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2,4,5-TRICHLOROPHENOL
AND ITS SODIUM AND POTASSIUM SALTS

POSITION DOCUMENT 1

EPA/SPRD - 80/79

2,4,5-Trichlorophenol Working Group
Mary Reece, Project Manager
U.S. Environmental Protection Agency

CONTENTS

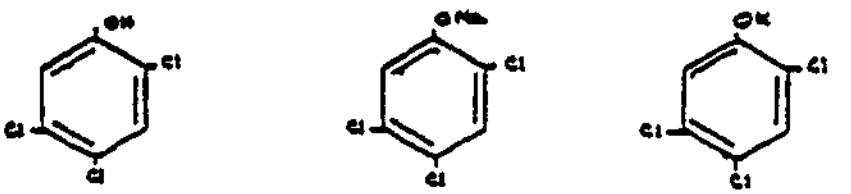
FOREWORD

All technical and formulated 2,4,5-trichlorophenol (2,4,5-TCP) products are contaminated in varying degree by a byproduct of the manufacturing process, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). For this reason all references to 2,4,5-TCP denote TCDD-contaminated 2,4,5-TCP. Numerous toxicity studies on purified TCDD are included in this position document. Many of these studies were done in connection with another pesticide, 2,4,5-trichlorophenoxyacetic acid or 2,4,5-T, which is manufactured from 2,4,5-TCP. 2,4,5-T, which is a candidate for rebuttable presumption against registration, is the subject of a separate position document.

I. Background

A. Chemical and Physical Characteristics

2,4,5-Trichlorophenol (2,4,5-TCP) and its sodium (Na-2,4,5-TCP) and potassium (K-2,4,5-TCP) salts are used as fungicides, algicides, and bactericides (Weissberg and Zinkl, 1973; Plimmer et al., 1973). The empirical formulas for 2,4,5-TCP and its sodium and potassium salts are $C_6H_2Cl_3OH$, $C_6H_2Cl_3ONa$, and $C_6H_2Cl_3OK$, respectively. The structural formulas of these compounds may be found in Figure 1. 2,4,5-TCP is also known by its trade name, Dowicide 2; the trade name of Na-2,4,5-TCP is Dowicide B.



2,4,5-TCP Na-2,4,5-TCP K-2,4,5-TCP

FIGURE 1. Structural formulas of 2,4,5-TCP and its sodium and potassium salts

2,4,5-TCP is a fairly weak acid and is considered to be the least toxic of the chlorophenols (Kirk-Othmer Encyclopedia, 1964). The sodium salt is slightly more toxic. 2,4,5-TCP occurs as gray flakes in sublimed mass with a strong phenolic odor. Although 2,4,5-TCP is relatively insoluble in water (< 0.2 g/100 g water at 25°C), it is soluble in organic solvents such as alcohol, ether, and acetone. The sodium salt is more soluble in water (113 g/100 g water at 25°C). 2,4,5-TCP has a molecular weight of 197.46 and a specific gravity of 1.678 (25°C/4°C). Its boiling point is 252°C; the melting point is 60-70°C.

B. Manufacturing Process and Resulting Contaminants

1. Formulation

2,4,5-TCP is produced commercially by the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene to 2,4,5-TCP. The reaction is carried out under pressure at 180 °C in the presence of aqueous sodium hydroxide and methanol (Kirk-Othmer Encyclopedia, 1964; Fishbein, 1973). 2,4,5-TCP can be converted to its sodium or potassium salts by the addition of sodium or potassium carbonate.

Polychlorinated dibenzo-p-dioxins are formed in the manufacturing process of all chlorophenols. However, the amount formed is dependent on the degree to which the temperature and pressure are controlled during production (Fishbein, 1973; Milnes, 1971; Schulz, 1968; Higginbotham et al. 1968; Mulder and Shadoff, 1973).

An especially toxic dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), is formed during the production of 2,4,5-TCP. As can be anticipated, TCDD has been associated with all synthetic compounds derived from 2,4,5-TCP (Kearney et al., 1973). This includes the widely used herbicide and defoliant 2,4,5-T (2,4,5-trichlorophenoxyacetic acid). The formation of 2,4,5-TCP and TCDD is illustrated in Figure 2.

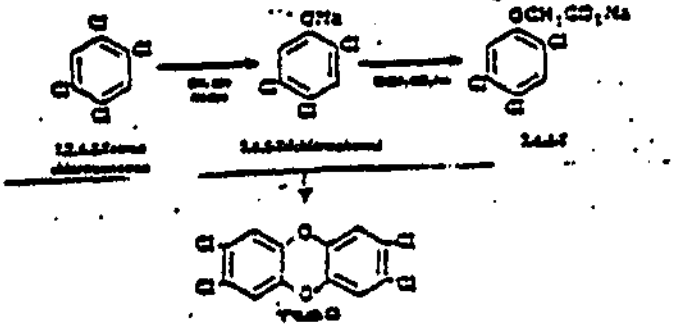


Figure 2. Formulation of 2,4,5-TCP and TCDD

2. Types of Dioxins

There are many different dioxins; the particular dioxin produced depends on the chlorophenols present (Poland and Kende, 1976). Different dioxins can be distinguished by the number and position of the chlorines they contain. Chlorine atoms may be attached at any of eight different positions, creating a theoretical possibility of 75 compounds or isomers (Crossland and Shea, 1973; Khera and Ruddick, 1973).

The toxicity of a dioxin varies with the position and number of chlorines attached to the aromatic rings. Generally, the toxicity increases with increased chlorine substitution. Those dioxins that have halogens at the 2, 3, and 7 positions are particularly toxic (Burger, 1973). TCDD, which has chlorine atoms at the 2, 3, 7, and 8 positions, is considered the most toxic of the dioxins (Sparschu et al., 1971).

3. TCDD Content in Formulated Pesticides

Although TCDD levels in 2,4,5-TCP have not been monitored consistently over the years, these levels have been measured in 2,4,5-T. Different manufacturers produced 2,4,5-T with various TCDD contents (Kearney et al., 1973). Samples of 2,4,5-T produced by one manufacturer from 1966 to 1968 often contained more than 10 ppm TCDD (Fishbein, 1973). Because there was concern about the extremely toxic effects of TCDD, manufacturing methods were changed and carefully controlled to minimize its formation. By 1971 industry had reduced the amount of TCDD in commercial samples of 2,4,5-T to less than 1 ppm (Greig et al., 1973; Hussain et al., 1972; Milnes, 1971). Production conditions and the amount of contaminant in the final product are now closely monitored by industry.

2,4,5-TCP is available in both a technical and analytical form. Technical grade 2,4,5-TCP (Dowicide 2) currently contains 95% active ingredient and 5% inert ingredients in which TCDD is present at a maximum of 0.099 ppm. Technical grade Na-2,4,5-TCP (Dowicide B) contains 85% Na-2,4,5-TCP and 15% inert ingredients in which TCDD is present at a maximum of 0.099 ppm (Dow Chemical Company Sales Specifications, 1976). The dioxin content in both of these products does not exceed the limit of 0.1 ppm recommended by the Advisory Committee to the EPA Administrator on May 7, 1971.

To obtain a meaningful assessment of the levels of TCDD present in the environment and to determine the amount that could be accumulated in the food chain, a sensitive analytical method had to be developed that could accurately identify TCDD in parts per trillion. During the past 10 years considerable advances have been made in this regard. The analytical procedure that is currently considered the most sensitive is gas-liquid chromatography coupled with high resolution mass spectrometry (National Academy of Sciences, 1977).

C. Registrations, Uses, and Production

The largest use of 2,4,5-TCP is as a starting material in the manufacture of a series of industrial and agricultural chemicals, the most notable of which is the herbicide 2,4,5-T and its related products including silvex [2-(2,4,5-trichlorophenoxy)propionic acid], ronnel [O, O-dimethyl O-(2,4,5-trichlorophenyl)-phosphorothioate], and the bactericide hexachlorophene.

2,4,5-TCP and its salts are used in the textile industry to preserve emulsions used in rayon spinning and silk yarns, in the adhesive industry to preserve polyvinyl acetate emulsions, in the leather industry as a hide preservative, and in the automotive industry to preserve rubber gaskets. The sodium salt is used as a preservative in adhesives derived from casein, as a constituent of metal cutting fluids and foundry core washes to prevent breakdown and spoilage, as a bactericide/fungicide in recirculating water in cooling towers, and as an algicide/slimicide in the pulp/paper manufacturing industry.

There are some minor uses of 2,4,5-TCP and its salts in disinfectants which are of major importance relative to human exposure. These include use on swimming-pool-related surfaces; household sickroom equipment; food processing plants and equipment: food contact surfaces; hospital rooms; sickroom equipment; and bathrooms (including shower stalls, urinals, floors, and toilet bowls).

2,4,5-TCP and its salts have been registered for pesticidal use since 1948. Current EPA records indicate that 42 registrants have 94 Federally-registered products and one State-registered product containing 2,4,5-TCP or its salts. These products are usually formulated as wettable powders, emulsifiable concentrates, dry powders, liquids, or ball briquettes. Dow Chemical Company is the major manufacturer of technical grade 2,4,5-TCP (Dowicide 2) and Na-2,4,5-TCP (Dowicide 3). 2,4,5-TCP and its salts are frequently mixed with other pesticides including pentachlorophenol, tetrachlorophenol, and sodium pentachlorophenate.

Section 7(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires manufacturers and formulators to submit to EPA information on the production, sales, and distribution of their products. According to Sections 7(d) and 10 of FIFRA, this information may not be made available to the public. A confidential memo summarizing this information (Reece, 1977) has been sent to the Deputy Assistant Administrator for Pesticide Programs.

D. Tolerances

There are no tolerances for 2,4,5-TCP, its salts, or TCDD in or on food crops. 40 CFR 180.302 does, however, establish a tolerance of 0.05 ppm hexachlorophene in or on cotton seed (a nonhuman dietary food item) and states that technical grade hexachlorophene shall not contain more than 0.1 ppm TCDD.

E. Metabolism, Degradation, and Residues

No data has been found on the nature of the degradation products of 2,4,5-TCP. However, there is evidence that 2,4,5-TCP itself is the metabolite or primary degradation product of a number of pesticides including 2,4,5-T, silvex, ronnel, lindane, and benzene hexachloride (Watts and Storherr, 1973; Crosby and Wong, 1973; Goto et al., 1972; Leng, 1972).

1. Soil

a. 2,4,5-TCP and Its Salts

Alexander and Aleem (1961) found that 2,4,5-TCP is persistent because it is resistant to microbial decomposition in certain soil populations. They also found that compounds containing a meta-substituted chlorine (such as 2,4,5-TCP) were more persistent than those that did not.

These results were verified by Helling et al., in 1973.

b. TCDD

Crosby et al. (1973) irradiated 2,4,5-TCP and its sodium salt and found that they discolored rapidly but did not degrade into dioxins. Kearney et al. (1972) incubated 2,4,5-TCP in two types of soil for 70 days to determine whether bacterial action might convert the 2,4,5-TCP to TCDD. The fact that no TCDD was detected demonstrated that TCDD was not formed under these laboratory conditions. Thus, TCDD is neither formed indigenously in soil (Kearney et al., 1972) nor produced biosynthetically from soils receiving applications of 2,4,5-T or 2,4,5-TCP (Helling et al., 1973; Kearney et al., 1972; Kearney et al., 1973).

TCDD is a remarkably stable compound in biological systems at temperatures up to 700°C (Crosaland and Shea, 1973; Piper et al., 1973). It is also immobile in soil and tends to remain on the surface (Helling, 1971). TCDD degrades slowly in soil; it has a half-life of 1 year (Kearney et al., 1972; Helling et al., 1973).

In 1973, Woolson et al. investigated the possibility that TCDD residues from old, extremely heavy 2,4,5-T applications might still pose a threat to wildlife. They analyzed soil samples from experimental plots of Lakeland sand in Florida that had received massive doses of 2,4,5-T (947 pounds 2,4,5-T/acre) by aerial application from 1962 to 1970. The authors estimated that the 2,4,5-T used at that time contained between 2 and 50 ppm TCDD. Twenty-five gram samples of 6-inch increments of a 3-foot core were taken in 1970. No TCDD residues were found in any of the increments; the detection limit was less than 1 ppb. The authors

had estimated that there could be up to 2.1 ppm TCDD present in the soil as a result of the aerial applications. They felt that the absence of detectable TCDD residues could be explained by several possibilities: 1) the 2,4,5-T applied contained less than 2 ppm TCDD, 2) the TCDD moved deeper than 36 inches into the soil, 3) the TCDD was decomposed in the soil photochemically or biologically, or 4) wind erosion removed the TCDD from the point of application. However, TCDD is immobile in soil and the likelihood of wind erosion or the amount of TCDD present being less than 2 ppm is remote. It is most likely that the TCDD photochemically degraded.

Plimmer et al. (1973) found that TCDD is readily photolyzed under certain conditions. Crosby and Wong (1977) found that herbicide formulations containing TCDD on leaves, soil, or glass plates lost most or all of the TCDD in a single day of exposure to sunlight due principally to photochemical dechlorination. However, Crosby et al. (1971) found that a film of "pure" TCDD on glass plates was not photodegraded when exposed to sunlight for 14 days.

2. Water

a. 2,4,5-TCP and Its Salts

2,4,5-TCP is soluble only in organic solvents such as alcohol, ether, or acetone. The sodium salt is more soluble in water but less soluble in organic solvents. However, some of the uses of 2,4,5-TCP and its salts could feasibly result in their reaching water bodies from industrial effluents or from cooling tower water that is not in a closed system.

b. TCDD

Because TCDD is relatively immobile in soil and soluble in water at only 0.2 ppb, the possibility of ground water contamination is virtually non-existent and water transport is limited (Helling et al., 1973; Harvey, 1973).

A recent National Academy of Science report (1977) stated that TCDD has never been detected in drinking water; the limit of detection in the studies cited was in the parts per trillion. The report did note the toxicity of TCDD and its acceptable daily intake from water (.0001 ug/kg/day), and suggested no-adverse-effect levels (7×10^{-4} ug/kg/day).

3. Wildlife

a. 2,4,5-TCP and Its Salts

No studies identifying 2,4,5-TCP residues in wildlife were found.

b. TCDD

i. Terrestrial Ecosystems

To assess the ecological importance of chlorinated dioxins, Woolson et al. (1973) examined tissues of 19 bald eagles (Haliaeetus leucocephalus) collected in 15 widely separate States. No TCDD residues were found; the limit of detection was 50 ppb. Because eagles are at the top of a food chain, the authors concluded that TCDD residues from past pesticide applications were not available to this food chain.

ii. Aquatic Ecosystems

Isensee and Jones (1975) conducted an experiment in which TCDD was absorbed on three different types of soil at concentrations ranging from 0.001-7.45 ppm. The soil was then placed in aquatic model ecosys-

tems. TCDD accumulated in all organisms (mosquito fish, daphnid, duckweed, catfish, and snails). The amount of accumulation was directly related to the concentration of TCDD in the water (0.05-1330 ppt). Therefore, the authors concluded that under certain conditions TCDD residues could accumulate in fish or other aquatic organisms.

Zitco (1972) was unable to detect chlorinated dibenzodioxin residues in several aquatic animals from various locations in Canada; the limit of detection was 0.01-0.04 ug/g (ppm). The author concluded that there is no detectable contamination of food by chlorinated dibenzodioxins since the species analyzed are in high trophic levels of the aquatic food chain and serve as good indicators of environmental contamination by cumulative compounds. However, analytical methods have improved considerably since then and scientists can now detect dioxins in the parts per trillion.

Matsumura and Benezet (1973) found that TCDD pickup (biological transfer) was low in brine shrimp and fish but high in mosquito larvae, which are bottom feeders. This led them to believe that TCDD is not likely to accumulate in aquatic systems due to TCDD's low solubility in water.

Baughman and Meselson (1973) reported the presence of TCDD in fish and crustaceans taken from four locations in Vietnam. Concentrations ranged from 18 to 810 ppt.

4. Plants

a. 2,4,5-TCP and Its Salts

No studies identifying 2,4,5-TCP residues in plants were found.

b. TCDD

TCDD was not detected in the seeds or mature plants of soybeans or oats sprayed with TCDD or grown on soils contaminated with 60 ppb TCDD. The limit of detection was less than 1 ppb. Researchers concluded that plants do not absorb or translocate TCDD from soil or leaves after foliar application (Isensee and Jones, 1971; Matsumura and Benezet, 1973). Crosby and Wong (1977) found that herbicide formulations containing known amounts of TCDD that were exposed to natural sunlight on leaves, soil, or glass plates lost most or all of their TCDD during a single day. They felt this was due principally to photochemical dechlorination. TCDD that is sprayed on leaf surfaces can be readily washed off (Isensee and Jones, 1971; Helling et al., 1973; Kearney et al., 1973).

Matsumura and Benezet (1973) concluded that any translocation of TCDD in the environment would be limited to traces of the compound adhered to soil particles, dispersed by the wind, or biologically transferred in aquatic environments.

5. Animals

a. 2,4,5-TCP and Its Salts

No studies on the metabolism of 2,4,5-TCP in laboratory animals were found.

b. TCDD

TCDD is eliminated from biological systems principally through the feces but also through the urine (Allen et al., 1975; Piper et al., 1973; Vinopal and Casida, 1973; Kimbrough, 1974).

Rose et al. (1976) detected radioactivity only in the feces of

rats administered a single oral dose of 1 ug/kg ^{14}C-labeled TCDD. Liver and fat contained ^{14}C-TCDD concentrations over 10 times greater than those in other tissues examined 22 days after ingestion. When oral doses of 0.01, 0.1, or 1 ug ^{14}C-TCDD kg/day were administered for 13 weeks, the major route to excretion was again via the feces, and the half-life of the ^{14}C-TCDD in the rats was 23.7 days.

In Sprague-Dawley rats intubated with ^{14}C-labeled TCDD, only 4.5% of the radioactivity from a single oral dose was eliminated through the urine in 21 days. A large percentage of the radioactivity remaining in the body at the end of this period was in the liver and over 90% was within the microsomal fraction (Allen et al., 1975).

In a preliminary report of a two-year chronic toxicity feeding study, Dow Chemical USA (Traynor, 1977) reported the following residue data for rats fed indicated TCDD doses: 24,000 ppt in liver and 8,100 ppt in fat of females ingesting 2,200 ppt/day; 5,100 ppt in liver and 1,700 ppt in fat of females ingesting 220 ppt/day; and 540 ppt in liver and fat of females ingesting 22 ppt/day. The preliminary report gives no residue data for treated males, or for control of either sex.

6. Humans

The National Human Monitoring Program for Pesticides is currently sampling human urine and analyzing these samples for silvex, 2,4,5-T, and 2,4,5-TCP through its cooperative arrangement with the EPA Health and Nutritional Examination Survey II (Hanes II project). The survey is scheduled for completion in 1979. Some preliminary results that relate to 2,4,5-TCP residues in the first 400 of an estimated 7,500 sam-

ples are available. These results are only tentative and of course subject to change as further data are received.

Of the initial samples analyzed, 1.68% have shown detectable levels of 2,4,5-TCP with a maximum amount of 32.4 ppb. The arithmetic mean is less than 1 ppb. In addition, 32.69% of the samples have shown trace amounts (< 5 ppb) of 2,4,5-TCP. Residues of this compound may also be derived from the metabolism of other pesticides and from exposure to 2,4,5-TCP that was used as a disinfectant (Kutz, 1977).

7. Animal Products

a. 2,4,5-TCP and Its Salts

No information is available on the presence of 2,4,5-TCP residues in animal products. However, in tests with cattle, sheep, and calves that were fed diets containing 2,4,5-T and silvex, residues of 2,4,5-TCP were detected in the kidney, liver, muscle, fat, and milk (Clark et al. 1975; Lang, 1976; Bjerke et al., 1972).

b. TCDD

When beef fat samples that had been fortified with 2000 ppm 2,4,5-TCP or its sodium salt were cooked at 500°F for 6-22 hours and analyzed, no TCDD was found in any of the samples. The limit of detection was 0.05 ppm (Watts and Stocherr, 1973).

Eighty-five samples of beef fat were analyzed for TCDD content under the auspices of the EPA Dioxin Implementation Plan (see discussion p. 20). The beef fat samples included 18 samples from control areas and 67 samples from areas previously treated with 2,4,5-T. None of the 18 control samples had detectable amount of TCDD at a detection limit

of 10 ppt. Of these 67 samples from areas previously exposed to 2,4,5-T, one showed a positive TCDD level of 60 ppt; 2 appeared to have TCDD at 20 ppt; and 5 may have had TCDD levels which ranged from 5-10 ppt. The values for these 5 samples were at or below the limits of detection of 10 ppt.

Forty-three beef liver samples were analyzed and showed no TCDD residues at a detection limit of 10 ppt.

F. Accidental Human Exposure

In the cases of human exposure to 2,4,5-TCP, the only adverse effects reported were caused by occupational exposure or accidents that occurred during the manufacture of chlorinated phenols or products derived from them.

In 1949, intermediary chemicals of the manufacturing process were released in a U.S. 2,4,5-T plant. This accident led to 117 cases of chloracne among exposed workers (Whitside, 1977).

In 1953 there was an accident in a Middle Rhine factory manufacturing 2,4,5-TCP from 1,2,4,5-tetrachlorobenzene. In addition to contracting chloracne (Goldman, 1972), many workers had liver cirrhosis, heart complaints, and nervous system disorders, and were depressed (Bauer et al., 1961).

In 1958, 31 employees of a Hamburg, Germany, plant in which 2,4,5-T was made from technical 2,4,5-TCP contracted chloracne and suffered the physical and psychological symptoms associated with it (Poland et al., 1971). In 1961 Bauer et al. conclusively identified TCDD as the cause of the chloracne.

An explosion occurred in a 2,4,5-T plant in Amsterdam in 1963. Six months later, nine of the 18 men, who were attempting to decontaminate the plant, developed chloracne. All of the men had worn deep sea diving suits, and all but one wore face masks with goggles while working in the plant. Of these men, three died within 2 years. The man without the face mask or goggles was severely affected. He was unable to walk and is still undergoing treatment (Whiteside, 1977).

In 1964, workers in a 2,4,5-T plant in the United States developed chloracne from exposure to TCDD (Poland et al., 1971).

There was an explosion at the Coalite Company's 2,4,5-TCP plant in Great Britain in 1968. TCDD had accidently been produced as the result of an exothermic reaction (Milnes, 1971; May, 1973). Seventy-nine cases of chloracne were reported; many of them were severe.

In 1971 there was an accidental poisoning episode in the United States that affected humans, horses, and other animals. Waste oil contaminated with TCDD had been sprayed on a riding arena to control dust. Later analyses showed that the arena contained TCDD in concentrations of 31.8 to 33.0 ug/g (Carter et al., 1975). Commoner and Scott (1976) found that the most important route of entry of dioxin into the body was the skin. (This does not preclude the effects of ingesting food contaminated with dioxin from handling.) A 6-year-old girl was the most severely affected. She had an inflammatory reaction of the kidneys and bladder bleeding that was diagnosed as acute hemorrhagic cystitis with signs of focal pyelonephritis. Nine less severely affected persons developed diarrhea, headaches, nausea, polyarthralgias, and

persistent skin lesions (U.S. EPA, 1975). The girl most affected was thoroughly reexamined in 1976. Results indicated that all of her original symptoms had completely disappeared. She had grown normally and all tests, including a detailed neurological examination, were normal (Beale et al., 1977).

In July 1976, 2-10 pounds of TCDD were accidentally released in the Seveso Region of Italy (Dewse, 1976). Most of the inhabitants were adversely affected. Reports of immediate symptoms and indications of many long-term effects are just becoming available. The first overt reaction was the appearance of numerous burn-like lesions on many of the inhabitants. These lesions generally receded. Whiteside (1977) believes that they were probably caused by direct contact with the sodium hydroxide and phenolic components in the fallout. However, 2 1/2 months after the explosion, an increasing number of children and young people in the zone most affected began to develop symptoms of chloracne on their faces and bodies, a definite mark of dioxin poisoning. By November 28 people had confirmed cases of chloracne. This number rose to 38 by December and to 130 a year after the explosion. A number of the victims exposed underwent a "complete change of character": they became extremely nervous, tired, moody, and irritable, and had a marked loss of appetite.

There were a number of Seveso women who were pregnant at the time of the accident. Whiteside (1977) reported that the total number of legal and illegal abortions performed as a result of the explosion probably totaled 90. There were 51 spontaneous (as distinct from induced) abortions. A survey conducted by an epidemiological commission has shown

that 183 babies were delivered in the 2 months following the accident. Eight cases of birth abnormalities have been noted among babies born to women in the Seveso area who were pregnant at the time of the explosion. However, local physicians have had difficulty relating those abnormalities directly to the explosion because the incidence of birth abnormalities was not significantly higher than the normal incidence of abnormal births (Whiteside, 1977).

II. Regulatory History

The regulation of many polychlorinated ring compounds has been related to the presence of TCDD as a contaminant in the commercial product. Historically, regulation has focused on 2,4,5-T.

In October 1969, Bionetics Research Laboratory, a contractor for the National Cancer Institute, released information on their large scale screening of a number of pesticides and industrial chemicals for mutagenicity, carcinogenicity, and teratogenicity. They found 2,4,5-T to be teratogenic in mice when 113 mg/kg body weight was administered during early pregnancy. Birth defects included cleft palates and cystic kidneys. On later examination researchers ascertained that the 2,4,5-T was contaminated with approximately 30 ppm TCDD. This and other scientific studies summarized in this Section are fully discussed in Sections III and IV.

On October 29, 1969, the President's Science Advisor responded to the release of the Bionetics' report by announcing that a series of coordinated actions would be taken by several government agencies to restrict the use of the herbicide 2,4,5-T.

In early 1970, animal experiments confirmed that when the purest available 2,4,5-T, which contained less than 0.05 ppm TCDD, was fed to pregnant mice in large doses, the offspring would be malformed (Courtney and Moore, 1971).

On April 15, 1970, the Secretaries of Agriculture; Health, Education and Welfare; and Interior announced the suspension of the following registrations of 2,4,5-T: all uses in lakes, ponds, or ditch banks; and liquid formulations for use around the home, recreational areas, and similar sites (USDA-PRD PR 70-1, April 20, 1970). A notice of cancellation of registration was issued on May 1, 1970, for all granular 2,4,5-T formulations for use around the home, recreational areas, and similar sites, and all 2,4,5-T uses on crops intended for human consumption (USDA-PRD PR 70-13, May 1, 1970).

On September 28, 1970, the Department of Agriculture issued a Pesticide Registration Notice stating that all products containing TCDD were in violation of FIFRA because they constituted a possible hazard to humans. The notice indicated that appropriate regulatory action would be taken if TCDD were found in any economic poison (USDA-PRD PR 70-22, September 28, 1970).

On May 5, 1971, the Report of the Advisory Committee to the EPA Administrator recommended that use of 2,4,5-T be permitted only under certain conditions in forests, ranges, and rights-of-way providing:

1) that a limit of 0.1 ppm TCDD be set for all future production of 2,4,5-T;
2) that 2,4,5-T be applied no more than once a year

at any one site; and

3) that 2,4,5-T be applied with caution so it will not contaminate other areas where it may come into human contact.

In July 1972 Dow Chemical Company obtained an injunction against EPA. The Court of Appeals for the 8th Circuit overturned this injunction in 1973. EPA withdrew cancellation and information gathering proceedings initiated against 2,4,5-T and related compounds on June 24, 1974, due to the Agency's inability to monitor food for residues of TCDD with the necessary analytical precision.

In July 1974 EPA held a Dioxin Planning Conference in Washington, D.C. Participants of the public meeting discussed data analysis, analytical methodology, toxicology, and monitoring. There was an emphasis on developing analytical methodology for detecting TCDD in parts per trillion. As a result, the Agency promulgated the Dioxin Implementation Plan (DIP) to identify a preferable analytical method to monitor human and environmental samples for TCDD residues in the low parts per trillion (ppt) range.

DIP consisted of a short-term monitoring program involving beef fat and liver samples and a broad 2- to 5-year research plan. The Environmental Defense Fund, the Department of Agriculture, and Dow Chemical Company participated in the monitoring program, which utilized improved analytical methodology capable of detecting TCDD in the parts per trillion range.

On-going TCDD studies under the DIP include: an analytical method validation study to produce statistically defensible data; monitoring for

residues in human milk in the Pacific Northwest; additional beef fat residue studies; additional technical pesticide residue studies; and an environmental monitoring program for TCDD residues in soil, water, and biota.

III. Summary of Scientific Evidence Relating to Rebuttable Presumption

A. Oncogenic Effects in Test Animals

40 CFR Section 162.11(a)(3)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s)...induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure..." Section 162.3(bb) defines the term oncogenic as "the property of a substance or a mixture of substances to produce or induce benign or malignant tumor formation in living animals."

1. 2,4,5-TCP

Because all 2,4,5-TCP contains a certain amount of TCDD, any reference to 2,4,5-TCP denotes a product that is contaminated. As a result, all the information used to assess 2,4,5-TCP in relation to Section 162.11 risk criteria is derived from studies in which the test substance was 2,4,5-TCP contaminated with TCDD. The Agency knows of no data relating to pure 2,4,5-TCP.

The National Cancer Institute tested 2,4,5-TCP for carcinogenicity (Innes et al., 1969). Two hybrid strain of mice [(C57BL/6xC3H/Anf)F_1 and (C57BL/6xAKR)F_1] were given a single subcutaneous injection of 1000 mg/kg 2,4,5-TCP/kg (97% pure, contaminant not specified) in corn oil when the mice were approximately 28 days old. No significant difference in tumor frequency was found between the 2,4,5-TCP treated groups and the control mice at necropsy.

In a short-term study on BHC (benzene hexachloride) isomers and their metabolites including 2,4,5-TCP, Goto et al. (1972) fed twenty 5-week-old male ICR-JCL mice a diet containing 600 ppm 2,4,5-TCP (contaminant in 2,4,5-TCP not specified) each day for 6 months. They observed no unusual weight increases in the hearts, kidneys, or livers of treated mice as compared to the controls. No tumors were noted in the mice fed 2,4,5-TCP although malignant and benign tumors were noted in the livers of mice fed technical BHC, alpha-BHC, beta-BHC, and gamma-BHC.

The EPA Carcinogen Assessment Group (CAG) judged these studies inadequate for assessing the oncogenic potential of 2,4,5-TCP. The Working Group concurs.

2. TCDD

a. Van Miller Study

A recent paper by Van Miller et al. (1977) reports the results of a 2-year feeding study with Sprague-Dawley rats. Groups of 10 rats were administered a diet containing TCDD in one of the following concentrations: 0, 1, 5, 50, and 500 parts per trillion (ppt, 10^{-12} g TCDD/g food), and 1, 5, 50, 500, or 1000 parts per billion (ppb, 10^{-9} g TCDD/g food).

Laparotomies were performed on all surviving rats during the 65th week. Biopsies were performed from all tumors observed. Rats were maintained on the diet for 78 weeks and were then placed on the control diet. Surviving rats were killed at 95 weeks. Complete necropsies were done at this time and tissue samples were microscopically examined. Special staining methods were used as an "aid in the diagnosis of neoplasms."

Food intake was significantly lower in rats that ingested 50, 500,

or 1000 ppb TCDD than it was in the control animals. All of the rats administered these doses died between the second and fourth weeks of treatment.

At the sublethal doses, there were toxic and tumorigenic effects. Three of the 10 deaths which occurred in the 5 ppb dose group were attributed to aplastic anemia. One animal in the 500 ppt group had severe liver infarction. The overall incidence of neoplasms in the six experimental groups was 38% (23/60), compared with no lesions or 0% (0/10) in the control group. This difference is statistically significant. Neoplastic nodules and cholangiocarcinomas of the liver were observed in 4 of 10 rats (40%) that ingested 5 ppb TCDD (two animals had both neoplastic plastic nodules of the liver and cholangiocarcinomas). One rat (10%) in the group that ingested 1 ppb had a carcinoma compared to none of the controls. Hepatic tumors were not found in rats administered the other doses (Table 1).

TABLE 1. Liver tumors in rats that ingested TCDD[1/]

Dose, ppb	Rats With Neoplastic Nodules		Rats With Cholangio-carcinomas		Rats With Nodules plus Carcinomas	
	No.	%	No.	%	No.	%
0	0/10	0	0/10	0	0/10	0
1	0/10	0	1/10	10	1/10	10
5	4/10	40[2/]	2/10	20[2/]	4/10	40[2/]

1/ Data from Van Miller (1977).
2/ Two animals had both neoplastic nodules of the liver and cholangiocarcinomas.

Benign and malignant tumors developed in rats that ingested 5, 50, or 500 ppt and 1 or 5 ppb TCDD, compared to none in the control rats. Twenty-three of the rats (46%) in these 5 groups had tumors. Nineteen of these rats (57%) that died in the 6 groups fed subacute levels of TCDD had neoplastic alterations. Three rats that ingested 5 ppb died of aplastic anemia. Carcinomas were observed in the ear duct, kidney, and liver. Three retroperitoneal histiocytomas were described as metastasizing to the lungs, kidney, liver, and skeletal musculature. Statistically significant increases in tumors at all sites were found in the rats fed 5, 50, 500, 1000, and 5000 ppt as compared with the control animals ($p = 0.05$) (Table 2).

b. Preliminary Report: Dow Chemical Company Study

The Dow Chemical Company has just completed a chronic toxicity study of TCDD with 472 Sprague-Dawley rats (Traynor, 1977). Fifty rats of each sex were maintained for 2 years on diets which contained 0.001, 0.01, and 0.1 ug TCDD/kg body weight/day. This dose is equivalent to approximately 22, 210, and 2,200 ppt in the diet. Eighty-six rats of each sex were maintained on a control diet. Table 3 lists the tumors found.

c. Conclusion

The Working Group has concluded that there is evidence to indicate that TCDD can produce oncogenic effects in rats. Since 2,4,5-TCP contains TCDD (at a maximum amount of 0.099 ppm), a rebuttable presumption against the registration of 2,4,5-TCP products has arisen because of the oncogenic effects of its contaminant, TCDD.

TABLE 2. Benign and malignant tumors in rats that ingested TCDD[1]

Dose[2]	No. Tumors			Rats with Tumors	
	Benign	Malignant	Total	No.	%
0	0	0	0	0/10	0[3]
1 ppt	0	0	0	0/10	0
5 ppt	1	5	6[6]	5/10	50[4]
50 ppt	2	1	3[7]	3/10	30
500 ppt	2	2	4[8]	4/10	40[5]
1 ppb	0	5	5[9]	4/10	40
5 ppb	8	2	10[10]	7/10	70

1/ Data from Van Miller (1977).
2/ Rats administered 50, 500, and 1000 ppb were all dead within 4 weeks.
3/ Forty male rats that were used as controls for another study were received at the same time as the rats in this study and kept under identical conditions. They did not have neoplasms when killed at 18 months.
4/ Three rats died of aplastic anemia.
5/ One rat had severe liver infarction.
6/ One rat had an ear duct carcinoma and lymphocytic leukemia.
One rat had an adenocarcinoma (kidney).
One rat had a malignant histiocytoma (retroperitoneal).
One rat had an angiosarcoma (skin).
One rat had a Leydig cell adenoma (testis).
7/ One rat had a fibrosarcoma (muscle).
One rat had a squamous cell tumor (skin).
One rat had an astrocytoma (brain).
8/ One rat had a fibroma (striated muscle).
One rat had a carcinoma (skin).
One rat had an adenocarcinoma (kidney).
One rat had a sclerosing seminoma (testis).
9/ One rat had a cholangiocarcinoma and malignant histiocytomas (retroperitoneal).
One rat had an angiosarcoma (skin).
One rat had a glioblastoma (brain).
One rat had a malignant histiocytoma (retroperitoneal).
10/ One rat had a squamous cell tumor (lung) and a neoplastic nodule (liver).
Two rats had cholangiocarcinomas and neoplastic nodules (liver).
Three rats had squamous cell tumors (lung).
One had a neoplastic nodule.

TABLE 3. Tumors in Sprague-Dawley rats that ingested TCDD

Dose, ppt	Tumors
0	0
22	0
210	Hepatocellular Nodules
	Squamous Cell Carcinoma 2/
	Alveolar Hyperplasia
2,200	Squamous Cell Carcinoma 3/
	Hepatocellular Carcinoma

1/ Data from the preliminary report of the Dow Chemical Company Study, 1977.
2/ Hardpalate squamous cell carcinomas were observed in one female rat.
3/ Squamous cell carcinomas were observed in the lung, hardpalate/nasal turbinates, or tongue.

B. Fetotoxic and Teratogenic Effects in Mammalian Species

40 CFR 162.11(a)(3)(ii)(B) provides that a rebuttable presumption shall arise if a pesticide's ingredients "...(p)roduces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety."

Embryotoxic effects are considered to denote all transient or permanent toxic effects induced in an embryo or fetus, regardless of the mechanism of action. These effects include teratogenicity, mortal-

ity, and/or retardation of growth. Embryo mortality refers to death at any stage of embryonic or fetal development. Teratogenic effects are characterized by generally irreversible abnormalities originating from an impairment in the embryonic or fetal development.

1. 2,4,5-TCP

Neubert and Dillmann (1972) tested NMRI mice for the embryotoxic and teratogenic effects of 2,4,5-TCP. Pregnant mice were given 0.9 or 9 mg 2,4,5-TCP/kg body weight by intubation on days 6-15 of gestation. There was an increase in embryomortality in mice treated at the higher dose: resorptions were observed in 78% (7/9) of the litters as compared to 32% (21/65) of the oil-treated control litters (Table 4). The number of resorptions in each litter was significantly greater at the 9 mg/kg dose level than it was in the oil-treated controls ($p = 0.05$). No significant increases in teratogenic effects were observed at either dose.

TABLE 4. Summary of fetotoxic and teratogenic effects of 2,4,5-TCP in NMRI mice[1/]

Dose, mg/kg	Litters Affected/Live Litters			
	Resorptions		Cleft Palate	
	No.	%	No.	%
0				
Oil	23/95	24	6/95	6
0.9 mg/kg	21/65	32	4/65	6
9.0 mg/kg	4/14	29	1/14	7
	7/9	78	0/9	0

1/ Data from Neubert and Dillmann (1972).

2. TCDD

A number of studies on the embryotoxicity of TCDD indicate that there are two major types of teratogenic effects generally associated with test animals receiving doses of TCDD during pregnancy: cleft palates in mice and kidney anomalies in rats and mice. TCDD is also fetotoxic in these species.

a. Mice

The first evidence that TCDD might represent a reproductive hazard to humans appeared in 1970 in a Bionetics Research Institute study which reported that 2,4,5-T was teratogenic (Courtney et al., 1970). When a dosage of 113 mg/kg 2,4,5-T was administered to AK mice on days 6 to 15 of pregnancy, 49% of the fetuses were deformed. Cleft palates, cystic kidneys, and fetal mortality were the common anomalies found. However, analysis using gas chromatography later showed that the 2,4,5-T used in the Bionetics study was contaminated with 27 $\pm$ 8 ppm TCDD. The question of whether dioxin rather than 2,4,5-T caused these adverse effects was raised.

Courtney and Moore (1971) studied the embryotoxic and teratogenic effects of TCDD in three strains of pregnant mice (Table 5). Test animals were administered 1 and 3 ug TCDD/kg body weight subcutaneously in solutions of 100% DMSO (dimethylsulfoxide) on days 6-15 of gestation. DMSO was administered as the control. TCDD produced cleft palates in all three strains of mice. In the CD-1 mice 30% of the litters (3/10) had fetuses with cleft palates at 3 ug/kg as compared to 0% of the controls (0/9). Seventy-one percent of the litters of C57B1/6 mice (5/7) had cleft palates at 3 ug/kg body weight as compared to 0% (0/23) of the controls. Twenty-

two percent (2/9 litters) of the DBA/2 mice also had cleft palates at this same dosage as compared to 0% (0/23) of the controls. The authors also found a marked increase in the incidence of kidney anomalies in all mice strains (Table 5). There was a dose-related response in the CD-1 mice. One strain of inbred mice, C57B1/6, which was especially sensitive, developed kidney anomalies in all seven (100%) of the litters as compared to 9% (2/23) in the controls. Although TCDD produced a significant increase in the ratio of maternal liver weight to body weight in the inbred mice strains (C57B1/6 and DBA/2), the CD-1 (randomly bred) mice were not significantly affected. TCDD had no effect on fetal mortality, fetal weights, or maternal weights at the doses administered.

In another study in which six dioxins were administered subcutaneously and orally to CD-1 mice, Courtney (1976) found TCDD to be the most fetotoxic and teratogenic by either route of exposure at all dose levels tested. On days 7-16 of gestation, TCDD was administered orally at 25-400 ug/kg/body weight and subcutaneously at 25-200 ug/kg/body weight. The results are given in Table 6.

Mortality per litter increased with the dose and reached 97% (oral) and 76% (subcutaneous) in the litters administered TCDD, as compared with a mortality of 6 and 14% in the oral and subcutaneous control groups, respectively. The most common anomalies observed were cleft palates and malformed kidneys. All of the fetuses in the 200 and 400 ug/kg (oral) and 200 ug/kg (subcutaneous) groups exhibited cleft palates as compared to 0% of the controls. Of the fetuses in the 200 ug/kg (oral) group, 100% had kidney malfunctions as compared to 1% of the controls. Other

TABLE 5. Summary of the teratogenic effects of TCDD in mice and rats[1/]

Strain	Dose, ug/kg	Litters Affected/Live Litters: Cleft Palate No.	Cleft Palate %	Kidney Anomalies No.	Kidney Anomalies %	Average Fetuses Affected/Live Litters: Cleft Palate No.	Cleft Palate %	Kidney Anomalies No.	Kidney Anomalies %
MICE									
CD-1	0 (DMSO)	0/9	0	3/9	33	0/9	0	1/9	11
	1	1/9	11	5/9	56	2/9	22	4.6/9	51
	3	3/10	30	10/10	100	1/10	10	6.5/10	65
DBA/2	0 (DMSO)	0/23	0	3/23	13	0/23	0	1/23	4
	3	2/29	22	8/9	89	1/9	11	1.8/9	20
C57B1/6	0 (DMSO)	0/23	0	2/23	9	0/23	0	1/23	4
	3	5/7	71	7/7	100	2.6/7	37	3/7	43
RATS									
CD	0 (DMSO)	0/9	0	0/9	0	0/9	0	0/9	0
	0.5	0/6	0	4/6	67	0/6	0	1.8/6	30

1/ Data from Courtney and Moore (1971).

TABLE 6. Fetotoxic and teratogenic effects of TCDD in CD-1 mice [1/]

Dose, ug/kg/day	Route of Administration	Average Fetal Mortality/ Litter, %	Average No. Abnormal Fetuses/Litter	Abnormal Anomalies/Total Fetuses		
				Cleft Palate, %	Kidney Anomalies, %	Club Foot, %
25	oral	6	4.6	3	3	3
50	oral	13	8.1	19	72	7
100	oral	14	8.3	66	71	13
200	oral	87	1.5	100	100	14
400	oral	97	0.4	100	50	50
25	subcutaneous	36	6.7	82	53	11
50	subcutaneous	56	5.0	79	58	17
100	subcutaneous	72	3.5	85	95	0
200	subcutaneous	76	3.1	100	38	18
5% anisole corn oil (0.1 ml)	oral	6	0.8	0	1	4
DMSO [2/]	subcutaneous	14	0.2	0	0	1

1/ Data from Courtney (1976).
2/ DMSO = dimethylsulfoxide

anomalies observed were hydrocephalus, open eye, and club foot. Edema and petechiae were also observed in fetuses administered the high doses. Responses appeared to be dose-related. Subcutaneous injection produced greater responses than did oral administration.

Moore et al. (1973) also found that TCDD caused fetotoxic and teratogenic responses in C57B1/6 mice at a dose level as low as 1 ug/kg administered on days 10 through 13 of gestation. Compared with 0% incidence (0/27) in the control litters, 94% (15/16) of the treated litters exhibited kidney anomalies and 19% (3/16) had cleft palates. At 3 ug/kg the incidence of these anomalies was 100% (14/14) and 86% (12/14), respectively.

Neubert and Dillmann (1972) tested the embryotoxic and teratogenic effects of TCDD in NMRI mice. In one test pregnant mice were given varying doses of TCDD (0.3-9 ug/kg) by intubation on days 6-15 of gestation. Results are shown in Table 7. Very high embryomortality was observed, as expressed by the percent of fruitful wombs showing evidence of resorptions. At 9 ug/kg, all viable litters (3/3) evidenced resorptions; 67% (6/9) of all litters had total resorptions. Oil control values were 32 and 0% for litters with resorptions and litters with total resorptions, respectively. Cleft palate was observed in all of the litters and 82% of the fetuses at 9 ug/kg; comparable oil control values were 6 and 0.7%, respectively. Statistically significant ($p < 0.01$) proportions of the fetuses evidenced cleft palate at 3, 4.5, and 9 ug/kg (3, 13, and 82%, respectively) when compared with the oil control.

In another test in which high doses of TCDD were given orally on a

TABLE 7. Embryotoxic and teratogenic effects of TCDD on NMRI mice[1/]

Dose,[2/] ug/kg	Litters Affected/Viable Litters			
	Resorptions		Cleft Palate	
	No.	%	No.	%
0	23/95	24	6/95	6
Oil	21/65	32	4/65	6
0.3	7/13	54	0/13	0
3.0	16/24	67	7/24	29
4.5	5/12	42	6/12	50
9.0	3/3	100	3/3	100
9.0[3/]	3/6	50	5/6	83

1/ Data from Neubert and Dillmann (1972).
2/ Dose administered on days 6-15.
3/ Dose administered on days 9-13.

single day of gestation, Neubert and Dillmann (1972) observed the same type of effects on embryomortality and the incidence of cleft palate. The authors administered 23 and 45 ug/kg TCDD on day 6. The maximum effect on mortality (resorption in 100% of the viable litters) was seen in the mice administered 45 ug/kg. The highest incidence of cleft palate (71% of viable litters) was noted at 45 ug/kg on day 11. Control values were 24% for litters with resorption and 6% for litters with cleft palates.

Smith et al. (1976) studied the teratogenicity of TCDD in CF-1 mice. Dosages of 0.001, 0.01, 0.1, 1, and 3 ug TCDD/kg body weight/day

were administered by gavage on days 6 through 15 of gestation. The percentage of resorptions per implantation was significantly higher than it was in the controls only in the 1 ug/kg group. The incidence of cleft palates in the 1 and 3 ug/kg dose groups was significantly higher than it was in the controls (Table 8). At 3 ug/kg there was also a significantly greater incidence of litters that had fetuses with bilateral dilated renal pelvises than there was in the controls. The authors concluded that the no-effect level for teratogenic effects from TCDD was 0.1 ug/kg/day.

Neubert et al. (1973) found that TCDD was highly embryotoxic and fetotoxic in mice. Extrapolating from a dose-response curve, they estimated the ED_{50} for cleft palate in fetuses was 40 ug/kg/day. The no-effect level during days 6 to 15 of gestation was estimated to be 2 ug/kg/day for NMRI mice. No pronounced fetal mortality was observed when 3 ug TCDD/kg body weight was administered on days 6-15 of pregnancy (Table 9).

b. Rats

Sparschu et al. (1971) studied the teratogenicity of TCDD in Sprague-Cawley rats. TCDD was administered orally in concentrations of 0.03, 0.125, 0.5, 2, and 8 ug/kg/day on days 6-15 of gestation. There was a high incidence of fetal mortality. At 8 ug/kg/day all fetuses (100%) were resorbed as compared to 63/309 (20%) in the controls. Fetal weights were depressed in the 0.125, 0.5, and 2 ug/kg/day groups. The occurrence of this effect was statistically significant in all groups except the females administered 0.5 ug/kg. Most of the abnormalities

TABLE 8. Fetotoxic and teratogenic effects of TCDD in CF-1 Mice[1/]

Dose, mg/kg	Incidence of Cleft Palate in Litters/Live Litters		Litters with Resorbed Fetuses/ Live Litters		Litters with Dilated Renal Pelvises/Live Litters	
	No.	%	No.	%	No.	%
0	0/34	0	25/34	74	0/34	0
0.001	2/41	5	30/41	73	0/41	0
0.01	0/19	0	17/19	89	0/19	0
0.1	1/17	6	16/17	94	0/17	0
1.0	4/19	21[2/]	18/19	95	1/19	5
3.0	10/14	71[2/]	11/14	78	4/14	28[2/]

1/ Data from Smith et al. (1976).
2/ Statistically different from the control by the Fishers exact probability test ($p < 0.05$)

TABLE 9. Occurrence of cleft palate in offspring of mice fed TCDD

Strain	Dose, ug/kg	Cleft Palates/Total Fetuses Examined, %	Affected Litters/ Total Litters No.	%
CD-1	0	< 0.3	0/29	0
	3	3	3/10	30
DBA	0	< 1	0/23	0
	3	4	2/9	22
NMRI	0	0.7	10/160	6
	3	3	7/24	29
C57Bl	0	< 1	0/23	0
	3	22	5/7	71

1/ Data from Neubert et al. (1973).

noted were intestinal hemorrhages. No adverse effects were noted in the fetuses whose mothers were fed 0.03 ug/kg/day. Table 10 shows the dose/response relationship. The authors concluded that TCDD induced a high level of maternal and fetal toxicity and that 0.03 ug/kg/day was the no-effect level for fetal and embryotoxic effects in rats.

Khera and Ruddick (1973) studied the effect of TCDD on reproduction in Wistar rats. In the first test, rats were orally administered 0.125-1 ug TCDD/kg on days 6-15 of gestation. Observations of visceral lesions showed a dose-response relationship at 0.25 ug/kg and above; slight decreases in fetal weight were also seen (Table 11). Postnatal effects of prenatal exposure to TCDD were studied by allowing offspring

TABLE 10. Intestinal hemorrhages in offspring of Sprague-Dawley rats fed TCDD[1/]

Dose, ug/kg/day	Fetuses Affected/ Fetuses Examined		Litters Affected/ Litters Examined	
	No.	%	No.	%
0 (control)	0/246	0	0/24	0
0.03	0/115	0	0/10	0
0.125	18/127	14	7/10	70
0.5	36/99	36	10/12	83
2.0	4/7	57	2/4	50
8.0	-	-	-	-

1/ Data from Sparschu et al. (1971).

of treated dams to be reared by untreated dams until weaning. Reduced survival, body weight, and reproductive ability in the progeny were observed after the mothers were treated with 0.5 and 1.0 ug/kg. No fetotoxic effects were observed at 0.125 ug/kg.

In a second experiment rats were treated orally with 1-16 ug TCDD/kg body weight/day on days 6-15 of gestation. Doses of 4 ug/kg or more produced maternal toxicity and 100% embryomortality. Fetal weight, number of live fetuses per litter, and incidence of visceral lesions were all adversely affected by treatment. The incidence of skeletal anomalies was comparable to that in the controls at all dose levels tested. The authors concluded that oral treatment of pregnant Wistar rats with 0.25 ug (or more)/kg/day on days 6-15 of gestation results in adverse effects

TABLE 11. Teratogenic effects of TCDD in Wistar rats[1/]

Dose, ug/kg	Average No. Live Fetuses/ Litter	Average Fetal Weight, g	Fetuses with Skeletal Anomalies/ Total No. Examined		Fetuses with Microscopic Visceral Lesions/ Total No. Examined	
			No.	%	No.	%
			TEST I			
Untreated Control	10.7	4.82	5/107	5	0/13	0
Treated Control[2/]	11.0	4.51	21/116	18	0/11	0
0.125	10.6	4.64	3/121	2	0/38	0
0.25	10.9	4.79	6/109	6	1/33	3
0.5	10.5	4.46	10/105	10	3/31	10
1.0	9.3	4.10	6/81	7	3/10	30
			TEST II			
Untreated Control	11.5	4.68	8/116	7	0/10	0
Treated Control[2/]	9.8	4.77	9/89	10	0/10	0
1.0	6.5	4.17	7/80	9	3/6	50
2.0	6.0	3.31	7/57	12	3/7	43
4.0	0	-	-	-		
8.0	0	-	-	-		
16.0	0	-	-	-		

1/ Data from Khera and Ruddick (1973).
2/ Anisole - corn oil.

on rat development.

Courtney and Moore (1971) studied the teratogenicity and embryotoxicity of TCDD in CD rats. TCDD was administered subcutaneously in solutions of 100% DMSO on days 6-15 of gestation. DSMO was administered as the control. Kidney anomalies were found in four of the six litters (67%) whose dams were administered 0.5 ug/kg as compared to 0% (0/9) in the controls. Results also showed that TCDD did not cause an increase in fetal mortality, fetal weight, or cleft palates in the fetuses. Table 5 summarizes the results of the study.

Dow Chemical USA (Traynor, 1977) conducted a three-generation reproductive study on Sprague-Dawley rats continuously fed the equivalent of 0.001, 0.01, or 0.1 ug TCDD/kg/day. A preliminary report cites reduced fertility and litter survival in f_0 rats as the reasons for discontinuing the 0.1 ug/kg dose level; significantly reduced fertility was also observed at 0.01 ug/kg. "Clearly evident" indications of toxicity at 0.01 ug/kg among f_2 and f_3 litters, included smaller litter size at birth, plus decreased survival and growth of neonates. Dilated renal pelvis was observed in each of the three f_1 rats at 0.1 ug/kg which survived to adulthood. Increased frequency of this anomaly was also seen among weanlings at lower doses; however, a dose-related or generational correlation could not be made. In summary, Dow concluded that "the reproductive capacity of rats ingesting TCDD was clearly affected at dose levels of 0.01 and 0.1 ug/kg per day, but not at 0.001 ug/kg per day, through three successive generations." The preliminary report did not include the numerical data necessary for Agency evaluation. Analysis will continue as these become available.

In summary, studies have established that TCDD is fetotoxic and teratogenic at doses as low as 0.25 ug/kg in the rat (Khera and Ruddick, 1973) and at 0.3 ug/kg in the mouse (Neubert and Dillmann, 1972). Table 12 lists the no-effect levels for teratogenicity in rats and mice from TCDD. No fetotoxic or teratogenic effects have been observed at doses of 0.03 ug/kg in rats (Sparschu et al., 1971) and 0.1 ug/kg in mice (Smith, 1976).

c. Chick Embryos

Bui Hoi et al. (1971) established that 0.02 ug/kg TCDD caused teratogenic effects in chick embryos. Bowes et al. (1973) and Verrett (1970) confirmed their results. They found abnormalities in the beaks, eyes, and feet of chick embryos.

TABLE 12. Summary of no-effect levels for teratogenesis from 2,3,7,8-TCDD

Reference	Species	Route of Administration	No-Effect Levels, Ug/kg/day
Courtney and Moore (1971)	Rat	SC	< 0.5
	Mouse	SC	< 1.0
Khera and Ruddick (1971)	Rat	Oral	0.125
Sparschu et al. (1971)	Rat	Oral	0.03
Neubert and Dillman (1972)	Mouse	Oral	< 0.3
Smith et al. (1976)	Mouse	Oral	0.1

SC = Subcutaneously

3. Exposure Analysis

In order to determine whether a rebuttable presumption should be issued based on reproductive and fetotoxic effects, pursuant to Section 162.11(a)(3)(ii)(B), the Working Group must determine whether or not an ample margin of safety exists between the levels of 2,4,5-TCP or its salts and/or TCDD which produce reproductive and fetotoxic effects, and the level(s) to which the population at risk (women of child-bearing age) can reasonably be anticipated to be exposed.

Social changes over the last few years, however, have given women the opportunity for employment in areas that were once considered open only to men. Since women of child-bearing age are now employed in all types of occupations, they have become part of the population at risk with potential exposure to 2,4,5-TCP, its salts and/or TCDD.

In order to determine whether an ample margin of safety exists, the Working Group must first determine how much 2,4,5-TCP (or salts) a woman could be exposed to. Both inhalation and dermal exposure routes were examined.

For each of these analyses, the Working Group assumes a woman to weigh 60 kg. The following calculations are based on an exposure analysis for 2,4,5-TCP, its salts and TCDD performed by EPA's Criteria and Evaluation Division.

For purposes of this analysis, the Working Group considered currently registered uses where the possibility of exposure to 2,4,5-TCP, its salts and/or TCDD existed.

Large quantities of 2,4,5-TCP and its sodium and potassium salts

are used in industrial and other non-agricultural pesticide formulations for controlling bacteria and fungi. The following industries are the largest users of formulated products containing 2,4,5-TCP and its sodium and potassium salts: cooling towers; paper and pulp mill systems; hide and leather processing; miscellaneous industrial and institutional uses, including disinfectant use.

To a large extent most of the above industries use the sodium salt of 2,4,5-TCP because of its higher water solubility. About 10-15% of the commercial products for these uses contain 2,4,5-TCP itself. The commercial products can contain other chemicals including pentachlorophenol, tetrachlorophenol, and lower chlorophenols, as well as other active ingredients, organic solvents, and emulsifiers. A contaminant in 2,4,5-TCP-containing pesticides is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) which is currently present up to a maximum concentration of 0.1 ppm (Crosby et al., 1973).

To estimate human exposure to 2,4,5-TCP or its salts in the above four major use patterns, available published literature was consulted. It should be noted that exposure data for 2,4,5-TCP or its salts was unavailable from the Occupational Safety and Health Administration (OSHA) or from other sources associated with occupational exposure of workers in the aforementioned industries. However, by making certain assumptions, estimates of potential human exposure to 2,4,5-TCP or its salts and TCDD can be made. Such estimates of human exposure in terms of dermal and inhalation exposure are described in four sections of this analysis, specifically addressed to the major use patterns.

For the purpose of this analysis, it is assumed that the penetration of 2,4,5-TCP or its salts and TCDD into the human skin has a value of about 10%. This is similar to the penetration value of several other chlorinated hydrocarbons which is about 7-15% (Maibach and Feldman, 1974). It is also assumed that the TCDD content in commercial 2,4,5-TCP or its salts is at a maximum of 0.099 ppm. For the purpose of this analysis a maximum figure of 0.1 ppm TCDD is used. Lung absorption of TCDD by inhalation is assumed to be 100%.

SUMMARY

This report discusses levels of human exposure to 2,4,5-TCP or its salts and TCDD that can be expected at specific use sites. The estimated values for TCDD dermal and inhalation exposure to women are summarized in Table 13. Table 14 shows the estimated exposure to 2,4,5-TCP and/or its salts. Because of the possible teratogenic effects from TCDD, this analysis is predicated on the basis that the workers are women even though many of the positions that may result in exposure are held by men. No estimates of total individuals that may be exposed are available at this time.

a. Exposure Analysis for 2,4,5-TCP or its Salts in Industrial Cooling Water Systems

There are two types of cooling tower water systems in industry, one totally enclosed and the other open to the atmosphere. A typical enclosed cooling water system usually contains water storage tanks connected to an application manifold; water circulates between a storage reservoir, chiller, and open gutters below the point of application such

TABLE 13. Human exposure levels to TCDD

Use Site	Product Number*	Micrograms/kg body wt/day Dermal Exposure	Micrograms/kg body wt/day Inhalation Exposure
Industrial			
Cooling Tower Water Systems	Product A	0.37×10^{-6}	2.3×10^{-6}
	Product B	1.4×10^{-6}	9.0×10^{-6}
Paper & Pulp Mills	Product C	0.2×10^{-6}	5.5×10^{-6}
Leather	Product D	4.9×10^{-6}	8.7×10^{-6}
Non-Industrial			
Hospital- Applicators	Product E	7×10^{-6}	0.88×10^{-6}
- Patients	Product E		0.49×10^{-6}

* Product refers to examples of commercial formulation discussed in the text of this report under specific use site.

Product	% 2,4,5-TCP or Na 2,4,5-TCP
A	7.2% (sodium salt)
B	85% (sodium salt)
C	15% (trichlorophenol)
D	17.5% (sodium salt)
E	2.32% (sodium salt)

TABLE 14. Human exposure levels to 2,4,5-TCP and/or its salts

Use Site	Product Number	Milligrams/kg body wt/day Dermal Exposure	Milligrams/kg body wt/day Inhalation Exposure
Industrial			
Cooling Tower	Product A	0.0037	0.023
Water Systems	Product B	0.014	0.0903
Paper & Pulp Mills	Product C	0.002	0.055
Leather	Product D	0.049	0.087
Non-Industrial			
Hospital- Applicators	Product E	0.07	0.009
- Patients	Product E		0.005

* Product refers to examples of commercial formulation discussed in the text of this report under specific use site.

Product	% 2,4,5-TCP or Na 2,4,5-TCP
A	7.2% (sodium salt)
B	85% (sodium salt)
C	15% (trichlorophenol)
D	17.5% (sodium salt)
E	2.32% (sodium salt)

as dies, rolling mills, etc. These systems usually contain 20,000-100,000 gallons of coolant. At the point of application considerable evaporative losses occur so make-up water is constantly pumped from the water storage tanks. The cooling water systems are generally very large. Such systems, called "cooling towers", are found in heavy industrial manufacturing sites dealing with millions of gallons of water. These large towers are designed to provide a large evaporative surface where water cascades over heat exchangers. They are usually built outside of the production buildings, but maintenance workers and cooling tower operators could be exposed to this cooling water.

In both situations, regardless of the size of the cooling water systems, periodic water discharge occurs as blowdown. Such discharges are needed to maintain a clean system.

There are a large number of commercial algicidal formulations recommended for cooling tower application which contain 2,4,5-TCP or its salts. In some commercial formulations, it is noted that 2,4,5-TCP and/or its salts are the only active ingredients. For most products 2,4,5-TCP, or its sodium and potassium salt, is used in conjunction with pentachlorophenol, sodium and potassium pentachlorophenate, and other chlorophenols. Pentachlorophenol and its salts are used whenever a wood preservative effect is needed in cooling towers. In the cooling tower systems, the pesticide is periodically added to maintain an effective algicidal concentration.

Factory workers, in the vicinity of the cooling water systems and the cooling tower, are potentially exposed to 2,4,5-TCP or its salts and

its impurity TCDD by dermal contact or inhalation. Upon investigation, it was learned that automatic metering devices are generally used to add the 2,4,5-TCP-containing pesticide.

Two specific pesticide formulation products are considered for the purposes of estimating the levels of exposure. According to label data, the percent concentration of technical Na 2,4,5-TCP in the product and the concentration level of the product recommended for effectiveness is:

	Percent Concentration of Technical Na 2,4,5-TCP	Recommended Product Use Concentration	Na 2,4,5-TCP Active Ingredient
Product A	7.2%	300 ppm	22 ppm
Product B	85%	0.85 lbs/1000 gal	87 ppm

i. Dermal Exposure

It is assumed that maintenance workers and cooling tower operators could be exposed to some dermal contact with the cooling water. It is estimated that possibly 100 ml/day of cooling water could come in contact with a person. The Na 2,4,5-TCP content in each ml of cooling water is calculated, and then, based on an assumed skin penetration rate of 10% for Na 2,4,5-TCP, the dermal exposure for a 60 kg woman to this compound is estimated as follows:

Product A

For Product A the content of Na 2,4,5-TCP in the treated cooling water is 22 ppm or 22 mg/l. Therefore, the 100 ml that might contact the skin per worker per day will contain 2.2 mg of Na 2,4,5-TCP. Since the

penetration of the pesticide into the human body is assumed to be 10%, the dermal exposure to Na 2,4,5-TCP can be estimated to be: 2.2 mg x 10% ÷ 60 kg = 0.0037 mg/kg/day. Dermal exposure to TCDD will then be 0.00037 mg ($0.0037 \text{ mg/kg/day} \times 0.1 \times 10^{-6}$) or 0.37×10^{-6} ug/kg body wt/day.

Product B

Cooling water treated with Product B contains 87 mg/l of Na 2,4,5-TCP. One hundred ml of this cooling water, the quantity estimated to contact the skin per worker per day will contain 8.7 mg Na 2,4,5-TCP. Since the penetration of the pesticide into the human body is rated at 10%, the dermal exposure to Na 2,4,5-TCP is estimated to be 8.7 x 0.1 (10%) ÷ 60 kg = 0.014 mg/kg/day. Dermal exposure to TCDD will then be $0.014 \text{ mg} \times 0.1 \times 10^{-6}$ or 1.4×10^{-6} ug/kg body wt/day.

ii. Inhalation Exposure

While working in and around cooling towers for approximately 2 hours a day, workers are subject to inhalation exposure from pesticides added to cooling water. Because of the high evaporation rate it is assumed that the air a worker will breathe in the cooling tower will have 100% relative humidity at 20°C. Under these conditions, 1 m^3 of air contains 17.3 grams of water. It is assumed that the pesticide is carried into the air in proportion to its concentration in the cooling water.

Product A

If the Na 2,4,5-TCP content is 22 ppm or 22 mg/l, and the breathing rate is 1.8 m^3 hr; then, a 60 kg worker will receive the following exposure $0.0173 \text{ l/m}^3 \times 22 \text{ mg/l} \times 1.8 \text{ m}^3\text{/hr} \times 2 \text{ hrs} \div 60 \text{ kg}$ or 0.023 mg/kg/day Na 2,4,5-TCP, which implies a dose of $0.023 \times .1 \times 10^{-6}$ or 2.3×10^{-6} ug TCDD/kg/day.

Product B

As above, the exposure to Product B is calculated as follows: $0.0173\ l/m^3 \times 87\ mg/l \times 1.8\ m^3/hr \times 2\ hrs \div 60\ kg$ or 0.0903 mg/kg/day Na 2,4,5-TCP which is equivalent to $0.0903 \times 0.1 \times 10^{-6}$ or 9.03×10^{-6} ug TCDD/kg/day.

b. Exposure Analysis for 2,4,5-TCP and its Salts in Paper and Pulp Industry

Paper and pulp mills use commercial formulations containing 2,4,5-TCP or its salts for controlling bacteria and fungi. In this analysis commercial products recommended for white water and stock systems of the paper mills, and the commercial products used in pulp, paper, and paper board manufacturing have been studied. The typical commercial product recommended for the control of bacteria and fungi in the above processes contains 15% 2,4,5-TCP by weight with the corresponding TCDD impurity. Customarily, the pesticide is added directly to the system using a metering device.

i. Dermal Exposure

Product C (15% 2,4,5-TCP) is added to pulping systems at the rate of 0.825 lb/1000 gallons under the most demanding conditions. This is equivalent to approximately 100 ppm of the formulation and therefore, 15 ppm 2,4,5-TCP.

Workers in pulp/paper mills periodically take samples to monitor the process for quality control. Assuming sampling is done hourly and each time the worker wets one hand (10 ml); then, an exposure of 80 ml/day is possible. A 60 kg worker could then be exposed to 0.08 l/day x 15 mg/l x 0.1 (absorption) ÷ 60 kg or 0.002 mg 2,4,5-TCP/kg/day. TCDD

exposure would then be $0.002 \times 0.1 \times 10^{-6}$ or 0.2×10^{-6} ug TCDD/kg/day.

(ii) Inhalation Exposure

At the exposed tank areas, open conveyors, and open-spurting locations, the mill worker will be exposed to contaminated air. It is assumed that conditions of 100% relative humidity and 20°C prevail. In that case the air would contain 17.3 grams water/m^3. If it is assumed that the pesticide is present in the same proportion as the proportion in the process water, then an inhalation can be calculated. This would represent a worst case situation as salts are generally not volatile. Using a value of 15 ppm (15 mg/l) and the worker's breathing rate of 1.8 m^3/hr, the worker would be exposed to 1.8 m^3/hr x 15 mg/l x .0173 l/m^3 = 0.47 mg TCP/hour. It is reasonable to assume that during an 8-hour shift, the worker will be exposed at least 7 hours to mill spray and contaminated air at specific locations. On this basis, the inhalation exposure (100% absorbed) to 2,4,5-TCP for the worker having a body weight of 60 kg will be 0.47 mg/hr x 7 hrs ÷ 60 or 0.055 mg/kg body weight/day. Based on a TCDD content of 0.1 ppm in 2,4,5-TCP, the inhalation of TCDD by the factory worker is 55 ug x 0.1 x 10^{-6} or 5.5 x 10^{-6} ug TCDD/kg/day.

d. Exposure Analysis for 2,4,5-TCP in the Leather Industry

According to Anderson (1976), fungicides and bactericides that contain 2,4,5-TCP or its salts can be used at any stage of operation requiring control of fungi or bacteria; however, it is most commonly used in the tanning process. Upon evaluation of all the processes dealing with the preparation of hides and tanning operations, i.e. tanning, soaking, bating, beam house washing, and fleshing and washing, it is evident

that several workers constantly handle wet leather and wash waters used in the leather treating process, which contain anti-bacterial and anti-fungal agents to cope with the heavy growth of bacteria and fungi. Data on exposure levels of pesticides in tanneries are not available; however, it is reasonable to make the following assumptions.

1. There is a percentage of workers exposed to pesticide-containing water. The difference in the exposure is based on specific tannery operations which may vary in the pesticide amount and frequency. The tanning and fleshing/washing operation appear to provide the most exposure.
2. It has been observed that a person wearing gloves and an apron could possibly get the diluted formulation on exposed skin areas during certain operations. Each time a worker is wet in that manner, approximately 50 ml of water containing small quantities of organic substances could reach the exposed skin surface. The penetration of 2,4,5-TCP through the skin is assumed to be 10%.

i. Dermal Exposure

For the purposes of estimating the dermal exposure of factory workers in the leather industry, a representative pesticide product used in tanneries is considered. This product contains 17.5% of sodium 2,4,5-trichlorophenate (Product D). The label directions of the product recommend a dilution of the commercial formulation at a rate of 1 pound per 1000 gallons of water. This is equivalent to 0.021 mg/ml of Na 2,4,5-

TCP in the process water:

1 lb/1000 gal = 0.454 gm/gal = 454 mg/gal x 17.5% Na 2,4,5-TCP ÷ 3,785 ml/gal or 0.021 mg/ml Na 2,4,5-TCP

Based on the assumption that during the fleshing and washing operation (the worst case) in the leather industry, the worker could possibly be exposed to 1400 ml of the process water containing the pesticide per day. Further, based on the assumption that the penetration of the Na 2,4,5-TCP into the human body is 10%, Na 2,4,5-TCP exposure is estimated to be 0.1 (10%) x 1400 ml x 0.021 mg/ml = 2.94 mg Na 2,4,5-TCP/day. The average body weight of a woman worker is assumed to be 60 kg, then a woman tannery worker would receive a dermal exposure of 2940 ug ÷ 60 = 49 ug Na 2,4,5-TCP/kg body weight/day. An additional factor of 0.1×10^{-6} converts this to the TCDD exposure: 4.9×10^{-6} ug TCDD/kg body wt/day.

Similarly, the dermal exposure to TCDD for the tanning operation in which approximately 200 ml instead of 1400 ml might contact a worker, results in 0.7×10^{-6} ug/kg TCDD of body wt/day. This range of values, 0.7 to 4.9×10^{-6} ug TCDD/kg/day, is calculated on the total quantity of treated water contacted per person/day by exposure to different types of operations.

ii. Inhalation Exposure

In tanneries, workers will be exposed to water vapor from tanks and processing vats. If 100% humidity and 20°C conditions prevail, then the air will contain 17.3 gm/m^3. It is assumed that the breathing rate is 1.8 m^3/hr and that the pesticide is present in the air in the same proportion as in the process water. Then, a 60 kg worker could be exposed to

$17.3\ ml/m^3 \times 0.021\ mg/ml \times 1.8\ m^3/hr \times 8\ hr \div 60\ kg = 0.087\ mg$ Na 2,4,5-TCP/kg/day. TCDD exposure would equal $0.087 \times 0.1 \times 10^{-6}$ or 0.0087×10^{-6} mg or 8.7×10^{-6} ug/kg/day.

e. Exposure Analysis for 2,4,5-TCP Used in Hospitals

(1) Introduction

Exposure is estimated in this analysis for pesticide formulations which are used as disinfectants in hospitals. These commercial products used as disinfectants/bactericides contain 2,4,5-TCP or its salts (sodium and potassium), other active ingredients, and inerts. These commercial products are concentrates for which the manufacturer prescribes a specific dilution ratio in water prior to application. To estimate quantitatively how much TCDD in Na 2,4,5-TCP may be released into the hospital environment, the usage pattern of typical commercial pesticide formulations that contain Na 2,4,5-TCP which are recommended for hospital use have been considered. For this purpose, data on a commercial pesticide formulation is summarized below.

Product	% Na 2,4,5-TCP	Recommended Dilution	Na 2,4,5-TCP g/100 gal
Product E	2.32%	1:128	68.6

100 gallons of such a diluted solution will contain 0.78 gallons of formulated product. Since Product E contains 2.32% Na 2,4,5-TCP, 100 gallons will contain 0.018 gallons Na 2,4,5-TCP. There are 3,785 gm/gal (density of 1), and therefore 68.6 grams of Na 2,4,5-TCP are present in 100 gallons.

Data on dermal or inhalation exposure of pesticides containing 2,4,5-TCP in hospital use are not available. Therefore, to provide estimates, the following assumptions are made:

1. Uniform dispersion of 2,4,5-TCP and TCDD in the confined areas of the hospital.
2. Possible contact of hospital workers with the disinfectant solution on the hands, face, and "v" of neck of hospital workers.
3. The application of the product is made on relatively low absorptive surfaces. All of the 2,4,5-TCP contained in the applied film of the disinfectant solutions probably escapes into the interior atmosphere due to volatilization. The application of the pesticide is made at regular intervals by hospital workers mopping, wiping, or swabbing the interior surface of the hospital.
4. A typical hospital wing uses 100 gallons of disinfectant solution per day.

1. Dermal Exposure

Using Product E (the one having the highest Na 2,4,5-TCP content) the Na 2,4,5-TCP concentration would be 0.686 gm/gal of solution. Making the assumption that one cup of the diluted solution may spill on her skin, the worker could then be exposed to 1 cup x 0.686 gm/gal ÷ 16 cups/gal or 0.043 gm of Na 2,4,5-TCP of which 10% (4.3 mg) could be absorbed during an 8-hour workday at the hospital. Based on a 60 kg body weight, a woman could be exposed to 4.3 mg ÷ 60 kg or 0.07 mg Na 2,4,5-TCP/kg/day. For

TCDD the exposure would be 0.07 mg x 1000 ug/mg x 0.1 x 10^{-6} or 7 x 10^{-6} mg TCDD/kg/day.

ii. Inhalation Exposure

Both hospital workers and patients breathe the air in the hospital wards and work area. It is recognized that because of the restful conditions of the patients, they have a somewhat lower breathing rate, while the hospital worker may have a higher breathing rate.

For the purposes of estimating the relative quantity of TCDD release, it is assumed that 50 patients occupy semiprivate rooms having a volumetric space of approximately 60 m^3/room (20 ft x 10 ft x 10 ft). The volumetric air space of the hospital wing with 10 employees is estimated to be approximately 1800 m^3 which includes the 25 patient rooms, (1500 m^3) corridor, and necessary support area (300 m^3). For the size of the hospital wing and recommended air ventilation of 1800-2400 ft^3/hr/person (approximately 60 m^3) (Air Quantities for Ventilation, 7th ed.), the total circulated air volume for an 8-hour period would be 60 m^3 (ventilation) x 60 (patients and employees) x 8 (hr/day) or 28,800 m^3.

Of the 100 gallons of disinfectant applied, about one cup per gallon or 6.25 gallons (100 cups) will be distributed in the hospital wing interior. This quantity contains 0.043 gm Na 2,4,5-TCP/cup x 100 cups or 4.3 gm Na 2,4,5-TCP/100 cups or 4.3 x (0.1 x 10^{-6}) gm TCDD or 0.43 gm x 10^{-6} gm TCDD/100 cups.

Since it is estimated that in a water solution, 25% of the TCDD could volatilize before drying, it is assumed that 25% x 0.43 x 10^{-6} gm

(amount of TCDC/100 cups dilutad formulation) or 0.108×10^{-6} gm TCDD is volatilized. Based on the total circulated air volume for an 8-hour period, 28,800 m^3, then: 3.7×10^{-6} ug/m^3 would be available. ($0.108 \times 10^{-6} \div 28{,}800\ m^3 = 3.7 \times 10^{-12}$ gm TCDD/m^3 or 3.7×10^{-6} ug/m^3.

If the breathing rate of the patients is 1.0 m^3/hr and that of the workers is assumed to be 1.8 m^3/hr, then the exposure could be:

a. Hospital worker (60 kg): 1.8 m^3/hr x 8 hr x 3.7×10^{-6} ug TCDD/m^3 ÷ 60 kg or 0.88×10^{-6} ug TCDD/kg/day.

b. Hospital worker (60 kg): 1.8 m^3/hr x 8 hr x 4.3 gm TCP/100 cups x 25% volatilization ÷ 28,800 m^3 ÷ 60 kg = 0.00895 mg Na 2,4,5-TCP/kg/day.

c. Hospital patient (60 kg): 1.0 m^3/hr x 8 hr x 3.7×10^{-6} ug TCDD/m^3 ÷ 60 kg or 0.49×10^{-6} ug TCDD/kg/8 hrs.

d. Hospital patient (60 kg): 1.0 m^3/hr x 8 hr x 4.3 gm TCP/100 cups x 25% volatiliznation ÷ 28,800 m^3 ÷ 60 kg = 0.00497 mg Na 2,4,5-TCP/kg/day.

f. Conclusions

The sum of the dermal and inhalation exposures to TCDD (per Table 13, page 44) were compared to the TCDD no-adverse-effect level for teratogenicity and fetotoxicity, 0.03 ug/kg body weight/day (Sparschu et al., 1971). The difference between this no-adverse effect level and the calculated exposure represents an adequate margin of safety. However, preliminary data (Traynor, 1977) indicates the no-effect level may be one order of magnitude less.

The dermal and inhalation exposures for 2,4,5-TCP or its salts (see Table 14, page 45) were also compared to the no-adverse-effect level for

fetotoxicity, 0.9 mg/kg body weight/day (Neubert and Dillmann, 1972). Since the difference between this no-adverse-effect level and the calculated exposure did not represent an adequate margin of safety, the Working Group recommends issuance of a rebuttable presumption against registration based on fetotoxicity. The Working Group realizes that this decision is based on only one test performed in 1971. The 2,4,5-TCP used in this test was specified as being of analytical grade from a company in Switzerland with no TCDD content specified. The technology for manufacturing 2,4,5-TCP with low TCDD content, as well as the capability for the identification of low levels of TCDD, probably was not as advanced in 1971/1972 as it is today.

The Working Group requests registrants and other interested persons, who have comments or relevant data regarding 2,4,5-TCP/TCDD, exposure estimates and margins of safety to submit such information to the Agency.

IV. Evidence Not Sufficient to Support a Rebuttable Presumption

A. Mutagenic Effects of TCDD in Test Animals

40 CFR 162.11 provides that a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) "(i)nduces mutagenic effects, as determined by multitest evidence." The genetic effects of TCDD have been studied by several researchers. Some of the tests suggest that this dioxin is a mutagen.

1. Studies Demonstrating the Mutagenic Effects of TCDD

Hussain et al. (1972) evaluated the mutagenic activity of TCDD (99% pure) on three different microbial test systems. In the first study TCDD

significantly increased the incidence of reverse mutations in Escherchia coli Sd-4 administered 2 ug/ml TCDD from streptomycin dependence to streptomycin independence. This was the only dose at which mutations were clearly observed. No details of the experimental protocol were given and statistical methods were apparently not employed in assessing the data.

The second test by Hussain studied reverse mutation from histidine dependence to histidine independence in Salmonella typhimurium strains TA 1532 and TA 1530. TCDD was positive in TA 1532 but negative in TA 1530. This indicates that TCDD acts as a frameshift mutagen. ICR-170 was used as a positive control in the test with TA 1532. No positive or negative controls were tested in TA 1530.

In the third test, Hussain observed slight prophage induction in E. coli K-39. However, data from this test were difficult to evaluate because the solvent used, DMSO, causes cellular effets.

A preliminary report on the chromosomal analysis of hospital patients exposed to TCDD in the accident at the Seveso, Italy, factory was presented at a Department of Health, Education, and Welfare meeting on October 12, 1976 (Pertal, 1977). An increased number of chromosomal lesions (gaps, chromatidic and chromosomal breaks and rearrangements) were observed in the somatic cells of the 2- to 28-year-old males and females tested. Cytogenetic studies of tissues from the therapeutic abortions performed on women who were exposed to TCDD during the accident indicated that there was chromosomal damage to cells in maternal peripheral blood and placental and fetal tissues. These preliminary results were based on a small number of samples and no specific data is available at this time.

3. Studies in Which Mutagenic Effects Were Not Observed

Khera and Ruddick (1973) conducted dominant lethal tests in which male Wistar rats received TCDD at dosages of 4 and 8 ug/kg/day. The studies indicated that no dominant lethal mutations arose during the 35 days posttreatment. The period examined corresponded to postmeiotic stages of spermatogenesis.

A cytogenetic screening study of the effects of TCDD on the bone marrow cells of male Osborne-Mendel rats was performed by the Food and Drug Administration (Green, 1975). Two separate experiments were performed. The first was a multiple dose test in which 10 ug/kg/day was administered by intubation daily for 5 consecutive days. In the second test, single doses of 5, 10, and 15 ug/kg TCDD were administered intraperitoneally and 20 ug/kg (the highest dose) was administered orally. There was no evidence from these studies to indicate that TCDD produced cytogenetic damage in the bone marrow of these male rats. Toxicity, which was indicated by a slight weight loss, was noted in the rats that received a single dose of 15 or 20 ug/kg (the highest dose levels). This suggested that the dose level may have been too low.

Therefore, the Working Group concludes that, although there is some evidence that TCDD is a mutagen in microbial systems, the data is not sufficient to form the basis of a rebuttable presumption. Additional information or studies on the mutagenic effects of TCDD should be submitted to the Agency for further review.

B. Other Effects of TCDD

1. Enzymatic Effects

Whether there is a relationship between the effects of TCDD and

chemical carcinogenesis has been the subject of several studies. Marquardt et al. (1974) found evidence that aryl hydrocarbon hydroxylase (AHH) is strongly involved in chemical carcinogenesis because many chemically non-reactive compounds must be metabolized by cellular enzymes before they can act as carcinogens. Bar-Hoi et al. (1971) found that even in very low doses TCDD could greatly disturb the enzymatic character of an organism as do certain typical carcinogenic substances (e.g., benzo/a/ pyrene and p-dimethylaminoazobenzene).

In a paper on AHH, Kouri et al. (1974) stated that TCDD itself is not a potent carcinogen in mice. However, the extent to which the synergistic action of TCDD and 3-methylcholanthrene (MC) produces cancer in different strains of mice is directly proportional to the increase in hydroxylase activity and associated cytochrome P-450 content. They reported that the basal enzyme activity might correlate with the enzyme activities that could be induced by either TCDD or MC. They found TCDD to be 40 to 60 times more potent as a inducer of AHH in cultured human lymphocytes than was MC. Poland and Glover (1974) showed that TCDD is approximately 30,000 times more potent than MC as an inducer of AHH in rat liver.

2. Toxic Effects on Humans

There are several adverse effects that occur in humans as a result of exposure to TCDD. The most well known is chloracne, a severe and persistent disease of the skin that is very difficult to cure (Schulz, 1957). Porphyria cutanea tarda (PCT) is another disease that is caused by exposure to TCDD and often accompanies chloracne (Bleiberg, 1964).

PCT is a defect of hepatic prophyria metabolism characterized by an over-production of porphyrins, fragility and photosensitivity of the skin, hyperpigmentation, hirsutism, and neurological and intestinal disorders (Poland and Kende, 1976).

3. Toxic Effects on Other Mammals

The extreme toxicity of TCDD to a variety of animal species has been well documented (Abelson, 1970; Bur-Hoi et al., 1971; Rose et al., 1976; Farquharson et al., 1958; Higginbotham et al., 1968; Milnes, 1971; Sparschu et al., 1971). The LD_{50} for TCDD is as low as 0.6 ug/kg TCDD body weight in the guinea pig (Table 15).

TABLE 15. LD-50 values for TCDD

Animal	LD-50,ug/kg	Reference
Guinea pig	0.6	Sparschu et al. (1971)
Rabbit	10	Schulz (1968)
Rat		
Female	22	Schwetz et al. (1973)
Male	45	
Mouse	114	Vos et al. (1974)
Dog	1000	Schwetz et al. (1973)

4. Miscellaneous Toxic Effects

Many researchers have found the liver to be the main target for the toxic action of TCDD. Liver necrosis (Norback and Allen, 1973; Courtney and Moore, 1971), stimulation of hepatic microsomal enzymes

(Piper et al., 1973; Gupta et al., 1973), and the formation of multinucleate parenchymal cells (Greig et al., 1973) are examples of the many adverse effects also attributed to TCDD exposure.

Chick edema factor (Higgenbotham et al., 1968), severe weight loss, atrophy of the thymus, and induction of hepatic and renal microsomal drug metabolizing enzymes (Fowler et al., 1973) are some additional adverse effects that have been noted.

C. Other Effects of 2,4,5-TCP and its Salts

Technical grade 2,4,5-TCP can irritate the eyes, skin, nose, and throat. Depending on the degree of exposure, ocular damage may include burns of the conjunctival membrane, severe conjunctival swelling, slight to moderate iritis, and corneal damage. Those exposed to 2,4,5-TCP have contracted chloracne and porphyria tarda. However, these effects were attributed to the presence of TCDD as a contaminant (Schulz, 1968). The toxic properties of Na-2,4,5-TCP are similar to those of 2,4,5-TCP but are somewhat more intense.

The LD_{50} for 2,4,5-TCP has been established at concentrations varying from 820 to 2960 mg/kg body weight in the rat. No nonreversible pathological changes were noted at the doses cited. The acute feeding studies with both 2,4,5-TCP and its sodium salt are summarized in Table 16.

McCollister et al. (1961) administered a single dose of 1-3.98 g/kg 2,4,5-TCP (97-98% pure) by intubation to male rats. The acute oral LD_{50} was calculated to be 2.96 g/kg/body weight, a finding which led the authors to conclude that 2,4,5-TCP is low in oral toxicity.

In a 3-month study the authors fed rats 0 (control), 0.01, 0.03,

TABLE 16. Summary of acute effects of 2,4,5-TCP and its sodium salt on rats

Chemical	Route of Administration	LD-50, mg/kg body weight	Reference
2,4,5-TCP	oral	2960	McCollister et al. (1961)
2,4,5-TCP	oral	820	Deichmann (1943)
2,4,5-TCP	oral	2460-2830	Dow Chemical Company (1976)
2,4,5-TCP	oral	620-835	Deichmann and Nergard (1948)
2,4,5-TCP	intraperitoneal injection	355	Farquharson et al. (1958)
2,4,5-TCP	subcutaneous injection	2100-2260	Deichmann and Nergard (1948)
Na 2,4,5-TCP	oral	1620-1870	Dow Chemical Company (1976)

0.1, 0.3 or 1 g 2,4,5-TCP/kg body weight in the diet for 98 days. Rats maintained at the 1 g/kg/day level had only slight pathologic changes in the liver and kidneys. The kidneys showed moderated degenerative changes in the epithelial lining of the convoluted tubules and early proliferation of the interstitial tissue. The effects of 0.3 g/kg/day were milder than those at 1 g/kg/day. No adverse effects were noted in either male or female rats maintained at 0.01, 0.03, or 0.1 g/kg. The authors concluded that 2,4,5-TCP is low in acute oral toxicity to rats when administered in their diet for a period of 98 days.

In repeated feeding tests (20 oral doses in 28 days), the authors administered doses of 2,4,5-TCP (0.001, 0.01, 0.1, and 0.5 g/kg) to rabbits by intubation. There were very slight kidney changes in rabbits administered 0.1 g/kg, and very slight kidney and liver changes in those given 0.5 g/kg. No pathologic changes were observed in rabbits in the two lowest dose groups.

2,4,5-TCP and its sodium salt caused no dermal effects on guinea pigs (Dugois and Colomb, 1957), and only a slight reddening of rabbit skin after brief exposure and mild to moderate chemical burns after longer exposures (Dow Chemical Company, 1976). Refined 2,4,5-TCP also did not cause chloracne or other adverse effects in rabbits (Kimmig and Schulz, 1957). Rather it was the TCDD formed in the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene into 2,4,5-TCP that produced chloracne.

Blackman et al. (1955) determined that the LD_{50} for 2,4,5-TCP on the green water plant (Lemna minor) was 1.65 mg/liter. The authors defined the LD_{50} as the concentration which caused chlorosis in 50% of the

plant fronds.

Amer and Ali (1974) studied the cytological effects of 2,4,5-TCP on the meiosis, pollen viability, and yield of Vicia faba plants that had been sprayed or whose seeds had been soaked in the chemical. 2,4,5-TCP had no significant effect on the pollen mother-cells and no harmful effect on yield.

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