource Recovery and Conservation Act (RCRA), the Clean Water Act (CWA), and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

SUMMARY AND DISCUSSION

There are no enforceable federal or California state standards for CDDs or CDFs. The advisory levels listed in Table 5.1 are guidelines only, with the exception of standards set by the state of New York.

The federal, state and provincial regulatory agencies which have proposed advisories or standards to protect humans consuming fish contaminated with 2,3,7,8-tetraCDD or hexaCDD are as follows:

Agency	Compound	Guideline
FDA	2,3,7,8-tetraCDD	$\geq$25 ppt (fish flesh) Consume no more than twice per month
		$\geq$50 ppt (fish flesh) Unfit for human consumption
EPA (AWQC)	2,3,7,8-tetraCDD	1.4×10^{-8} ug/l (ingestion of fish and shellfish only)
EPA (AWQC)	2,3,7,8-tetraCDD	1.3×10^{-8} ug/l (ingestion of 2 liters drinking water and 6.5 grams of fish and shellfish)
EPA (CAG)	2,3,7,8-tetraCDD	6.4×10^{-9} ug/kg/day (intake from all sources)

Agency	Compound	Guideline
Ontario Ministry of the Environment	2,3,7,8-tetraCDD	20 ppt (fish flesh)
State of New York	2,3,7,8-tetraCDD	1×10^{-6} ug/l[1/] (for human and wildlife consumers of fish and shellfish)
State of New York	2,3,7,8-tetraCDD	10 ng/kg (ppt) (fish flesh)
State of Michigan	2,3,7,8-tetraCDD	10 ppt fish flesh (for humans consuming fish)
National Research Council of Canada (Ottawa)	hexaCDD	1.26×10^{-2} ug/l (for humans consuming fish)

1/ Standard
AWQC = Ambient Water Quality Criteria
CAG = Carcinogen Assessment Group

Some agencies have proposed advisories for drinking water as follows:

Agency	Compound	Guideline
EPA (AWQC)	2,3,7,8-tetraCDD	2.2×10^{-7} ug/l
EPA (CAG)	2,3,7,8-tetraCDD	2.2×10^{-7} ug/l
National Academy of Sciences	2,3,7,8-tetraCDD	7.0×10^{-4} ug/l
State of New York	2,3,7,8-tetraCDD	3.5×10^{-5} ug/l (groundwater)
EPA (CAG)	hexaCDD	5.5×10^{-6} ug/l

AWQC = Ambient Water Quality Criteria
CAG = Carcinogen Assessment Group

TABLE 5.2

REGULATIONS

COMPOUND	AGENCY	APPLICABLE REGULATIONS	REFERENCE
2,3,7,8-tetraCDD	CDHS	Soluble Threshold Limit Concentration (STLC) for 2,3,7,8-tetraCDD is .001 mg/1. (The STLC is based upon the potential for soluble substances from improperly disposed wastes to migrate via surface or ground water to sensitive aquifer systems such as drinking water supplies or aquatic wildlife environments.) Total Threshold Limit Concentration (TTLC) for 2,3,7,8 tetraCDD is 0.01 mg/1. (The TTLC is based upon the potential impacts on land, resulting from improper disposal of particulate toxic wastes.) STLCs and TTLCs are used to classify wastes as either hazardous or extremely hazardous. The method of disposal depends upon this classification of the wastes.	CAC, 1984
CDDs and CDFs	U.S. EPA	A final rule has been made which promulgates CDD and CDF treatment standards and prohibits land disposal of certain CDD- and CDF-containing wastes unless the treatment standards are achieved. Treatment standards for hexaCDDs, hexaCDFs, pentaCDDs, pentaCDFs, tetraCDDs, and tetraCDFs require that the waste extract be below the 1 ppb limit. Treatment standards for 2,4,5-trichlorophenol, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol and pentachlorophenol require that the waste extract be below 50, 50, 100 and 10 ppb respectively. However, EPA has granted a nationwide two-year variance to the effective date (November 8, 1986), due to lack of alternative destructive technologies. During this two-year variance, wastes must be managed in facilities that are in compliance with Section 3004(o) [42 U.S.C. 6924(o)]. Citation: U.S. Environmental Protection Agency. November 7, 1986. Hazardous Waste Management System; Land Disposal Restrictions; Final Rule, Federal Register, 40 CFR Part 260, Vol. 51, No. 216. Washington, D.C.	U.S. EPA, 1986b

TABLE 5.2 (continued)

REGULATIONS

COMPOUND	AGENCY	APPLICABLE REGULATIONS	REFERENCE
CDDs and CDFs	U.S. EPA	Certain associated wastes from chlorophenolic formulations used by wood preserving or surface protection facilities (either at sawmills or at wood treaters before air seasoning) may be subject to regulation as acutely hazardous wastes under the Resource Conservation and Recovery Act (RCRA) because of their contamination with CDDs and CDFs. The hazardous waste listings which may apply are found in 40 CFR Part 260 et al. of the Code of Federal Regulations as Hazardous Wastes Nos. F020, F021, F022, F023, F026, F027, and F028. An explanation of these wastes follows: F020-Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production or manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of tri- or tetrachlorophenol or of intermediates used to produce their pesticide derivatives. (This listing does not include wastes from production of hexachlorophene from highly purified 2,3,5-trichlorophenol). F021-Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production or manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of pentachlorophenol, or of intermediates used to produce its derivatives. F022-Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the manufacturing use (as a reactant, chemical intermediate, or component in a formulation process) of tetra-, penta-, or hexachlorobenzenes under alkaline conditions. F023-Wastes (except wastewater and spent carbon from hydrogen chloride (purification)) from the production of materials on equipment previously used for the production or manufacturing use (as a reactant, chemical intermediate, or component in formulating process) of tri- and tetrachlorophenols. (This listing does not include wastes from equipment used only for the production or use of hexachlorophene made from highly purified 2,4,5-trichlorophenol.)	U.S. EPA, 1985a

TABLE 5.2 (continued)

REGULATIONS

COMPOUND	AGENCY	APPLICABLE REGULATIONS	REFERENCE
CDDs and CDFs (cont.)	U.S. EPA	F026-Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production of materials or equipment previously used for the manufacturing use (as a reactant, chemical intermediate, or component in a formulation process) of tetra-, penta-, or hexachlorobenzenes under alkaline conditions. F027-Discarded unused formulations containing tri-, tetra-, or pentachlorophenols, or compounds from these chlorophenols. (This listing does not include formulations containing hexachlorophene synthesized from prepurified 2,3,5,-trichlorophenol as the sole component). F028-Residues resulting from incineration or thermal treatment of soil contaminated with U.S. EPA Hazardous Wastes Nos. F020, F021, F022, F023, F026, and F027.	
Pentachlorophenol	U.S. EPA	Process wastewater effluent discharges from wood preserving facilities which use arsenicals, chromates, creosote, and/or pentachlorophenol are regulated under the Clean Water Act (CWA). The final regulations were promulgated in 1981 and vary according to whether the facility was in existence at the time of the regulation (pretreatment standards for existing sources) or is a new plant (new sources performance standards). The release of pentachlorophenol and creosote in wood treatment wastewaters is controlled by the use of the indicator pollutant, oil and grease.	U.S. EPA, 1981

TABLE 5.2 (continued)

REGULATIONS

COMPOUND	AGENCY	APPLICABLE REGULATIONS	REFERENCE
Pentachloro-phenol	U.S. EPA	At present, wastewater treatment sludges from wood preserving processes which use creosote and/or pentachlorophenol are regulated as Hazardous Waste No. K001 under 40 CFR Part 261.31. This includes oil/water separator sludges at the bottom of surface impoundments used to treat or dispose of wastewater (percolation or evaporation ponds), filter media (carbon, sand, soil), spray irrigation fields (considered land treatment units), sludge dewatering/drying beds, etc. The RCRA management standards would not apply to top wastewater treatment sludges (or wastewaters if they are listed as hazardous wastes in the future) while they are managed on-site in tanks which meet certain design requirements of 40 CFR Part 264.1(g) (6) and Part 265.1 (c) (10). However, if sludges are removed from these units the full RCRA permitting requirements apply.	U.S. EPA, 1983
2,4,5-Trichloro-phenoxy acetic acid (2,4,5-T)	U.S. EPA	Because formulations of 2,4,5-T have been found to contain 2,3,7,8-tetra CDD as a contaminant, cancellations of registrations of products which contain 2,4,5-T as an active ingredient is in effect. Except for those products whose registrations were suspended in 1979, all existing stocks which were packaged and labeled for non-suspended end use(s) and released for shipment before the receipt of the October 18, 1983 Federal Register notice may be distributed and sold for one year after the effective date of cancellation. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) an individual or organization which is adversely affected by a cancellation may contest such action in an adjudicatory hearing. Because some registrants of 2,4,5-T products have pursued this course, regulatory action on this products will not be final until cancellation disputes have been resolved.	U.S. Congress, 1983

TABLE 5.2 (continued)

REGULATIONS

COMPOUND	AGENCY	APPLICABLE REGULATIONS	REFERENCE
Penntachloro-phenol (based on hexaCDD)	U.S. EPA	This regulation requires registrants of pentachlorophenol to reduce the concentration of hexaCDD in three phases: 1. The maximum batch concentration initially is 15 ppm. 2. After February 2, 1988, the maximum batch hexaCDD concentration will be 6 ppm, with a maximum monthly average of 3 ppm. 3. Finally, after February 2, 1989, the maximum batch hexaCDD concentration will be 4 ppm, with a maximum average of 2 ppm.	U.S. EPA, 1987

In addition to the above advisories and standards, the Centers for Disease Control in Atlanta, Georgia have recommended a cleanup level to EPA of 1 ppb 2,3,7,8-tetraCDD in soil, a site specific value for a residential area in Times Beach, Missouri.

Some state and federal regulations exist which control CDD and CDF impurities in PCP and pesticide compounds. These regulations put restrictions on pesticide registrations, waste and effluents, and specify treatment of material with CDD and CDF impurities (Table 5.2).

CHAPTER 6: WOOD TREATMENT PRACTICES AND CALIFORNIA SITE CONTAMINATION

This chapter presents a brief overview of wood treatment practices. Three California wood treatment facilities are described to provide examples of chlorophenol-related CDD and CDF contamination.

WOOD TREATMENT PRACTICES

Chlorophenols, such as pentachlorophenol (PCP), tetrachlorophenol and their potassium and sodium salts, creosote, coal tars and copper arsenate compounds have been used routinely at sawmills and wood treatment facilities in California. At sawmills, salts of PCP are used to treat freshly cut wood to prevent sap stains caused by the action of fungi and molds, an example being "blue stain" which leaves a dark discoloration on unprotected wood. Unlike pentachlorophenol, which is highly insoluble in water, the sodium and potassium salts (pentachlorophenates) are very soluble.

PCP is commonly sold as a solid containing 95 percent PCP, and is applied to wood products as a 5 percent solution after being dissolved in a petroleum solvent (Baker and Matheson, 1981). It is used also in the form of sodium and potassium chlorophenate salts, usually as aqueous solutions of approximately 0.15 percent pentachlorophenate. Most chlorophenate products are mixtures of chlorophenols with one compound normally present in greater amounts than others. For example, one such product has approximately 14 percent pentachlorophenol, 8 percent tetrachlorophenol, 6 percent other chlorophenols and the remainder composed of inert ingredients. Such a solution would then be diluted with water for surficial wood treatment purposes.

At sawmills where surficial treatment is used to prevent fungal damage, rough sawn lumber may be treated by either dipping it into large tanks containing the preservative solution, or by spraying the solution on the wood after sawing. The wood is then set aside and allowed to dry. Provisions may or may not be made to recover the excess treatment solution, and in many cases it is lost to the soil in the sorting or drying areas. A recent improvement employed by some operations is the construction of treating and drying facilities with sloping floors and sumps, which allow the excess treatment solution to be collected and either recycled or disposed of.

Other wood preservation methods may use pressure treatment methods, usually a pressurized retort, to more fully saturate the cells of the wood for more complete and longer lasting protection; utility poles are commonly treated in this manner. Several carriers have been used in pressure retort operations; for example, PCP may be dissolved in oil, liquified petroleum gas

and isopropyl ether mixture, mineral spirits or methylene chloride (Morgan, 1986). In some cases the PCP may be dissolved in a solvent such as diesel oil, and wood products may be soaked in the solution without the use of a pressure system.

Over time there is an accumulation of treating process residuals in the form of sediments and sludge in most systems. In sawmill dip tank operations, these residuals consist of sawdust and other debris which collect at the bottom of the treatment tank and must be periodically removed. Disposal of these wastes is currently a problem, since they contain CDDs and CDFs at much higher levels than found in the treatment solution. Since CDD and CDF containing wastes are no longer accepted at California landfills due to potential liability problems (see Chapter 7; Criteria, Standards, and Regulations), this waste must be either temporarily stored on-site or disposed of outside of California. (The U.S. Hazardous and Solid Waste Amendments of 1984 specifically banned landfilling of "dioxin-containing wastes" effective November 8, 1986. However, the Amendments allowed issuance of a national variance on the ban for up to 2 years. Citing the lack of disposal and treatment options, the U.S. EPA issued a variance that will expire on November 8, 1988.)

One available means of disposal has been to burn the sludge on-site by various low-temperature methods, such as in a tepee burner. Burning under such conditions not only does not reliably destroy CDDs and CDFs, but also produces them from precursor chlorophenol compounds. In addition, it releases them to the environment adsorbed to the soot (Tiernan et al., 1983). Burial of these wastes on-site has also been a common practice. Recently, as a temporary measure, on-site storage and containment of these materials in drums has been recommended as an interim measure, but a long-term solution is still needed.

CASE STUDIES OF CONTAMINATED SITES IN CALIFORNIA

Annual production of PCP in the United States is estimated by U.S. EPA (Esposito et al., 1980) to be about 53 million pounds annually. In California, over 2 million pounds of PCP were sold in 1983 (CARB and CDHS, 1986). Approximately 90 percent of this amount was used in wood treatment facilities employing pressure treatment methods (pentachlorophenol), and 10 percent was used in sawmill operations (pentachlorophenate salts).

Three examples of contamination occurring as a result of wood treatment operations are described, with each in a different stage of the evaluation and cleanup process. They are also fairly representative of several additional sites in the State which are awaiting further investigation. California currently has approximately 10 wood treatment facilities and 86 sawmills in operation (CARB and CDHS, 1986), along with a number of facilities which are no longer functional. A recent consultant's

report to the CARB contains an inventory of California sawmills and wood treatment plants using chlorinated phenols as of December 1986 (Chinkin et al., 1987). According to the report, five pressure treatment plants account for 98 percent of current chlorophenol use in wood treatment. The remaining two percent reflects tetrachlorophenate use at four sawmills. This represents a decline in chlorophenol use at sawmills since 1983.

Oroville Wood Treatment Site

A wood treatment facility near Oroville, California is currently being evaluated for soil and ground water contamination resulting from long-term wood preservative use. This 200 acre site has been associated with the lumber industry since about 1920. Both PCP and creosote have been found in soil and ground water both on and off-site (U.S. EPA, 1986a).

The investigation, still in its preliminary stages, has determined levels of PCP in the soil of at least 10 ppm with creosote also present. The depth to water is about 30 feet, and levels of PCP in the ground water below the site range up to 15,000 ppb. Ground water flows in a south-southwest direction, and private wells adjacent to and downgradient from the site have levels of PCP ranging up to 4000 ppb. To the south of the site a plume of contamination extending at least two miles and containing levels of PCP up to 2000 ppb has been detected. The depth to water in this second area is 90 to 120 feet (U.S. EPA, 1986a).

While approximately 30 domestic wells in this rural area have been found to be contaminated with PCP, no CDDs or CDFs have been detected in ground water. Residents have complained of adverse health effects they believe are related to the contamination, such as diarrhea and skin disorders, and an alternate domestic water supply has been provided. Recovery wells have been constructed in the area to the southwest of the site in an effort to reduce contaminant levels (U.S. EPA, 1986a).

In compliance with a U.S. EPA work plan, surface water, ground water, sediment and soil core studies will be performed along with other hydrogeological testing. The first phase of soil and ground water study is expected to better define the extent of contamination (U.S. EPA, 1986a).

Selma Wood Treatment Site

A facility near Selma in Fresno County has also been associated with soil and water contamination resulting from wood preserving operations. This 18 acre facility has been in operation since about 1936, and is bordered by residential, agricultural and industrial areas, some located as close as one-fourth of a mile. (U.S. EPA, 1986d).

A variety of wood preserving chemicals have been used at this site during its history, with those used since 1965 including chromated copper arsenate (CCA), copper-8-quinolinolate, and pentachlorophenol dissolved in ketone solvents, diesel fuel or mineral spirits. During 1982 it was estimated that, using pressure treating methods, about 1,000 gallons of 5 percent PCP solutions and 3,000 to 4,000 gallons of a 1.5 percent CCA solution were used daily to treat lumber products, including utility poles, grape stakes, and fence posts (CVRWQCB, 1982).

During its operation the disposal of treatment related wastes was accomplished by discharge into dry wells, into an unlined pond, runoff into drainage ditches, to the open ground and into a sludge pit. Relatively recent improvements include disposal of drummed waste, such as sludge off-site, and containment of contaminated surface runoff from the treatment area (CVRWQCB, 1982).

The Central Valley Regional Water Quality Control Board first sampled the site in 1971, with the Department of Health Services becoming involved in 1983, and the EPA assuming enforcement responsibility in 1984. The results of this sampling are summarized in Table 6.1.

The aquifers and aquitards in the area are composed of continuous and discontinuous layers of unconsolidated gravel, sand, silt and clay, with the depth to water approximately 30 feet. To the west of the site is found the Corcoran Clay layer, which divides the ground water into a confined and unconfined aquifer system. Because the facility is located on the eastern side of the Central Valley in what may be a recharge zone for those aquifers to the west (ground water flows to the southwest from the site), there is concern about off-site migration since the vertical and horizontal extent of soil and ground water contamination has not been completely defined (U.S. EPA, 1986d). Currently, the U.S. EPA is conducting a sampling program as part of its investigation to better define the vertical and lateral extent of contamination both on and off site.

The CDD and CDF results for 2 of the 25 soil samples and for both pressurized retort effluent samples taken in April 1986 are shown in Table 6.2. The CDD and CDF levels in the soil samples are similar to those of the retort effluent samples; however, some tetra- and pentaCDFs and pentaCDDs were detected in soil samples which were not present in the retort effluent samples.

Visalia Wood Treatment Site

Ground water contamination resulting from the use of PCP and creosote at a facility where electrical power poles were treated has been followed and documented since 1973. This site is located at Visalia, California, where a dip tank containing PCP

TABLE 6.1

SELMA PRESSURE TREATMENT PLANT CONTAMINATION SUMMARY
(adapted from U. S. EPA 1986c)

	PCP (ppm) [1]
Drinking Water Standard	1.0 [2]
Surface Water Sampling Results Range	0.24-2.3
Soil Sampling Range	
Surface to 2 ft. depth	0.06-4,500
2 ft. to 5 ft.	<0.8 -3,100
5 ft. to 10 ft.	0.1 - 600
10 ft. to 20 ft.	2.6 - 41
Greater than 20 ft.	<0.5 - 1.2
Ground Water Sampling Results Range	0.002

[1] Parts per million
[2] State of California Action Level

TABLE 6.2

CDD AND CDF CONCENTRATIONS (WET WEIGHT)
IN SOIL AND RETORT EFFLUENT AT SELMA
PRESSURE TREATMENT SITE
(Compiled from U. S. EPA, 1986c)

	Soil Samples		Retort Effluent Samples	
	A	B	A	B
CDD (ppb):				
tetra	ND[a/]	ND	ND	ND
penta	5.8*	ND	ND	ND
hexa	324*	383*	380*	275*
hepta	3,970*	5,100*	18,500*	19,400*
octa	13,300	14,900	10,500	110,000
CDF (ppb):				
tetra	2.3*	3.1*	ND	ND
penta	72.5*	80*	ND*	ND
hexa	601*	711*	917*	767*
hepta	1,410*	1,660*	11,300*	10,500*
octa	2,990	6,200*	43,700	49,200

[a/] Not detected
* Approximate values

dissolved in number 2 diesel oil was discovered leaking in late 1972. The tank was replaced and an investigation initiated to determine the extent of soil and ground water contamination. The plant used PCP for pole treatment from 1968 to 1980, when operations came to an end.

In this area ground water is contained in two saturated zones separated by an aquitard, a feature characteristic of the San Joaquin ground water basin (Figure 6.1; DWR, 1982). At the site, depth to water in the shallow unconfined aquifer is approximately 30 feet, with the aquitard varying between 10 and 20 feet in thickness encountered at about 65 feet confining the deeper aquifer (SCE, 1985d).

The unsaturated and unconfined layers, considered moderately permeable, are composed of alluvial silts and fine sands near the surface, progressing through medium and coarse grained sands to pebble gravel at the upper boundary of the aquitard (SCE, 1983). The aquitard is composed of silts and clays of low hydraulic conductivity and is considered a leaky, saturated confining layer for the deep aquifer, which consists of coarser grained more permeable alluvial deposits. Ground water in the shallow aquifer flows in a generally south-southwest direction, following a gradient of about 17 feet per mile. Flow in the deep aquifer is in a generally west-southwest direction, following a gradient of about 15 feet per mile (SCE, 1984). The deep aquifer is confined at its base by relatively impermeable beds, and is widely used as a source of drinking water by many in the area, including the City of Visalia.

Since the leak was discovered, a series of monitoring and recovery wells have been installed, as both the shallow and deep aquifers have been contaminated with PCP, creosote, CDDs and CDFs. To inhibit downgradient movement of the contaminants off-site, a bentonite-cement slurry wall has been built below the surface. This barrier surrounds the shallow aquifer beneath the site, and extends from the surface to its lower boundary.

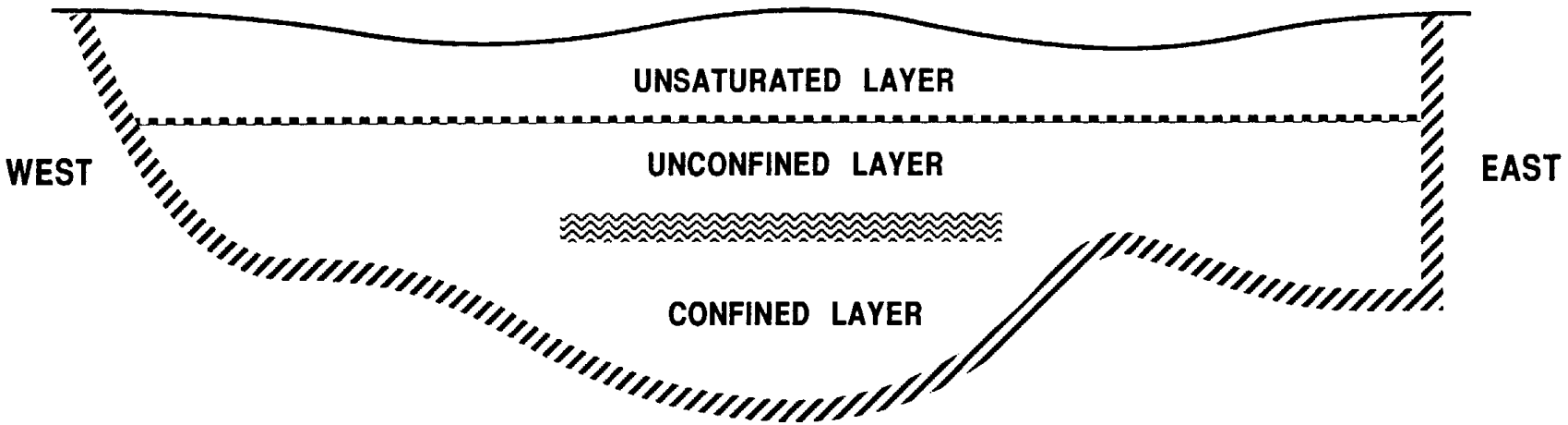
Contaminant levels in ground water have fluctuated significantly since the investigation began in 1973, with the highest levels reached in 1977, (Table 6.3). During this same period PCP was detected in monitoring wells 600 feet to the south of the site at levels of 0.3 to 37 ppm, and also 1600 feet to the soutwest at levels of 0.007 to 2 ppm, with creosote also present in both cases (SCE, 1983).

To reduce contaminant levels and prevent further migration away from the site, ground water has been pumped from the shallow aquifer since 1975, and from the deep aquifer since 1976. Over time, additional monitoring and recovery wells have been added. The water has been discharged to the City of Visalia Water Conservation Plant. CDDs and CDFs were found in the ground water

FIGURE 6.1

TYPICAL CROSS SECTION OF THE SAN JOAQUIN VALLEY GROUNDWATER BASIN

(ADAPTED FROM DWR, 1982)



LEGEND

- Aquitard (Confining Clay Layer)
- Water Table
- No Flow Boundary

TABLE 6.3

CONCENTRATIONS OF PCP, CDDs AND CDFs IN SOIL AND WATER AT VISALIA POLE TREATMENT SITE*

Contaminant	Shallow Unconfined Aquifer 1977	1984	1985	Deep Confined Aquifer 1977	1984	1985	Soil A 1985		Soil B 1985		Sewage Sludge 1985
							Lab 1	Lab 2	Lab 1	Lab 2	
PCP (ppm)	44,000	17.0	16.7	6.3	4.5	1.5	-		-		-
Creosote (ppm)	73,000	6.2	6.5	270	47.0	21.2	-		-		-
CDD (ppb):											
Tetra	-a/	<0.001	<0.00054	-	<0.001	<0.0007	<0.2	<0.07	<0.1	<0.05	<0.03
Penta	-	<0.001	<0.0013	-	<0.001	<0.00023	<0.2	<0.23	0.1	<0.17	<0.17
Hexa	-	<0.001	<0.00064	-	0.0025	0.0027	21	12	125	240	6.5
Hepta	-	<0.001	<0.0011	-	0.113	0.210	260	490	1730	500	110
Octa	-	0.049	0.0069	-	1.140	0.870	1810	2300	2388	1700	86
CDFs (ppb):											
Tetra	-	<0.001	<0.00044	-	<0.001	<0.00034	<0.2	<0.05	<0.1	<0.05	<0.04
Penta	-	<0.005	<0.00063	-	<0.01	<0.00051	0.4	2.3	3.8	9.3	<0.07
Hexa	-	<0.001	<0.0013	-	0.030	0.014	48	89	366	180	3.7
Hepta	-	<0.001	<0.0023	-	0.15	0.210	141	670	1047	600	12.0
Octa	-	<0.001	<0.0044	-	0.15	0.220	76	540	331	190	6.7

a/ Not Analyzed

* Compiled from SCE 1983, 1984, 1985a, 1985b, 1985c, 1985d

of both shallow and deep aquifers in 1984, and as shown in Table 6.3, the levels increased in 1985. Further investigation of soils from the site both at the surface and to a depth of eight inches detected significant levels of CDDs and CDFs, mostly hexa-, hepta-, and octa- isomer groups, with pentaCDFs also present.

Soil cores from the construction of additional monitoring wells in 1984 have provided data on the vertical distribution of PCP, creosote, CDDs and CDFs in the shallow aquifer (Table 6.4). The hexa-, hepta-, and octa- isomer groups again predominate. While no tetraCDDs or pentaCDDs were detected at any depth, tetraCDFs and pentaCDFs were present. The soil corings were taken from the location of the leaking tank, and began at a depth of 30.5 feet, as the contaminated soil above previously had been removed and replaced with clean fill. The aquitard material separating the two aquifers was also sampled at several locations at the site to determine if contaminants were able to penetrate this barrier. PCP, creosote, and low levels of hexa- through octaCDDs and penta- through octaCDFs (Table 6.4) were found within the aquitard under a location where treated poles had been stored.

Water recovered from both aquifers containing PCP, creosote, CDDs and CDFs has been discharged to the Visalia Water Conservation Plant since pumping began. PCP and creosote have been detected in the plant influent, effluent and sludge. CDDs and CDFs have also been detected in the influent, with the highest levels found in the sludge shown on Table 6.3. CDDs and CDFs have not been detected in the plant effluent.

Sludge from this plant is used as a soil amendment by farms and residents in the area, and a recent study (SCE, 1986) determined that sludge stockpiles at the distribution point contained CDDs and CDFs at levels similar to sludge from the water conservation plant. In this study sludge application rates ranged from 2.3 tons per acre to 259 tons per acre, and levels of CDDs and CDFs in the soils in these areas appeared to correlate with the application rate. While no tetraCDDs were found in the soil samples, tetraCDFs were present. Approximately 20 percent of the total tetraCDFs present were estimated to be the 2,3,7,8-tetraCDF isomer.

In 1985 a pretreatment system was installed at the site to remove contaminants from the extracted ground water before being received by the water conservation plant. The water is first passed through filters designed to trap CDD and CDF containing particulates, and then through carbon beds to remove PCP along with other organics. The system is designed to allow ground water to eventually be pumped directly into a nearby creek after treatment, bypassing the water conservation plant. Only trace levels of PCP (0.15 ppb) have been found after such treatment, with creosote, CDDs and CDFs not detected. A request based on this system's performance is before the Regional Water Quality Control Board to allow such a discharge (SCE, 1985c, 1986).

TABLE 6.4

VERTICAL DISTRIBUTION OF SOIL AND AQUIFER CONTAMINANTS AT VISALIA SITE[a/]

Depth (ft)	PCP (ppm)	Creosote (ppm)	CDD (ppb)					CDF (ppb)				
			Tetra	Penta	Hexa	Hepta	Octa	Tetra	Penta	Hexa	Hepta	Octa
Soil Core Samples												
30.5	61	3700	<0.01	<0.08	1.2	68	460	1.3	<0.38	36	100	180
35.5	48	1500	<0.02	<0.05	0.3	30	320	<0.02	<0.04	13	36	60
40.5	120	ND[b/]	<0.02	<0.06	7.0	340	1700	<0.02	0.33	49	455	200
40.5	5.9	ND	<0.02	<0.05	1.6	41	370	<0.01	<0.02	4.2	32	26
46.5	-[c/]	-	<0.02	<0.06	4.7	100	720	<0.01	0.19	100	100	41
54.5	14	160	<0.12	<0.3	<0.33	2.8	63	<0.18	<0.27	<0.42	2.8	<2.2
Aquitard Profile Samples												
45.0	0.16	620	-	-	-	-	-	-	-	-	-	-
50.0	0.27	250	-	-	-	-	-	-	-	-	-	-
52.0	1.3	900	-	-	-	-	-	-	-	-	-	-
54.0	0.82	110	-	-	-	-	-	-	-	-	-	-
56.0	3.6	1100	-	-	-	-	-	-	-	-	-	-
58.0	8.0	2000	<0.0092	<0.036	2.4	216	327	<0.010	0.27	9.5	197	167

a/ Data from SCE, 1984, 1985a
b/ Not Detected
c/ Not Analyzed

Progress in removing contaminants from both aquifers has generally been good; in most cases a greater than 90 percent reduction of peak levels has been seen. Since about 1980, levels have been erratic from one analysis to the next, and the level of improvement somewhat uncertain, particularly for wells on the site. Contaminant levels in wells located further away from the site in the path of the plume have been more consistent, and do indicate a downward trend. The proposed level of clean up for ground water at the extraction wells before treatment is 1 ppm total phenols, 30 ppb for PCP, and below detection limits for creosote, CDDs and CDFs.

CHAPTER 7: CALIFORNIA WATER RESOURCES CONTROL BOARD STUDY

The State Board study described in this chapter proceeded in three stages over a two year period: (1) analysis for presence of pentachlorophenol (PCP); (2) preliminary screening for CDDs and CDFs; and (3) analyses for specific CDD and CDF compounds of toxicological concern. The study began by examining potential contamination by PCP and related chlorophenols from wood treatment operations. While sampling for PCP at these facilities, the State Board learned of a Swedish study (Levin et al., 1976) that reported high levels of CDFs detected in sludges from sawmill dip tanks.

When significant levels of PCP contamination were found at sampling sites, the State Board initiated a preliminary screening for CDD and CDF isomer groups to determine if the Swedish CDF findings were representative of California conditions. The screening confirmed the presence of both CDDs and CDFs. These findings were presented to a California interagency task force which recommended that (1) future samples be split between different laboratories for verification and (2) if possible, analyses should be performed for 2,3,7,8-chlorinated compounds since these are the specific congeners of toxicological concern.

Based on these recommendations, the State Board staff designed a two phase study of congener specific analyses. These results are presented in detail later in the chapter and form the basis for the hazard evaluation strategy described in Chapter 8.

ANALYTICAL METHODS

The search for CDDs and CDFs in various industrial, occupational and environmental settings has pushed analytical methodology to its limits, and the gas chromatography-mass spectrometry (GC-MS) methods in current use represent the state-of-the-art. The extreme toxicity of 2,3,7,8-tetraCDD at very low levels of exposure has determined the need for very sensitive and specific methods of analysis, and has lowered the limit of detection from 1 ppm in 1969 to sub-parts per trillion levels today (NRCC, 1984). Analytical methods are discussed in detail by the U.S. EPA (Esposito et al., 1980; U.S. EPA, 1985b, 1986a), NRCC (1981), and Tiernan (1983); an overview is presented in Appendix E, with the analytical methods used by State Board contract labs described in Appendices F and G.

STATE BOARD ISOMER GROUP STUDY

This preliminary study was designed to determine if CDDs and CDFs were present as a result of using chlorinated phenols for wood treatment. Included in the study were sawmills or wood treatment

facilities both currently operational and some that had discontinued operations. Operating sawmills were located in Shasta County, Tehama County, and Trinity County. Abandoned sawmills in Glenn County, Humboldt County, and a combined sawmill-wood treatment plant in Sonoma County which had discontinued operations were also part of the study. Samples were obtained of the chlorophenol products in use, the dilute dip tank solution, accumulated sludge from the bottoms of these tanks, and of the soil in the area of treatment operations.

Chlorophenol Products

Samples of two pentachlorophenates and one tetrachlorophenate products used in sawmill operations were obtained and analyzed for chlorophenol, CDDs and CDFs. The results shown in Table 7.1 demonstrate the high variability between different lots, which is common to products from different manufacturers and processes. The higher chlorinated Cl_6 to Cl_8 CDDs and CDFs are present in the largest amounts, which is typical (see Appendix D, Table D.1).

Of these higher chlorinated CDDs and CDFs, the hexa isomer group is of chief toxicological concern, with the isomers chlorinated in the 2,3,7, and 8 positions having about 1/100 of the acute toxicity of 2,3,7,8-tetraCDD in the guinea pig. The mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexaCDDs has also been determined to be an animal carcinogen and potential human carcinogen.

The results, shown in Table 7.1, are similar to those obtained in other studies, especially with regard to the relative abundance of isomer groups in products from different manufacturers. When pentachlorophenol and pentachlorophenate (PCP salts) products are compared, the chlorophenates generally contain greater amounts of CDFs than the pentachlorophenols, which usually have greater amounts of CDDs compared with pentachlorophenates.

Product and Soil Residues

Results of the isomer group analyses are presented in Table 7.2. The samples of dip tank solution, sludge and soil all show the same general pattern of CDD and CDF isomer group distribution seen in the products, with the higher chlorinated Cl_6 to Cl_8 groups present at the highest levels. CDDs and CDFs appear to be concentrated in the sludge from the dip tanks. The levels in the dried sludge are anywhere from about 10 to almost 1,000 times greater than those of the dip tank liquid, with hepta- and octa-CDFs showing the greatest enrichment.

TABLE 7.1

CDD AND CDF CONCENTRATIONS IN COMMERCIAL CHLOROPHENOL PRODUCTS[a/]

	Tetrachlorophenate (Sodium)	Pentachlorophenate "A" (Sodium)	Pentachlorophenate "B" (Sodium)
TetraCP (ppm)	140,000	140,000	77,000
PCP (ppm)	31,000	170,000	150,000
CDDs (ppb):			
Tetra	<1.0	<0.5	16
Penta	238	11	1,400
Hexa	1,100	4,800	14,000
Hepta	614	88,000	64,000
Octa	700	216,000	69,000
CDFs (ppb):			
Tetra	1,060	190	2,800
Penta	22,100	380	3,400
Hexa	17,600	1,900	18,000
Hepta	3,000	4,100	18,000
Octa	62	2,900	840

[a/] State Water Resources Control Board data developed for the present report.

TABLE 7.2

CDD AND CDF CONCENTRATIONS IN SOIL AND PRODUCT RESIDUES RELATED TO CHLOROPHENOL USE[a/]

	Shasta County Sawmill		Glenn County Sawmill		Tehama County Sawmill	Trinity County Sawmill
	Dip Tank Liquid	Dip Tank Sludge	Dip Tank Wet Sludge	Dip Tank Dry Sludge	Dip Tank Liquid	Dip Tank Sludge
TetraCP(ppm)	1,700	4,000	300	37,000	11,000	2,300
PCP (ppm)	2,200	5,700	880	160,000	3,700	2,600
CDDs (ppb)						
Tetra	<0.002	1.7	0.57	51	<0.34	<0.35
Penta	0.2	16	19	2,000	6.4	84
Hexa	7.7	799	360	13,000	86	2,300
Hepta	112	3,066	1,200	23,000	111	13,000
Octa	352	3,066	3,500	7,400	428	26,000
CDFs (ppb)						
Tetra	0.84	54	21	5,600	32	110
Penta	3.7	259	92	3,600	106	2,200
Hexa	4.3	1,143	140	12,000	936	1,600
Hepta	0.37	369	350	5,700	90	1,500
Octa	1.3	1,066	17	250	90	65

a/ State Water Resources Control Board data developed for the present report.

TABLE 7.2 (continued)

CDD AND CDF CONCENTRATIONS IN SOIL AND PRODUCT RESIDUES RELATED TO CHLOROPHENOL USE[a/]

	Tehama County Sawmill Soil	Trinity County Sawmill Soil	Humboldt County Sawmill Soil	Sonoma County Wood Treatment Plant Soil
TetraCP (ppm)	3,700	1,400	-	-
PCP (ppm)	6,400	1,600	-	260
CDDs (ppb):				
Tetra	<2.2	<0.48	<0.088	<0.014
Penta	11	5.5	<0.20	<0.18
Hexa	180	245	9.4	44
Hepta	185	3,100	37	4,400
Octa	977	1,600	188	1,500
CDFs (ppb):				
Tetra	48	100	12	0.23
Penta	105	45	33	9.6
Hexa	1,593	540	126	230
Hepta	229	730	183	2,100
Octa	242	120	41	1,200

a/ State Water Resources Control Board data developed for the present report.

CONGENER SPECIFIC SURVEY

Background

The CDD and CDF isomer group data obtained from sampling sawmill soils and sludge tanks indicated that these contaminants would be of toxicological concern if a significant fraction were chlorinated at the 2,3,7, and 8 molecular positions. Several approaches can be used that either estimate or directly measure the concentrations of 2,3,7,8 congeners present. From a health standpoint, the most conservative estimate is to assume that all tetra through hepta CDDs and CDFs are chlorinated at positions 2,3,7, and 8. A second method, which has been used to estimate toxicity in municipal solid waste emissions (CARB and CDHS, 1986), assumes equal distribution for each isomer within an isomer group. For example, the level of 2,3,7,8-tetraCDD, as one of 22 possible isomers in the tetraCDD isomer group, would be assigned 1/22 or 4.5 percent, of the total tetraCDD reported in a sample. A third method is direct measurement of individual CDD and CDF congeners present in a sample. The latter is difficult, time-consuming, expensive, and truly state-of-the-art chemistry, particularly in complicated media such as soil and sludge.

Members of the State Board and its management were informed of the sawmill sampling data for CDDs and CDFs in August 1984. The Secretary of Environmental Affairs and representatives of several state agencies were briefed during the following October. The consensus was that, while the CDD and CDF findings were provocative, the results should be considered tentative until confirmed by another laboratory. Further, it was recommended that the State Board attempt to determine if the congeners of greatest concern (those CDDs and CDFs chlorinated at the 2,3,7, and 8 positions) were present in sawmill residues where tetrachlorophenol and pentachlorophenol had been used. Table 7.3 lists the seven CDDs and ten CDFs that contain the 2,3,7,8 pattern of chlorination. The State Board's congener-specific sampling program focused on these 17 CDDs and CDFs and did not analyze for non-2,3,7,8 congeners.

State Board staff planned a two phase program of analysis. Phase 1 would examine a limited number of samples from two sawmills for congener-specific analysis, utilizing samples previously collected and identified as containing high isomer group levels of CDDs and CDFs. If Phase 1 identified the presence of 2,3,7,8 congeners of CDDs and CDFs, then a second more extensive phase would examine samples from two additional sites, a third sawmill and a wood pressure treatment plant. The locations of sites sampled in Phases 1 and 2 and the number of samples taken at each site are shown in Table 7.4.

TABLE 7.3

2,3,7,8-CHLORINE SUBSTITUTED CONGENERS OF CDDs AND CDFs

Isomer Group	Total Isomers in Isomer Group	Number of Isomers in Isomer Group with 2,3,7,8 Substitution	Specific Isomers
CDDs:			
Tetra-	22	1	2,3,7,8-tetraCDD
Penta-	14	1	1,2,3,7,8-pentaCDD
Hexa-	10	3	1,2,3,4,7,8-hexaCDD
			1,2,3,6,7,8-hexaCDD
			1,2,3,7,8,9-hexaCDD
Hepta-	2	1	1,2,3,4,6,7,8-heptaCDD
Octa-	1	1	1,2,3,4,6,7,8,9-octaCDD
Total tetra through octaCDD congeners	49	7	
CDFs:			
Tetra-	38	1	2,3,7,8-tetraCDF
Penta-	28	2	1,2,3,7,8-pentaCDF
			2,3,4,7,8-pentaCDF
Hexa-	16	4	1,2,3,4,7,8-hexaCDF
			1,2,3,6,7,8-hexaCDF
			1,2,3,7,8,9-hexaCDF
			2,3,4,6,7,8-hexaCDF
Hepta-	4	2	1,2,3,4,6,7,8-heptaCDF
			1,2,3,4,7,8,9-heptaCDF
Octa-	1	1	1,2,3,4,6,7,8,9-octaCDF
Total tetra through octaCDF congeners	87	10	

TABLE 7.4

STATE WATER RESOURCES CONTROL BOARD PROGRAM FOR CONGENER SPECIFIC ANALYSIS OF CDDs AND CDFs

A. Phase I

1. Sawmill A (Trinity County): 2 samples

   a. Commercial sodium pentachlorophenate
   b. Dip tank sludge

2. Sawmill B (Glenn County): 2 samples

   a. Wet dip tank sludge
   b. Dry mix tank sludge

B. Phase II

1. Sawmill C (Humboldt County): 4 samples

   a. Commercial potassium tetrachlorophenate
   b. Dip tank liquid
   c. Dip tank sludge (2 samples)

2. Wood Treatment Plant (San Joaquin County): 4 samples

   a. "Bloom"
   b. "Commercial"--recycled treatment material
   c. Soil at retort
   d. Sump liquid

Phase 1 Sampling Results

The samples for Phase 1 were collected at two non-functioning sawmills. Sawmill A, which has been dismantled, was located on the Trinity River in Trinity County. The lumber dip tank was located in a concrete-block structure covered by a sheet metal roof. The dip tank itself had been constructed by walling off a portion of one end of the building with additional cinder blocks so that two of the tank walls were actually part of the building's exterior walls. Four samples consisting of the commercial PCP formulation, dip tank liquid, dip tank sludge, and soil were collected and analyzed for CDD and CDF isomer groups. These results indicated that the commercial PCP and dip tank sludge were highest in CDDs and CDFs. These two samples, as well as two sludge samples from Sawmill B, were subsequently split two ways and sent to participating laboratories in California and Sweden. Since the samples were not split homogeneously, differences in laboratory results beyond expected analytical variation are possible.

The results for Sawmill A are shown in Appendix H, Results of State Board 2,3,7,8 Congener Specific Analyses, Table H.1. The 2,3,7,8-chlorinated CDD congeners present include 1,2,3,7,8-pentaCDD; 1,2,3,6,7,8-hexaCDD; and 1,2,3,4,6,7,8-heptaCDD. Chlorinated dibenzofuran congeners include 2,3,7,8-tetraCDF; 1,2,3,7,8-pentaCDF; 2,3,4,7,8-pentaCDF; 1,2,3,6,7,8-hexaCDF; 1,2,3,7,8,9-hexaCDF; and 1,2,3,4,6,7,8-heptaCDF. Table 7.5 is a summary of results that shows the percentage of 2,3,7,8-chlorinated isomers present within a given isomer group.

Sawmill B was located in Glenn County. Based on CDD and CDF isomer group results, two samples were selected for congener-specific analysis: a mixture of liquid and sludge from the dip tank and a dry sludge from an elevated wood preservative mix tank. The mix tank sludge contained approximately 10 ppb 2,3,7,8-tetraCDD (Table H.2 of Appendix H). However, without a record of chemicals used in the mix tank, the source of 2,3,7,8-tetraCDD can not be determined. The mix tank also contained approximately 200 ppb of 1,2,3,7,8-pentaCDD and 4,000 ppb 1,2,3,6,7,8-hexaCDD.

Phase 2 Sampling Results

Samples for Phase 2 were obtained at two sites: Sawmill C in Humboldt County and a wood treatment plant in San Joaquin County. Four samples were taken at each site and split for analysis by laboratories in California and Illinois. Sawmill C is a functioning lumber mill that had been using a unit dip tank for 3-1/2 years. This below ground level tank is housed in a special facility designed to contain wood preservatives totally within the building and represents current thinking on best management

TABLE 7.5

CDD AND CDF CONGENER SPECIFIC ANALYSIS, PHASE 1: SAWMILLS A AND B

(Summary of isomer group data and percent of isomer group consisting of 2,3,7,8 chlorinated isomers; average of two laboratories except that, where differences exceed 5X, both values are reported).

	Commercial Na-PCP Formulation	Sawmill A Sludge	Sawmill B Liquid Sludge	Sawmill B Dry Sludge
CDDs (ppb):				
TetraCDD	-	-	-	8.4 60
2,3,7,8	-	-	-	8.3 11
% 2,3,7,8 of total tetraCDD	-	-	-	99% 18%
PentaCDD	222	68	25 246	1,009
1,2,3,7,8	26	<15.9 10	34 14	199
% 2,3,7,8 of total pentaCDD	12%	- 9%	136% 5.7%	20%
HexaCDD	9,850	3,115	520	7,400
total 2,3,7,8 (3 isomers)	3,825	1,795	258	4,187
% 2,3,7,8 of total hexaCDD	39%	58%	50%	57%
HeptaCDD	70,000	39,200	3,200	18,000
1,2,3,4,6,7,8	30,900	23,500	2,050	11,015
% 2,3,7,8 of total heptaCDD	44%	60%	64%	61%
CDFs (ppb):				
TetraCDF	1,436	383	78	1,997
2,3,7,8	201	105	17	95
% 2,3,7,8 of total tetraCDF	14%	27%	22%	4.8%
PentaCDF	8,200	4,035	575	11,050
2,3,7,8 (2 isomers)	614	220	50	280
% 2,3,7,8 of total pentaCDF	7.5%	5.5%	8.7%	2.5%
HexaCDF	49,000 7,200	8,600	1,530 900	7,900
2,3,7,8 (4 isomers)	705 500	373	45 ND	292
% 2,3,7,8 of total hexaCDF	1.4% 6.9%	4.3%	2.9% -0-	3.7%
HeptaCDF	91,000 9,700	8,650	830	3,550
1,2,3,4,6,7,8	6,344 3,900	2,635	373	1,510
% 2,3,7,8 of total heptaCDF	7% 40%	30%	45%	43%

of dip method wood treatment. For the first two years of unit dip tank operation, Sawmill C had used a formulation containing 15 percent each of pentachlorophenate and tetrachlorophenate.

That formulation then was replaced by a preservative containing approximately 22 percent potassium tetrachlorophenate and 6 percent potassium pentachlorophenate, a mixture used for 1-1/2 years at the time of sampling. One by-product in the unit dip tank has been the accumulation of sludge that must eventually be removed. Samples were taken of the current commercial formulation (22 percent K-tetraCP and 6 percent K-PCP), the dip tank liquid, and two sludge samples, one from the tank center and the second from a corner. Results from the two laboratories are summarized in Table H.3 of Appendix H. One laboratory reported approximately 7.0 ppb of 2,3,7,8-tetraCDD in a sludge sample, but the finding was not confirmed by the second laboratory (Table 7.6 presents the condensed results of Table H.3). No 1,2,3,7,8-pentaCDD was found. The predominant hexaCDD was the 1,2,3,6,7,8-isomer. As shown in Table 7.6, the predominant 2,3,7,8 CDFs of the toxicologically significant tetra-, penta-, and hexa- isomer groups were 2,3,7,8-tetraCDF and the two 2,3,7,8-pentaCDF isomers.

The wood treatment plant uses a pressurized retort system to treat poles and other wood with pentachlorophenol dissolved in butane. The label on the commercial PCP indicated that it contained 86 percent PCP and 10 percent other chlorinated phenols. When treated wood is removed from the retort under atmospheric pressure, solution oozes out and collects as crystals on the wood surface. The crystals are referred to as the "bloom". A sample of the bloom was scraped off for analysis.

The other three samples consisted of: (1) "commercial", a recycled wood preservative material that is combined with butane and reused in the treatment process; (2) soil from the mouth of the pressure retort system; and (3) liquid from a nearby sump that, when sampled, was characterized as "probably a mixture of penta and oil". Results are summarized in Table H.4 of Appendix H.

Only the bloom contained detectable levels of 1,2,3,7,8 pentaCDD. Table 7.7 provides information on the percent of 2,3,7,8 congeners present within CDD and CDF isomer groups.

SUMMARY AND DISCUSSION

The analytical methodology developed for 2,3,7,8-tetraCDD has progressed from the ability to analyze for isomer groups of CDDs and CDFs to the detection and quantification of individual congeners requiring the very latest developments in technology. Gas chromatography-mass spectrometry is the method of choice for CDD and CDF analysis, and was used by State Board contract

TABLE 7.6

CDD AND CDF CONGENER SPECIFIC ANALYSIS, PHASE 2: SAWMILL C

(Summary of isomer group data and percent of isomer group consisting of 2,3,7,8 chlorinated isomers, average of two laboratories except that, where differences exceed 5X, both values are reported.)

	Commercial Tetrachloro-Phenate Formulation	Sawmill Dip Tank Liquid	Sawmill Dip Tank Sludge[1/]	Sawmill Dip Tank Sludge[1/]
CDDs (ppb):				
TetraCDD	ND	0.5	ND	7.4[2/]
2,3,7,8	ND	ND	ND	ND
% 2,3,7,8 of total tetraCDD	-	0	-	0
PentaCDD	256 21	1.0	30	36
1,2,3,7,8	ND ND	ND	ND	ND
% 2,3,7,8 of total pentaCDD	0 0	0	0	0
HexaCDD	1,240	12	404	477
total 2,3,7,8 (3 isomers)	509	6.0	206	244
% 2,3,7,8 of total hexaCDD	41%	50%	51%	47%
HeptaCDD	1,083	20	1,472	1,582
1,2,3,4,6,7,8	688	12	886	937
% 2,3,7,8 of total HeptaCDD	64%	60%	60%	49%
CDFs (ppb):				
TetraCDF	1,230	8.2	384	401
2,3,7,8	200	2.0	54	65
% 2,3,7,8 of total tetraCDF	16%	24%	14%	16%
PentaCDF	4,478	33	904	933
2,3,7,8 (2 isomers)	205	2.8	117	106
% 2,3,7,8 of total pentaCDF	4.6%	8.5%	13%	11%
HexaCDF	5,449	47	1,638	2,039
2,3,7,8 (4 isomers)	48	12	35	61
% 2,3,7,8 of total hexaCDF	0.9%	26%	2.1%	3.0%
HeptaCDF	2,044	23	942	977
2,3,7,8 (2 isomers)	695	8.7	354	342
% 2,3,7,8 of total HeptaCDF	34%	38%	38%	35%

1/ One sludge sample from the tank center; the second from tank corner.
2/ Reported by one laboratory, but not confirmed.

TABLE 7.7

CDD AND CDF CONGENER SPECIFIC ANALYSIS, PHASE 2: WOOD TREATMENT PLANT

(Summary of isomer group data and percent of group consisting of 2,3,7,8-chlorinated isomers, average of two laboratories except that, where differences exceed 5X, both values are reported.)

	"Bloom"	"Commercial"	Soil (Mouth of Pressurized Retort)	Sump (Liquid)
CDDs (ppb):				
TetraCDD	ND	ND	ND	ND[1/]
2,3,7,8	ND	ND	ND	ND
% 2,3,7,8 of total tetraCDD				
PentaCDD	70	ND	ND[1/]	ND[1/]
1,2,3,7,8	56	ND	ND	ND
% 2,3,7,8 of total pentaCDD	80%	-	-	-
HexaCDD	1,580	136	243	1,420 84
total 2,3,7,8 (3 isomers)	557	65 ND	96	414 54
% 2,3,7,8 of total hexaCDD	35%	51% 0	39%	29% 64%
HeptaCDD	26,680	9,530	2,420	12,900 548
1,2,3,4,6,7,8	23,570	6,650	1,522	8,270 343
% 2,3,7,8 of total HeptaCDD	88%	70%	63%	64% 63%
CDFs (ppb):				
TetraCDF	31	ND[1]	2.8	15
2,3,7,8	4.4	ND	ND	ND
% 2,3,7,8 of total tetraCDF	14%	-	0	0
PentaCDF	382	ND	43	484 27
2,3,7,8 (2 isomers)	56	ND	ND	50 13
% 2,3,7,8 of total pentaCDF	15%	-	-	10% 47%
HexaCDF	4,079	225	215	2,440 168
total 2,3,7,8 (4 isomers)	1,106	25	12	136 ND
% 2,3,7,8 of total hexaCDF	27%	11%	5.3%	5.6% 0
HeptaCDF	13,003	3,427	458 388	2,590 111
2,3,7,8 (2 isomers)	9,546	701	847 157	900 56
% 2,3,7,8 of total HeptaCDF	73%	20%	185% 40%	35% 50%

1/ Reported by one laboratory, but not confirmed.

laboratories for both isomer group and congener-specific studies. Results indicate that CDD and CDF residues in soil and dip tank sludges generally reflect the isomer group pattern seen for the products. The isomer group studies provided evidence of significant CDD and CDF levels associated with chlorophenol use. This established the need to determine the presence of specific congeners.

Congener-specific analysis was performed on additional samples in an effort to characterize the contribution of congeners chlorinated in the 2,3,7 and 8 positions to the isomer group totals. Samples obtained from three sawmills and one wood treatment plant included commercial chlorophenol products, dip tank liquid, dip tank sludge, a pressure treated wood "bloom", and soil, with samples split between contract laboratories for analysis.

As discussed elsewhere in this report, several investigators have reported levels of CDDs and CDFs in chlorinated phenols used for treatment of wood. However, with the exception of the 2,3,7,8-tetraCDD and 2,3,7,8-tetraCDF congeners, the levels are reported as isomer group data; levels of specific 2,3,7,8-chlorinated congeners of possible concern such as 1,2,3,7,8-pentaCDD have not been measured.

An exception is the recent work of Miles et al. (1985a,b) who synthesized the 10 hexaCDD isomers and used these standards to perform isomer-specific analysis of nine commercial penta-chlorophenol samples (from three manufacturers) and six commercial sodium pentachlorophenate samples (from two manufacturers). The results of Miles et al. (1985b), summarized in Table 7.8, show that the specific isomer composition varies between pentachlorophenol and pentachlorophenate. Levels of total hexaCDD varied from 0.7 ppm to 38.5 ppm in the nine pentachlorophenol samples and from 1.6 ppm to 16.3 ppm in the pentachlorophenates. The predominant 2,3,7,8-hexaCDD isomer is 1,2,3,6,7,8 with a range of 50.6 percent to 64.5 percent of total hexaCDD in pentachlorophenols and 17.5 percent to 26.5 percent in pentachlorophenate. Much lower levels of the other two 2,3,7,8-hexaCDD isomers (1,2,3,4,7,8 and 1,2,3,7,8,9) were detected, although 1,2,3,7,8,9 was identified in all 15 samples.

The State Board's hexaCDD isomer-specific results agreed with Miles et al., that 1,2,3,6,7,8-hexaCDD was the predominant 2,3,7,8-hexaCDD (Table H.5 of Appendix H). The two commercial chlorophenate formulations contained 39 percent and 40 percent 1,2,3,6,7,8-hexaCDD of total hexaCDD. Dip tank sludges and liquids contained 50 percent to 58 percent 1,2,3,6,7,8-hexaCDD of the total hexaCDD group.

TABLE 7.8

PERCENTAGE OF 2,3,7,8-HEXACDD ISOMERS
IN TECHNICAL PCP AND ITS SODIUM SALT
(Adapted from Miles et al., 1985b)

PCP Sample	1,2,3,4,7,8,	1,2,3,6,7,8,	1,2,3,7,8,9,	Total Hexa-CDD	M*
1		50.6%	1.0%	38.5 ppm	A
2		52.2%	1.9%	36.8 ppm	A
3		56.8%	0.7%	37.5 ppm	A
4		58.9%	1.5%	0.7 ppm	B
5		60.1%	1.3%	1.9 ppm	B
6		62.8%	0.6%	1.4 ppm	B
7	0.6%	58.4%	1.0%	4.6 ppm	C
8	0.4%	62.5%	1.0%	2.8 ppm	C
9	1.1%	64.5%	1.0%	6.1 ppm	C
NA - PCP					
1	1.5%	19.7%	5.2%	15.4 ppm	D
2	1.5%	17.5%	5.2%	16.3 ppm	D
3	1.8%	19.0%	5.3%	14.8 ppm	D
4	1.4%	24.1%	2.8%	1.8 ppm	E
5	1.5%	25.2%	2.3%	1.6 ppm	E
6	1.7%	26.5%	2.4%	2.2 ppm	E

M* = Manufacturer

As shown in Table H.5 of Appendix H, the 2,3,7,8-chlorinated CDF congeners detected were 2,3,7,8-tetraCDF (approximately 15 percent of total isomer group in chlorinated phenol formulations), 1,2,3,7,8-pentaCDF, and 2,3,4,7,8-pentaCDF. The four 2,3,7,8-hexaCDF isomers represented only a small fraction (about one percent) of the total hexaCDFs. Reporting laboratories frequently disagreed on which specific 2,3,7,8 hexaCDF isomers were present.

At Sawmill A, the congener-specific CDD and CDF composition of the commercial formulation (sodium pentachlorophenate) used for treatment was compared to the dip tank sludge (see Table 7.5). Except for 1,2,3,7,8 pentaCDD, which was not detected in the sludge, the same 2,3,7,8 chlorinated congeners were present in both the formulation and the sludge. Concentrations of the CDDs and CDFs in the commercial formulation exceeded those in the sludge by roughly a factor of two. Because Sawmill A had been abandoned shortly before the samples were taken, no history of previous commercial formulations used for treatment was available. Thus, no direct comparison of sludge CDD and CDF content with that of chlorophenol treatment chemical(s) is possible.

At Sawmill C, concentrations in the commercial formulation (a potassium tetrachlorophenate) also exceeded the dip tank sludge by a factor of two (see Table 7.6). Again, no direct comparison is possible because the sludge had accumulated during the use of two different commercial formulations over a three and one-half year period. The concentration of CDDs and CDFs in the dip tank liquid were approximately one percent of those in the formulation, reflecting the one to one hundred dilution (formulation to water) used by the sawmill.

The highest CDD and CDF concentrations detected at the wood treatment plant were in the bloom, including 56 ppb 1,2,3,7,8-pentaCDD (see Table 7.7).

Based on the State Board's limited survey, Table 7.9 summarizes the tetra- through hexaCDD and CDF detected in chlorophenate formulations, dip tank sludges and a treatment plan "bloom".

TABLE 7.9

SUMMARY OF TETRA- THROUGH HEXA- 2,3,7,8-CHLORINATED CONGENERS DETECTED IN THE STATE BOARD SURVEY (CONCENTRATIONS IN ppb)

	Sawmill A		Sawmill C		
	Commercial Formulation	Dip Tank Sludge	Commercial Formulation	Dip Tank Sludge	Wood Treatmt Plant Bloom
CDDs					
2,3,7,8-tetraCDD	ND	ND	ND	ND	ND
1,2,3,7,8-pentaCDD	26	ND	ND	ND	56
2,3,7,8-hexaCDDs	3,825	1,795	509	225	557
CDFs					
2,3,7,8-tetraCDF	201	105	200	60	4.4
2,3,7,8-pentaCDFs	614	220	205	112	56
2,3,7,8-hexaCDFs	603	373	48	48	1,106

Table 7.10 compares levels of 2,3,7,8-chlorinated CDDs and CDFs detected in the twelve samples analyzed in the two phase congener specific program. Although 2,3,7,8-tetraCDD was confirmed in only one sample, 2,3,7,8-tetraCDF was detected in all of the sawmill samples and in the pressurized wood treatment "bloom". In 10 of 12 samples, 2,3,7,8-chlorinated CDD levels were higher than the CDFs. In four samples, the total level of tetra through hepta 2,3,7,8-chlorinated CDDs and CDFs exceeded 15,000 ppb: a commercial pentachlorophenate, two sawmill sludges, and the "bloom" taken from pressure treated wood. With the exception of the dip tank solution sample, all samples contained at least 1,000 ppb total tetra through hepta 2,3,7,8-chlorinated CDDs and CDFs.

This limited congener-specific survey has indicated the following tetra through hexa 2,3,7,8-chlorinated CDD and CDF congeners are most likely to be found as a result of tetrachlorophenol and pentachlorophenol use at sawmills and wood treatment plants:

1,2,3,6,7,8 hexaCDD
2,3,7,8 tetraCDF
1,2,3,7,8 pentaCDF
2,3,4,7,8 pentaCDF
1,2,3,6,7,8 hexaCDF

In addition, various other 2,3,7,8-chlorinated hexaCDFs were reported in some samples (in particular, these hexaCDFs were detected in the crystalline "bloom" that formed on pressure-treated wood).

TABLE 7.10

SUMMARY OF 2,3,7,8-SUBSTITUTED CDDs AND CDFs
IN TWELVE COMPOUND-SPECIFIC ANALYSES (TETRA, PENTA,
HEXA, AND HEPTA ISOMER GROUPS, CONCENTRATIONS GIVEN IN ppb)

Sample	2,3,7,8-Tetra CDD	2,3,7,8-Tetra CDF	Chlorinated CDDs	Chlorinated CDFs	Total 2,3,7,8 CDDs AND CDFs[1/]
Commercial Na-PCP, Sawmill A	0	201	34,751	6,540	41,291
Commercial K-TetraCP, Sawmill C	0	200	1,197	1,148	2,345
Sawmill Dip Tanks					
Sawmill A sludge	0	15	25,305	3,333	28,638
Sawmill B wet sludge	0	17	2,332	485	2,817
Sawmill B dry sludge	9.7	95	15,411	2,177	17,588
Sawmill C center sludge	0	54	1,092	560	1,652
Sawmill C corner sludge	0[2/]	65	1,161	574	1,735
Sawmill C liquid	0	2.0	18	26	44
Wood Treatment Plant-					
PCP "Bloom"	0	4.4	24,183	10,712	34,895
Recycled "Commercial"	0	0	6,715	726	7,441
Soil at Retort Mouth	0	0	1,618	169	1,887
Sump Liquid	0	0	8,684	69	8,753

1/ Does not include octaCDD and octaCDF.

2/ Reported at 6.8 ppb by one laboratory but not confirmed by second.

CHAPTER 8: HAZARD EVALUATION

Results of the State Board's program to perform congener-specific analyses for CDDs and CDFs present in samples taken at sawmills and a wood treatment plant have been presented in the previous chapter. Based on the study results, this chapter discusses approaches to evaluate CDD and CDF-contaminated sites.

Although 2,3,7,8-tetraCDD was confirmed in only one of twelve samples, other 2,3,7,8-congeners of toxicological concern were detected in all twelve. As a means to estimate potential risk, this chapter discusses three procedures to evaluate mixtures of CDDs and CDFs based on methods developed by the U. S. Environmental Protection Agency (Bellin and Barnes, 1986) and the California Department of Health Services (CARB and CDHS, 1986).

Various scenarios are summarized that evaluate the toxicity of CDD and CDF mixtures based on toxic equivalence relative to 2,3,7,8-tetraCDD. The State Board program included congener-specific analysis of 12 samples. The results indicated the proportion of 2,3,7,8-chlorinated isomers present within an isomer group. Based on this information, a simple procedure is suggested to estimate the concentration of 2,3,7,8-chlorinated CDDs and CDFs present in samples analyzed by less costly isomer group analysis.

Finally, the issue of determining cleanup levels for sites contaminated by mixtures of CDDs and CDFs is discussed. A site-specific approach that uses the California Site Mitigation Decision Tree Manual is suggested.

TOXIC EQUIVALENCY FACTORS

This section discusses three approaches to evaluate mixtures of CDDs and CDFs based on toxic equivalence to 2,3,7,8-tetraCDD. One approach has been developed by the U.S. EPA, and a second by the California Department of Health Services. A third procedure is simple summation of all tetra-through-heptaCDDs and CDFs.

U.S. EPA Approach

The U.S. EPA has developed an approach to assess the hazards presented by CDDs and CDFs in soot, incinerator fly ash, industrial waste, and soils (Bellin and Barnes, Interim Procedures for Estimating Risks Associated with Exposure to Mixtures of Chlorinated Dibenzo-p-Dioxins and Dibenzofurans [CDDs and CDFs], October 1986). EPA concluded that the preferred method to assess complex mixtures of CDDs and CDFs was by direct biological assessment. However, because the information for biological assessment of each 2,3,7,8-chlorinated congener is not currently available, the interim approach recommended has been

estimation of the risk potential of the most toxic CDDs and CDFs (i.e., 2,3,7,8-chlorinated congeners), by estimating their equivalence to 2,3,7,8-tetraCDD. EPA examined a range of experiments measuring the following systemic and biochemical effects:

- o cancer induction
- o reproductive effects
- o in vitro cell transformation
- o enzyme induction
- o receptor binding

EPA used the rationale listed below to establish the relative toxicity factors shown in Table 8.1.

1. Determination of toxicity factors for 2,3,7,8-tetraCDD and the 2,3,7,8-hexaCDDs was based on carcinogenic potency derived by the U.S. EPA's Cancer Assessment Group. Relative potency for the 2,3,7,8-hexaCDDs was four percent of 2,3,7,8-tetraCDD.

2. Relative toxicity for 1,2,3,7,8-pentaCDD was estimated to be 50 percent of 2,3,7,8-tetraCDD by using the arithmetic mean of carcinogenic potency values for 2,3,7,8-tetra- and hexaCDDs.

3. The 2,3,7,8-tetraCDF and 2,3,7,8-pentaCDFs were assigned a relative potency value of 0.1, based on in vitro and reproductive toxicity tests that showed these CDFs were one to two orders of magnitude less potent than 2,3,7,8-tetraCDD. Since in vitro tests show the hexaCDFs to be one tenth as potent as the pentaCDFs, the hexaCDFs were assigned a value of 0.01.

4. The heptaCDDs and heptaCDFs were assigned a value of 0.001 because their enzyme induction potency is about 0.001 of 2,3,7,8-tetraCDD.

5. EPA noted that, in most tests, the non-2,3,7,8 chlorinated CDDs and CDFs were one to three orders of magnitude less potent than their 2,3,7,8-chlorinated isomers. For non-2,3,7,8-chlorinated CDDs and CDFs, potency was set at 0.01 of the corresponding 2,3,7,8-chlorinated isomer(s). For example, 1,2,4,6,7,9-hexaCDD would have a toxic equivalency factor of 0.01 times the 0.04 value for a 2,3,7,8-hexaCDD, or 0.0004.

These estimates of relative potency can be refined if and when more information becomes available. Table 8.2 illustrates application of the U.S. EPA method to determine the toxic equivalency of the CDD and CDF mixture in a dip tank sludge that was analyzed as part of the State Board's congener-specific monitoring (Sawmill C). In this example, the CDFs contributed approximately twice as much relative toxicity concentration as

TABLE 8.1

CDD AND CDF CONGENERS OF MOST TOXIC CONCERN
(BELLIN AND BARNES, 1986)

Congener	TEF[1/]
CDD	
2,3,7,8-tetraCDD	1.0
1,2,3,7,8-pentaCDD	0.5
1,2,3,4,7,8-hexaCDD	0.04
1,2,3,6,7,8-hexaCDD	0.04
1,2,3,7,8,9-hexaCDD	0.04
1,2,3,4,6,7,8-heptaCDD	0.001
CDF	
2,3,7,8-tetraCDF	0.1
1,2,3,7,8-pentaCDF	0.1
2,3,4,7,8-pentaCDF	0.1
1,2,3,4,7,8-hexaCDF	0.01
1,2,3,6,7,8-hexaCDF	0.01
1,2,3,7,8,9-hexaCDF	0.01
2,3,4,6,7,8-hexaCDF	0.01
1,2,3,4,6,7,8-heptaCDF	0.001
1,2,3,4,7,8,9-heptaCDF	0.001

1/ TEF: Toxic Equivalency Factor: the estimated toxicity relative to 2,3,7,8-tetraCDD

TABLE 8.2

CALCULATION OF TOTAL RELATIVE TOXICITY CONCENTRATION
USING THE U.S. EPA METHOD:
CDD AND CDF CONCENTRATIONS MEASURED
IN SAWMILL C DIP TANK SLUDGE

Isomer Group	Concentration of 2,3,7,8 Congeners (ppb)	Toxic Equivalency Factor	Relative Toxicity Concentration(ppb)
CDDs			
TetraCDD	-	1.0	0
PentaCDD	-	0.5	0
HexaCDD	224	0.04	9.0
HeptaCDD	937	0.001	0.9
Total			9.9
CDFs			
TetraCDF	65	0.1	6.5
PentaCDF	106	0.1	10.6
HexaCDF	61	0.01	0.6
HeptaCDF	342	0.001	0.3
Total			18.0
Total Tetra-HeptaCDDs and CDFs			27.9

the CDDs. The estimated toxicity concentration related to 2,3,7,8-tetraCDD was 27.9 ppb. Using the U.S. EPA approach, the congeners contributing the most relative toxicity were the pentaCDFs (38 percent), the hexaCDDs (32 percent), and 2,3,7,8-tetraCDF (23 percent).

In September 1986, a U.S. EPA Science Advisory Board Subcommittee met to critique the Agency's interim approach of assessing toxicity of CDD and CDF mixtures by estimating the toxicity of individual CDD and CDF congeners relative to 2,3,7,8-tetraCDD. While the subcommittee made several suggestions to refine the method, the general conclusion was that the approach is a "successful interim attempt to articulate a scientific rationale and procedures for developing risk management decisions for mixtures which contain CDDs and CDFs related in structure and activity to 2,3,7,8-tetraCDD". The cover letter and text of the subcommittee's report are contained in Appendix J of this report.

California Department of Health Services Approach (CDHS Favored Scenario)

In Appendix B of "Health Effects of 2,3,7,8 Tetrachlorodibenzo-p-Dioxin and Related Compounds", the California Department of Health Services (CARB and CDHS, 1986) discussed four methods (scenarios) to estimate total potency of CDD and CDF mixtures. The first and most conservative scenario assumed that all CDDs and CDFs, including octaCDD and octaCDF, are as potent as 2,3,7,8-tetraCDD. Scenario 2 also assumed all CDDs and CDFs, except the hexaCDDs, octaCDD, and octaCDF, were equivalent to 2,3,7,8-tetraCDD. Based on carcinogenic potency, the hexaCDDs were rated as 3 percent as potent as 2,3,7,8-tetraCDD and the octaCDD and CDF were not rated. Scenario 3 was similar to the U.S. EPA method presented above, except that the hexaCDDs were assigned a potency of 0.03 instead of 0.04. Scenario 3 uses results of short-term tests in addition to carcinogenicity bioassays. Scenario 4, favored in the CDHS document, limits data examined to that provided by carcinogenicity bioassays. Since these bioassays have only tested 2,3,7,8-tetraCDD and a mixture of two 2,3,7,8-hexaCDD isomers, there are only two equivalence factors. In Scenario 4, CDHS assigns pentaCDD the same value as 2,3,7,8-tetraCDD and 1,2,3,4,6,7,8-heptaCDD the same value as the 2,3,7,8-hexaCDD isomers. The CDFs are given the same estimated potencies as the equivalent CDD isomer groups (pentaCDF equal to pentaCDD, hexaCDF equal to hexaCDD, etc.)

The CDHS document (CARB and CDHS, 1986) notes that the U.S. EPA approach is the least health conservative and requires the greatest number of assumptions about relative potency. Noting that most CDDs and CDFs have not been tested for long-term chronic toxicity, CDHS states that the use of short-term tests to estimate long-term effects (the method employed by the U.S. EPA) is "tenuous".

Table 8.3 shows calculation of estimated toxicity concentration by using CDHS's favored scenario for the same Sawmill C sludge sample determined earlier by the U.S. EPA method (Table 8.2). Whereas the U.S. EPA method totalled 27.9 ppb relative toxicity concentration, the CDHS favored scenario was 217.9 ppb. The CDFs accounted for 84 percent of the relative toxicity, with pentaCDFs accounting for 49 percent (106 ppb) and 2,3,7,8-tetraCDF for 30 percent (65 ppb). The heptaCDD dominated the CDD contribution, with 13 percent (28.1 ppb) of the total and exceeded the 2,3,7,8-hexaCDD isomers by a factor of 4.

Summation of All Tetra-Through-HeptaCDDs and CDFs Approach

This is the simplest of the three approaches: all 2,3,7,8-tetra-, penta-, hexa-, and heptaCDDs and CDFs are added together. All these congeners are assigned the same toxic equivalency factor of 1.0. This approach (also shown in Table 8.3) yielded a concentration of 1,735 ppb in the dip tank sludge with the CDDs accounting for 67 percent of the total CDDs and CDFs.

Comparison of Toxic Equivalency Approaches

Using the State Board's results from all 12 samples that underwent congener-specific analysis, Table 8.4 summarizes three approaches to determine toxic equivalency of CDD and CDF mixtures to 2,3,7,8-tetraCDD. The three approaches are:

- o U.S. EPA interim method
- o CDHS Favored Scenario
- o Total tetra- through heptaCDDs and CDFs

Use of the CDHS method resulted in higher estimated relative toxicity concentration. For the eight sawmill samples, CDHS estimates were four to nine times those of U.S. EPA. For the wood treatment plant, CDHS values were 11 to 28 times those of U.S. EPA's. Because the hexa and hepta isomer groups are given equal weight under the CDHS system of ranking, the presence of heptaCDDs and CDFs assumes more importance than with the U.S. EPA approach.

The method of adding all tetra- through hepta- 2,3,7,8 congeners provided much higher estimates of total relative toxicity concentration. Since this method treats all 2,3,7,8 chlorinated CDDs and CDFs as equal, very high estimates are given. The highest value, from the drum of commercial formulation at Sawmill A, totalled 41,291 ppb for total tetra- through heptaCDDs and CDFs. While the most health conservative, this approach excludes the results of long- and short-term studies that ranked CDDs and CDFs by relative potency.

TABLE 8.3

CALCULATION OF TOTAL RELATIVE TOXICITY CONCENTRATION
USING THE CDHS APPROACH:
CDD AND CDF CONCENTRATIONS MEASURED
IN SAWMILL C DIP TANK SLUDGE

Isomer Group	Concentration of 2,3,7,8 Congeners (ppb)	CDHS Toxic Equivalency Factor	Relative Toxicity Concentration (ppb)
CDDs			
TetraCDD	-	1.0	0
PentaCDD	-	1.0	0
HexaCDD	224	0.03	6.7
HeptaCDD	937	0.03	28.1
Total CDDs	1,161		34.8
CDFs			
TetraCDF	65	1.0	65
PentaCDF	106	1.0	106
HexaCDF	61	0.03	1.8
HeptaCDF	342	0.03	10.3
Total CDFs	574		183.1
Total Tetra-HeptaCDDs and CDFs	1,735		217.9

TABLE 8.4

HAZARD EVALUATION: TOTAL RELATIVE TOXICITY CONCENTRATIONS (ppb) OF 2,3,7,8 CHLORINATED CDDs AND CDFs USING THREE METHODS OF CALCULATION

SAMPLE	U.S. EPA (1986)[1/]	CDHS 1986[2/]	SUM OF ALL CDDs AND CDFs[3/]
Commercial Na-PCP			
Sawmill A	289.5	2,055	41,291
Commercial K-tetraCP			
Sawmill C	72.8	463	2,345
Sawmill Dip Tanks			
Sawmill A sludge	139.1	1,184	28,638
Sawmill B wet sludge	32.0	173	2,817
Sawmill B dry sludge	329.6	1,094	17,588
Sawmill C center of tank sludge	27.0	216	1,652
Sawmill C corner of tank sludge	27.9	218	1,735
Sawmill C liquid	0.8	8.4	44
Wood Treatment Plant-PCP			
"Bloom"	100.5	1,120	34,895
Recycled "Commercial"	11.3	223	7,441
Soil at Retort Mouth	5.6	64	1,887
Sump Liquid	9.8	274	8,753

1/ Bellin, J. and D. Barnes. 1986. Interim Procedures for Estimati Risks Associated with Exposure to Mixtures of Chlorinated Dibenzodioxins and Dibenzofurans

2/ CDHS, 1986; Favored Scenario where relative potency of 2,3,7,8-tetra- and pentaCDDs and CDFs = 2,3,7,8-tetraCDD and 2,3,7,8-hexa- and heptaCDDs and CDFs = 2,3,7,8 hexaCDD (or 0.03 2,3,7,8-tetraCDD).

3/ Excluding octaCDD and octaCDF.

ESTIMATION OF 2,3,7,8 CONGENER-SPECIFIC CONCENTRATIONS FROM ISOMER GROUP DATA

Because of the complexity and cost associated with 2,3,7,8 congener-specific analysis, most analyses of CDD and CDF mixtures have been reported in terms of isomer groups. Unfortunately, isomer group data do not provide an indication of concentrations of the most toxic congeners of concern. Results from the limited State Board study can be adapted to estimate the concentrations of 2,3,7,8 congeners present in analyses reported as isomer group data.

In previous studies, two simple alternative procedures have been used (CARB and CDHS, 1986):

1. Assume all isomers in an isomer group are chlorinated at the 2,3,7, and 8 positions. For example, if 100 ppb hexaCDD is reported in an analysis, the level of 2,3,7,8-hexaCDDs would be 100 ppb.

2. Assume each isomer in an isomer group has an equal chance of occurrence. Since there are ten possible hexaCDD isomers and three are chlorinated at the 2,3,7, and 8 positions, then the estimated amount of 2,3,7,8-hexaCDDs would be (3/10) (100 ppb) = 30 ppb.

In contrast, the State Board has conducted a limited program (12 samples) of congener-specific analyses. This allows for inferences to be made as to approximate percentages of 2,3,7,8-congeners present, based on measured concentrations instead of assumptions. Table 8.5 is a condensation of Table H.5 in Appendix H, "Results of State Board CDD and CDF 2,3,7,8 Congener-Specific Analyses", and the percentages given are based on this very limited number of analyses. For example (referring to Table 6.5), if an isomer group analysis of sawmill dip tank sludge shows 100 ppb hexaCDD, then the estimated 2,3,7,8-chlorinated hexaCDD level will be (100 ppb) (55%) = 55 ppb.

In performing a hazard evaluation, either the U.S. EPA or CDHS approach can be used after converting the results of isomer group analysis to calculated 2,3,7,8 congener-specific concentration. Analysis by isomer group of CDDs and CDFs has the advantage that it can be performed currently by many laboratories at less cost and more rapidly than congener-specific analysis, which only a few laboratories are capable of attempting. Further, if a discharger disagrees with the estimated percentage of 2,3,7,8 congeners, he can arrange for congener-specific analysis to support his argument.

TABLE 8.5

APPROXIMATE PERCENTAGE OF 2,3,7,8-CHLORINATED ISOMERS DETECTED IN EACH CDD AND CDF ISOMER GROUP

Isomer Group	Commercial Na-PCP	Commercial K-tetraCP	Dip Tank Sludge	Wood Treatment Plant-Bloom & Soil
CDDs				
TetraCDD (1 of 22)[1/]	ND	ND	ND	ND
PentaCDD (1 of 14)	12%	ND	ND	80%
HexaCDD (3 of 10)	39%	40%	55%	45%
HeptaCDD (1 of 2)	44%	64%	60%	70%
CDFs				
TetraCDF (1 of 38)	14%	16%	19%	14%
PentaCDF (2 of 28)	7%	5%	10%	14%
HexaCDF (4 of 16)	2%	1%	4%	20%
HeptaCDF (2 of 4)	10%	34%	34%	43%

1/ Numbers in parentheses indicate the number of 2,3,7,8-chlorinated isomers possible within an isomer group. For example: HexaCDD (3 of 10) indicates three of ten isomers are chlorinated at 2,3,7, and 8 positions.

SETTING A CLEANUP LEVEL

The U.S. EPA established a site-specific cleanup level of 1 ppb 2,3,7,8-tetraCDD for the town of Times Beach, Missouri. The level was recommended to U.S. EPA in an extensive analysis performed by the Centers for Disease Control (Kimbrough et al., 1984) and is based on reasonable human risk of exposure. Kimbrough et al. (1984) suggest that 2,3,7,8-tetraCDD at levels of 1 ppb or greater in residential soil is of concern and "cannot be considered safe". A level set for industrial locations, such as a sawmill or wood treatment plant, possibly may exceed that for residential soil.

In Table 8.4, the twelve samples analyzed by congener-specific analysis were examined for toxic equivalency to 2,3,7,8-tetraCDD. Using the U.S. EPA method, only one sample--the dip tank liquid at Sawmill C at 0.8 ppb--had a toxic equivalency factor of less than 1 ppb. With the CDHS method, all twelve exceed 1 ppb. It should be noted that the 1 ppb level was determined for residential exposure, a scenario that includes potential ingestion of contaminated soil by young children. Most sawmill and wood treatment plant sites examined during the State Board investigation do not fit a residential exposure scenario.

The Times Beach clean-up level of 1 ppb was site-specific and should not be used arbitrarily at other sites. Rather, each site found to contain CDDs and CDFs will require independent evaluation. If these compounds are detected in soils sampled at an abandoned sawmill, then the potential for human contact or environmental contamination needs to be determined. In California, The California Site Mitigation Decision Tree Manual (Decision Tree) (CDHS, 1986) has been developed by the State Department of Health Services to provide a basis for risk management decisions. The Decision Tree includes five components: (1) preliminary risk appraisal, (2) site assessment, (3) risk appraisal, (4) environmental fate and risk determination, and (5) determination of mitigation strategy and remedial action plan selection. A Decision Tree approach to cleanup of CDD and CDF-contaminated soils at the abandoned sawmill will require a number of important site-specific evaluations during site assessment. Field observations are required to identify the contaminants, the exposure pathways (air, soil, water, biota), and the biological receptors (e.g., humans, aquatic species).

Based on site-specific field observations, the Decision Tree process proceeds to risk appraisal. During risk appraisal, statewide criteria are established with Applied Action Levels (AALs). The AALs are set for each medium of exposure (air, soil, water, biota) to protect specific biological receptors. The Decision Tree defines an applied action level as "a criterion which delineates a concentration of a substance in a media which when exceeded is determined to present a significant risk of an

adverse impact to a biological receptor" (CDHS, 1986). The Department of Health Services is currently developing AALs for mixtures of CDDs and CDFs. The AALs are derived from maximum exposure levels at which no adverse effects appear in the biological receptor and are given in units of concentration. (An AAL for water would be expressed as mg/L; an AAL for soil as mg/kg.)

Derivation of AALs also takes into account the amount of medium taken in by inhalation, ingestion, and absorption as well as toxicokinetic factors (e.g., absorption, metabolism, distribution, and elimination) characteristic of the medium. For non-threshold agents (such as CDDs and CDFs), the AAL derivation is based on exposure at a level where risk is no greater than one in one million.

If an AAL is exceeded in any medium of exposure (soil, water, air, biota), and a significant risk identified, a risk management process should be identified that will mitigate the potential exposure. For further explanation, the Executive Summary to the CDHS Decision Tree is reproduced in Appendix J.

For the sake of illustration, the site-specific level of 1 ppb 2,3,7,8-tetraCDD set for Times Beach, Missouri can be applied to a hypothetical site in California. An abandoned sawmill contains CDDs and CDFs in surface soils and is adjacent to a residential area. Without mitigation measures, young children potentially will play in and ingest the contaminated soils. For this site, with potential exposure to children, the AAL (soil) will be 1 ug/kg (1 ppb). If analysis for CDDs and CDFs in the soil surface layer is performed, and the calculated toxic equivalency factor to 2,3,7,8-tetraCDD equals or exceeds 1 ppb, then remedial action will be required. The key to the Decision Tree approach is determination of the exposure pathway and potential exposure of a specific population. Because studies have shown that children five years old or younger ingest the highest amounts of soil, this age would compose the highest risk group. If only adults were potentially exposed, the AAL (soil) probably would be higher. And, if the contaminated soil was buried and the situation determined to be sufficiently stable that there would be no migration of CDDs and CDFs, then the Decision Tree would not require remedial action.

In summary, evaluation of a site containing mixtures of CDDs and CDFs should be site-specific before the necessity for cleanup can be determined. Characterization of the CDD/CDF mixture by toxic equivalence to 2,3,7,8-tetraCDD will allow an estimate of potential hazard. Site observations will determine if these compounds are likely to migrate (e.g., presence of solvents as co-contaminants, depth to groundwater, nearness to surface, etc.) or are essentially immobile. The pathways of potential exposure (air, soil, water, biota) can be established from site

evaluation. Potential biological receptors (aquatic life, occupationally-exposed workers, young children) to the CDD/CDF mixture need to be determined as part of the risk appraisal.

By using a thorough evaluation based on the Decision Tree approach, the options for remedial action can be identified. At some sites, moving the material may create more of a hazard than encapsulation and on-site storage. On-site storage, with material isolated from man and the environment, may be the most effective interim measure until acceptable methods of CDD/CDF destruction are available.

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