2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

CRITERIA

Aquatic Life

For freshwater aquatic life, no criterion for 2,3,7,8-tetrachlorodibenzo-p-dioxin can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for 2,3,7,8-tetrachlorodibenzo-p-dioxin can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to TCDD through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of TCDD estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 4.55×10^{-7} µg/l, 4.55×10^{-8} µg/l, and 4.55×10^{-9} µg/l, respectively.

Introduction

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a contaminant inadvertently formed during the production of 2,4,5-trichlorophenol (2,4,5-TCP) from 1,2,4,5-tetrachlorobenzene (Milnes, 1971; Kimmig and Schulz, 1959; Firestone, et al. 1972). 2,4,5-TCP represents the major chemical feedstock for the production of numerous herbicides and TCDD has been reported to be a contaminant of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4,5-T esters, Silvex, 2,4-dichlorophenoxyacetic acid (2,4-D), and clophen (Buser and Bosshardt, 1974; Courtney, et al. 1970; Edmunds, et al. 1973; Zitko and Choi, 1971). It has also been reported that TCDD may be formed during the burning of vegetation treated with 2,4,5-T (Buu-Hoi, et al. 1971a,b).

A survey prepared in 1974 for the Council on Environmental Quality indicates the wide range and vast quantity of TCP-related herbicides (2,4-D and 2,4,5-T) used by both the private and public sectors (Anonymous, 1974). It has been estimated that approximately 2 million acres in the United States have been treated for weed control on one or more occasions with approximately 15 million pounds of TCDD contaminated 2,4,5-T, 2,4-D, or combinations of the two.

TCDD is a symmetrical, nearly planar molecule with the empirical formula $C_{12}H_4Cl_4O_2$. Each of the four chlorine atoms is indistinguishable from one another (Poland and Glover, 1973). Other chlorinated dibenzodioxins have been identified and isomers containing from one to eight chlorine

atoms in various isomeric forms are possible although TCDD is the most toxic of all chlorodibenzodioxins (Anonymous, 1973; Kimbrough, 1974).

Characteristically, TCDD is a white crystalline solid with a melting point range of 302 to 305 degrees C (Sparschu, et al. 1971; Elvidge, 1971). Decomposition begins at 500 degrees C and is virtually complete within 21 seconds at a temperature of 800 degrees C (Stehl, et al. 1973). TCDD has a molecular weight of 321.98 and is not volatile (Kearney, et al. 1973). TCDD is lipophilic, exhibiting a high degree of solubility in fats, oils, and other relatively nonpolar solvents, and is only slightly soluble in water (0.2 to 0.6 µg/l) (Kearney, et al. 1973; Baughman and Meselson, 1973; Jackson, 1972). The partition coefficient of TCDD in a water:hexane system has been reported to be 1,000 (Matsumura and Benezet, 1973).

TCDD is considered to be a highly stable compound which can be degraded only by temperatures in excess of 500 degrees C or by irradiation with UV light under certain conditions.

TCDD is one of the most toxic substances known. It exhibits a delayed biological response in many species and is highly lethal at low doses to aquatic organisms, birds, and mammals, including man. It has been shown to be acneigenic, embryolethal, teratogenic, mutagenic (in certain organisms), carcinogenic, and to affect the immune responses in mammals. TCDD has also been shown to persist for 10 years after application to soils and to bioaccumulate in aquatic organisms by factors as high as 8,000-fold. These

findings in conjunction with the wide distribution of contaminated products, lead to the conclusion that TCDD represents a potential hazard to both aquatic and terrestrial life.

REFERENCES

Anonymous. 1971. Herbicide commission reports extensive damage. Nature 229: 223.

Anonymous. 1973. Proceedings of the National Institute of Environmental Health Sciences Conference, April 1973, on dibenzodioxins and dibenzofurans. Environ. Health Perspect. 5.

Anonymous. 1974. Production, distribution, use and environmental impact potential of selected pesticides. A survey prepared for the Council on Environmental Quality by the Midwest Res. Inst. Distributed by Natl. Tech. Inform. Serv., Springfield, Va.

Baughman, R., and M. Meselson. 1973. An analytical method for detecting TCDD in samples from Vietnam. Environ. Health Perspect. 5: 27.

Buser, H.R., and H.P. Bosshardt. 1974. Determination of 2,3,7,8-tetrachlorodibenzo-1,4-dioxin at parts per billion levels in technical grade 2,4,5-trichlorobenozyacetic acid, in 2,4,5-T alkyl ester and 2,4,5-T amine salt herbicide formulations by quadruple mass fragmentography. Jour. Chromotogr. 90: 71.

Buu-Hoi, N.P., et al. 1971a. Tetrachlorodibenzodioxin - Intimations of carcinogenicity? C.R. Hebol? Seanc. Acad. Sci., Paris 272: 1447.

Buu-Hoi, N.P., et al. 1971b. Comptes rendus des seances de l'Heademic des Sciences Ser. D. 273: 708.

Courtney, K.D., et al. 1970. Teratogenic evaluation of 2,4,5-T. Science 168: 864.

Edmunds, J.W., et al. 1973. Determination of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 2,4,5-trichlorophenoxyacetic acid and 2,4,5-T alkyl ester herbicides. Pestic. Sci. 4: 101.

Elvidge, D.A. 1971. The gas chromatographic determination of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 2,4,5-trichlorophenoxyacetic acid ("2,4,5-T"), 2,4,5-T ethylhexyl ester, formulations of 2,4,5-T esters and 2,4,5-trichlorophenol. Analyst 99: 721.

Firestone, D., et al. 1972. Determination of polychlorodibenzo-p-dioxin and related compounds in chemical chlorophenols. Jour. Assoc. Off. Anal. Pharm. 55-85.

Kearney, D.C., et al. 1973. Environmental significance of chlorodioxins. Adv. Chem. Ser. 120: 105.

Kimbrough, R.D. 1974. The toxicity of polychlorinated polycyclic chemicals and related compounds. Crit. Rev. Toxicol. 2: 445.

Kimmig, J., and K.H. Schulz. 1957. Berufliche akne (sog. chlorakne) durch chlorierte aromatische zyklische. Dermatologica 115: 540.

Matsumura, F., and H.J. Benezet. 1973. Studies on the bioaccumulation and microbial degeneration of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ. Health Perspect. 5: 253.

Milnes, M.H. 1971. Formation of 2,3,7,8-tetrachlorodibenzo-p-dioxin by thermal decomposition of sodium 2,4,5-trichlorophenate. Nature 232: 395.

Poland, A., and E. Glover. 1973. Chlorinated dibenzo-p-dioxins: Potent inducers of delta-aminolevulinic acid synthetase and aryl hydrocarbon hydroxylase. II. A study of the structure-activity relationship. Mol. Pharmacol. 9: 736.

Sparschu, G.L., et al. 1971a. Study of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Food Cosmet. Toxicol. 9: 405.

Stehl, A.H., et al. 1973. The stability of pentachlorophenol and chlorinated dioxins to sunlight, heat, and combustion. Adv. Chem. Ser. 120. Am. Chem. Soc., Washington, D.C.

Zitko, V., and P.M.K. Choi. 1971. PCB and other industrial halogenated hydrocarbons in the environment. FRB Tech. Rep. 272: 25.

AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The compound 2,3,7,8-tetrachlorodibenzo-p-dioxin has been studied in model ecosystmes with a variety of plant, invertebrate, and fish species. Exposures of fish and invertebrate species to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the water, food, and by intraperitoneal injection have demonstrated a variety of adverse effects over time at very low concentrations. No standard acute or chronic toxicity tests have been conducted with this compound.

Miscellaneous

Isensee and Jones (1975) conducted a model ecosystem study with 2,3,7,8-tetrachlorodibenzo-p-dioxin and observed bioconcentration factors between 3,600 and 26,000 over a 3- to 31-day period (Table 1). The accuracy of these factors is unknown due to the nature of these tests in which the water concentrations vary with time. However, it is obvious that this compound has a high affinity for the tissues of aquatic species.

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on survival, feeding, reproduction, and other functions have been demonstrated at very low concentrations (Table 1). The mortality observed by Miller, et al. (1973) among coho salmon is unique. They exposed coho salmon to an aqueous concentration of 0.000056 ug/l for 96 hours under static conditions and then transferred the fish to control water. After 60 days there was 12 percent mortality compared to 2 percent mortality among the control fish. Coho salmon exposed to 0.056 ug/l for 24 hours or longer were all dead within 40 days. After 60 days observation there was 55 percent mortality of those fish exposed to 0.0056 ug/l.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

Final Fish Acute Value = not available

Final Invertebrate Acute Value = not available

Final Acute Value = not available

Final Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = not available

Although few data are available for this compound, sufficient information exists to indicate a potential great environmental hazard. A variety of aquatic organisms bio-concentrated 2,3,7,8-tetrachlorodibenzo-p-dioxin to 20,000 times or more. When coho salmon were exposed for 96 hours and placed in uncontaminated water for observation over a 60-day period, there was 12 percent mortality of those fish exposed to 0.000056 ug/l.

No freshwater criterion can be derived for 2,3,7,8-tetrachlorodibenzo-p-dioxin using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 1. Other freshwater data for 2,3,7,8-tetrachlorodibenzo-p-dioxin

Organism	Test Duration	Effect	Result (ug/l)	Reference
Alga, *Oedogonium cardiacum*	31 days	Bioconcentration factor = 9,000	-	Isensee & Jones, 1975
Duckweed, *Lemna minor*	31 days	Bioconcentration factor = 3,600	-	Isensee & Jones, 1975
Cladoceran, *Daphnia magna*	31 days	Bioconcentration factor = 26,000	-	Isensee & Jones, 1975
Snail, *Physa sp.*	31 days	Bioconcentration factor = 20,000	-	Isensee & Jones, 1975
Snail, *Physa sp.*	1,152 hrs	Reduced reproduction	0.200	Miller, et al. 1973
Worm, *Paranis sp.*	1,176 hrs	Reduced reproduction	0.200	Miller, et al. 1973
Mosquito (larva), *Aedes aegypti*	408 hrs	No effect	0.200	Miller, et al. 1973
Coho salmon, *Oncorhynchus kisutch*	96 hrs*	12% mortality	0.000056	Miller, et al. 1973
Rainbow trout, *Salmo gairdneri*	672 hrs	Feeding decline	0.0023** (in food)	Miller, et al. 1973
Rainbow trout, *Salmo gairdneri*	30 days	Mortality, feeding decline, weight loss, fin erosion, fungal growth, liver degeneration	2,300** (in food)	Hawkes & Norris, 1977
Channel catfish, *Ictalurus punctatus*	6 days	Bioconcentration factor = 8,000	-	Isensee & Jones, 1975
Mosquitofish, *Gambusia affinis*	3 days	Bioconcentration factor = 25,000	-	Isensee & Jones, 1975
Guppy, *Poecilia reticulata*	120 hrs	Mortality	0.1	Norris & Miller, 1974

Table 1. (continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Guppy, *Poecilia reticulata*	120 hrs	Feeding decline, skin discoloration, fin necrosis, mortality	10	Miller, et al. 1973
American bullfrog, *Rana catesbeiana*	35 days	No mortality for larva and adults	1,000** (interperitoneal) injection	Beatty, et al. 1976

* Mortality occurred during 60-day period after one 96-hour exposure.

**Result expressed in mg/kg.

SALTWATER ORGANISMS

Introduction

No data on the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on saltwater aquatic life are available.

CRITERION FORMULATION

Saltwater - Aquatic Life

No saltwater criterion can be derived for 2,3,7,8-tetrachlorodibenzo-p-dioxin using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

REFERENCES

Beatty, P.W., et al. 1976. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in larval and adult forms of Rana catesbeiana. Bull. Environ. Contam. Toxicol. 16: 578.

Hawkes, C.L., and L.A. Norris. 1977. Chronic oral toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to rainbow trout. Trans. Am. Fish. Soc. 106: 641.

Isensee, A.R., and G.E. Jones. 1975. Distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in aquatic model ecosystem. Environ. Sci. Technol. 9: 668.

Miller, R.A., et al. 1973. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in aquatic organisms. Environ. Health Perspect. 5: 177.

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

Human Health Effects Section

EXPOSURE

Water. The amount of human exposure that can be directly attributed to drinking water alone is difficult to determine. However, a National Academy of Science document states that no 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has ever been detected in drinking water with limits of detection in the parts per trillion (ppt) range (National Research Council, 1977). Harvey (1973) listed the solubility of TCDD as 0.2 parts per billion (ppb) in water and Helling, et al. (1973) indicated that this is one major factor affecting mobility. Helling (1971), Kearney, et al. (1972) and Helling, et al. (1973) found that TCDD tended to remain on or near the surface of the soil and did not move. Kearney, et al. (1972) concluded that underground water supplies would probably not be contaminated with TCDD since vertical movement did not occur in their soil samples.

Food. The occurrence of TCDD in food could result from (1) accidental spraying of plant crops; (2) contaminated forage; or (3) food chain magnification.

Although 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) can no longer be used for food crops, it could possibly reach these crops accidentally. However, studies with either the seeds or the mature plants of soybeans or oats showed that TCDD was neither absorbed by the seeds after spraying nor taken up from the soil into the mature plants (Isensee and Jones, 1971; Matsumura and Benezet, 1973). When an aqueous suspension of pure TCDD was exposed to either artificial light or sunlight, photodecomposition was negligible (Crosby, et al. 1971). However, when the herbicides, Agent Orange and Esteron, containing TCDD, were exposed to light the TCDD was rapidly lost (Crosby and Wong, 1977). This loss was thought to be due principally to photochemical dechlorination. Crosby and Wong (1977) also stated about TCDD that "...opportunities for it to occur environmentally in pure form are negligible..."

Cattle feeding on contaminated forage could result in TCDD accumulation in tissues. Kocher, et al. (1978) found 3 out of 23 adipose tissue samples positive with a detection limit of from 3 to 6 ppt. These positive samples were very close to the low detection limit. The amount of TCDD to which the cattle were exposed is unknown. Studies done under the auspices of the EPA Dioxin Implementation Plan (U.S. EPA, 1978)
revealed 8 positive beef fat samples out of 67 samples from cattle in areas previously exposed to 2,4,5-T. Forty-three beef liver samples were negative. The detection limit was 10 ppt and 5 of the 8 positive fat samples were at or below this level. How much TCDD was in the forage was unstated.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured bioconcentration factor of 8.000 was obtained for 2,3,7,8-tetrachlorodibenzo-p-dioxin using channel catfish containing about 3.2 percent lipids (Isensee and Jones, 1975). Since this test only lasted 6 days, this BCF is probably lower than the steady-state value. An adjustment factor of 2.3/3.2 = 0.72 can be used to adjust the measured BCF from the 3.2

percent lipids of channel catfish to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for 2,3,7,8-tetrachlorodibenzo-p-dioxin and the edible portion of all aquatic organisms consumed by Americans is calculated to be 8,000 x 0.72 = 5,800.

Inhalation. No data pertaining to inhalation exposure were found for TCDD. However, calculations made by the 2,4,5-T working group of EPA (U.S. EPA, 1978) indicate that a person exposed to an aerial spray of 4.0 lbs. of 2,4,5-T (containing 0.1 mg/kg TCDD) per 10 gallons of water/acre for 8 hours would receive 2×10^{-6} μg/kg of TCDD.

Dermal. The highest dermal exposure to TCDD was 0.0007 μg/kg of body weight and was calculated for a 60 kg female applying 2,4,5-T (containing 0.1 mg/kg TCDD) using a backpack sprayer (U.S. EPA, 1978). The calculations are based on a female of child bearing age in order to determine if such a person would be overexposed.

PHARMACOKINETICS

Absorption. Sprague-Dawley rats were given a single oral dose of 1.0 ug ^{14}C-TCDD/kg of body weight and monitored (Rose, et al. 1976). Absorption from the intestinal tract was estimated at about 83 percent. The response to a repeated oral dosing was also monitored and absorption was observed to be 86 percent or approximately the same as that observed for the single oral dose.

Distribution. Piper, et al. (1973) used a single oral dose of ^{14}C labeled TCDD to study distribution and excretion of TCDD in male Sprague-Dawley rats. Most of the radioactivity (53 percent) was excreted via the feces but the urine and expired air accounted for 13 percent and 2 percent respectively. Analysis of the tissues showed liver and adipose tissue to contain the highest percent of the dose per gram of tissue, 3.18 percent and 2.60 percent, respectively after 3 days.

Rose, et al. (1976) also examined the distribution of TCDD throughout the rats' body. Twenty-two days after a single oral dose, liver and adipose tissue had retained most of the ^{14}C activity, 1.26 percent and 1.25 percent per gram of tissue respectively. With repeated oral doses, the activity was again localized mainly in the liver and adipose tissue but the liver had five times as much radioactivity as did the fat. With the single oral dose, no radioactivity was detected in either the urine or expired air so most if not all of the elimination of TCDD and/or its metabolites was through the feces. With repeated oral doses, the ^{14}C activity was also excreted primarily through the feces, but significant amounts were found in the urine especially of the female rats. Male rats given 1.0 μg/kg/ day of TCDD for seven weeks excreted an average of 3.1 percent of the cumulative dose in the urine while the female rats excreted an average of 12.5 percent in the urine (Rose, et al. 1976). These results are somewhat different than Piper, et al. (1973).

Studies performed by Van Miller, et al. (1976) on rhesus monkeys and rats using tritiated TCDD showed that while rats had over 40 percent of the TCDD in the liver, the monkeys had only about 10 percent in the same organ.

Metabolism. There does not seem to be complete agreement as to whether or not TCDD is actually metabolized. Piper, et al. (1973) using oral doses concluded that, since small amounts of radioactivity were found in the urine and expired air of male rats, during the first 10 days, metabolic alteration or breakdown occurs. The study by Rose, et al. (1976) using oral doses stated that while the ^{14}C activity found in the rats' liver was unchanged TCDD, preliminary work indicated that a significant amount of radioactivity in the

rats' feces came from materials other than TCDD. Van Miller, et al. (1976) using intraperitoneal injections claimed that the slow elimination of TCDD from both rats and monkeys suggested that it was not readily metabolized. Whether the alterations in chemical form were due to microbial activity in the intestinal tract when TCDD was administered orally is unknown.

Excretion. The data reported by Piper, et al. (1973), Rose, et al. (1976) on rats and Van Miller, et al. (1976) on rats and monkeys indicated that the feces removed more of the radioactivity of labeled TCDD than did urination.

The half-life of radioactive TCDD in rats following a single oral dose was 31 ± 6 days while that following repeated oral doses was 23.7 days (Rose, et al. 1976).

EFFECTS

Acute, Subacute, and Chronic Toxicity. The 50% lethal dose (LD_{50}) for several species is shown (Table 1). The oral LD_{50} values range from 0.6 µg/kg of body weight for guinea pigs to 115 µg/kg of body weight for rabbits (Schulz, 1968; Schwetz, et al. 1973; Vos, et al. and McConnell, et al. 1978). The dermal LD_{50} for rabbits was 275 µg/kg of body weight (Schwetz, et al. 1973). Death was sometimes delayed as long as 40 days. Of the laboratory animals studied, the guinea pig was the most susceptible to the toxic effects of TCDD (Schwetz, et al. 1973; Gupta, et al. 1973).

Gupta, et al. (1973) reported that atrophy of the thymus gland was a sensitive indicator of exposure to TCDD in rats, guinea pigs and mice. The only other organ reported to have consistent microscopic changes was the liver. Rats receiving a lethal dose of TCDD had the most severe hepatic effects.

Harris, et al. (1973) also reported thymic atrophy as a common acute symptom and found that female rats actually lost weight while the male rats at the same doses only showed a 30-40 percent reduction in weight gain. Harris, et al. (1973) and Gupta, et al. (1973) showed jaundice as a common symptom.

Greig, et al. (1973) showed weight loss and mortality occurring in guinea pigs at much lower doses than those that affected the rats.

Cunningham and Williams (1972) studied the effect of single oral doses ranging from 0 to 10 μg/kg of body weight of TCDD on body weight gain and synthesis of lipids and protein. Weight gain was frequently diminished. The authors concluded that TCDD somehow restricts the transport of lipids out of the liver.

Vos, et al. (1974) found depletion of both the thymus and spleen in mice that died after being given a single oral dose of 100, 150 or 200 μg/kg of body weight of TCDD. Adema and terminal hemorrhages were frequently seen.

Schwetz, et al. (1973) reported that dogs are less sensitive to TCDD than rabbits. Symptomatology in dogs included anorexia, weight loss, dehydration, depression, emaciation, intestinal hemorrhage and alopecia.

Somewhat similar findings were made by McConnel, et al. (1978) when rhesus monkeys were given single doses of 0, 70, or 350 μg/kg of body weight of TCDD by oral gavage. Weight loss, blepharitis, facial alopecia with acne-form eruptions, and anemia were present. Death occurred after the animals appeared to waste away.

Groups of male and female rats were given a dose of 0, 0.1, or 1.0 μg/kg of body weight per week by twice weekly intubation for a 28-week period and then held for 12 additional weeks by King and Roselr (1974). A certain number of these rats were killed at 2, 4, 8, 16, 28, 32 and 40 weeks. The rats did not die from the subacute exposure but did manifest toxic effects in the liver such as centrilobular fatty change and increased hepatocellular turnover. These effects were more severe in the male rats.

Vos, et al. (1974) gave oral doses of 0, 0.2, 1.0, 5.0 or 25.0 μg/kg of body weight TCDD to male mice once a week for from 2 to 6 weeks. Growth retardation occurred with the 25.0 μg/kg dose and some mice died. The three highest doses caused increased liver weight and decreased thymus weight.

Chronic studies with rats (Gupta, et al. 1973; Kociba, et al. 1976) and with guinea pigs (Gupta, et al. 1973) also showed thymic atrophy in both species but less liver damage in the guinea pigs.

Allen, et al. (1977) gave young female rhesus monkeys a diet containing 500 parts per trillion (ppt) for up to nine months. Early symptomatology included loss of facial hair and eyelashes, edema, accentuated hair follicles and dry scaly skin. Eventually, 5 of the 8 monkeys died from severe pancytopenia.

Human exposure would generally be classified as chronic since the duration of exposure is unknown in most cases. TCDD has been produced during the synthesis of 2,4,5-trichlorophenol (TCP) or 2,4,5-T (Int. Agency. Res. Cancer, 1977).

The International Agency for Research on Cancer (1977) states in relation to occupational exposure that: "Chloracne was observed in 1952 in workers involved in the manufacture of TCP in two factories in the Federal Republic of Germany where some 60 cases were observed (W. Hergt, cited by Bauer, et al. 1961)."

Two years later, 31 cases of chloracne occurred within a few months at a factory manufacturing 2,4,5-T near Hamburg after a change in the industrial process. On this occasion the investigators were able to show that chloracne was not caused by purified TCP, and it was attributed to TCDD which occurred as a contaminant of technical TCP. Many of the exposed workers showed clinical manifestations of systemic toxicity, mainly muscular weakness, loss of appetite and weight, sleep disturbances, orthostatic hypotension, abdominal pain and liver impairment; most of them had psychopathological changes that were interpreted as a specific syndrome (Bauer, et al. 1961; Kimmig and Schulz, 1957; Schulz, 1957).

A similar outbreak of chloracne affected 60 workers at the 2,4,5-T factory of the Dow Chemical Company in Midland, Mich. in 1964 (Firestone, 1977).

Chloracne, as well as hyperlipaemia and hypercholesterolaemia, were reported in 17 workers at a factory producing TCP in France (Dugois and Colomb, 1956, 1957; Dugois, et al. 1958).

Of 29 subjects with features of chloracne working in a 2,4-D and 2,4,5-T-producing factory of the Diamond Alkali Co., Newark, N.J. 11 had increased excretion of uroporphyrins. In 3 cases a diagnosis of porphyria cutanea tarda was unquestionable; 2 of these had raised serum glutamic-oxaloacetic transaminase levels. Many of the workers, whether or not they had uroporphyrinuria, had hirsutism, hyperpigmentation, increased skin fragility and vesicobullous eruptions on exposed areas of skin (Bleiberg, et al. 1964; Firestone, 1977).

Poland, et al. (1971) re-examined all of the employees of the same factory in 1969, after the level of TCDD in the TCP had been reduced from 10-25 mg/kg to less than 1 mg/kg, and found chloracne in 13/73 workers. A number of subjects had hyperpigmentation or facial hypertrichosis, but no definite diagnosis of porphyria could be made, and only one worker had mild uroporphyrinuria. The authors suggested that chloracne and phorphyria cutanea tarda are essentially independent syndromes. About 30 percent of the workers suffered from gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pains or blood in the stools); about 10 percent of the workers had other symptoms, such as lower extremity weakness, headaches

and/or decreased auditory acuity. The severity of chloracne was associated with the degree of hypomania as measured on the Minnesota Multiphasic Personality Inventory hypomanic scale. Serum cholesterol was elevated in 10 percent of cases and serum lactic dehydrogenase in 29 percent. Seven persons (10 percent) had a white blood cell count of less than $5000/mm^3$.

In a report of occupational exposure at a factory in the USSR where production of 2,4,5-T was begun in 1964, 128 workers showed skin lesions, and among 83 examined, 69 had acne. Many, especially those with severe skin lesions, also had liver impairment; 18 workers had a neurasthenic syndrome (Telegina and Bikbulatova, 1970).

Similar findings were described by Jirasek, et al. (1973, 1974), who reported 76 cases of chloracne following exposure to TCDD between 1965-1968 in a factory in Czechoslovakia producing 2,4,5-T and penthachlorophenol. Fifty-five patients were submitted to medical follow-ups for over 5 years; some had symptoms of porphyria cutanea tarda, uroporphyrinuria, abnormal liver tests (bilirubin, serum glutamic-oxaloacetic transaminase serum,glutamic-pyruvic transaminase and bromosulphthalein) and liver enlargement. The majority of patients suffered from severe neurasthenia and depressive syndrome. In 17 subjects, signs of peripheral neuropathy, especially in the lower extremities, were confirmed by electromyographic examinations. More than half of the patients showed raised blood levels of cholesterol and total lipids.

Three scientists were poisoned in the course of experimental preparation of TCDD by heating potassium trichlorophenate (Oliver, 1975). Two of them developed typical chloracne 6 and 8 weeks after exposure, respectively.

Delayed symptoms, most likely due to TCDD, developed about 2 years after initial exposure in two of the scientists; these symptoms included personality changes, mainly loss of energy and drive, impairments of vision, taste and muscular coordination, sleep distrubances, gastrointestinal symptoms and hirsutism. Hypercholesterolaemia (in excess of 300 mg/100 ml) occurred in all 3 patients."

In relation to exposure due to accidents the International Agency for Research on Cancer (1977) further states: "The first reported cases of industrial poisoning due to the formation of TCDD in uncontrolled exothermic reactions occurring during the manufacture of TCP were seen in 1949 at a 2,4,5-T-producing factory of the Monsanto Chemical Company in Nitro, W.Va.; 228 people were affected. Symptoms included chloracne, melanosis, muscular aches and pain, fatigue, nervousness and intolerance to cold (Firestone, 1977)."

In November 1953, an accident occurred at the Badische Anilin and Soda Fabrik (BASF) factory in Ludwigshafen, Federal Republic of Germany, during the manufacture of TCP (Goldmann, 1972, 1973; Hofmann, 1957); 53 workers were affected by chloracne, 42 in a severe form; 21 of the 42 suffered consequent damage to internal organs or disturbances of the nervous system. The most relevant features were polyneuritis, sensorial impairments and liver damage. The son of one of the workers developed chloracne following contact with his father's clothes. An additional case of poisoning occurred 5 years later in a worker who was involved in repair work at the contaminated site; this worker subsequently died with necrotic pancreatitis.

In a follow-up study of these workers, Thiess and Goldmann (1977) reported that of the 53 workers exposed to TCDD in the 1953 accident, 22 were still working at the factory, 16 had retired, and 15 had died (6 while still employed at the factory and 9 in retirement). Of the 22 workers still employed, 2 still had acne of the face and scrotum, 1 had paralysis of the left leg, and 1 had permanent loss of hearing; the remaining workers were well, except for scars left by the chloracne. Of the 15 deaths, 7 were from cardiovascular disease, 2 of which were myocardial infarctus and 1, mitral stenosis, 4 from cancer, 2 from suicide, 1 from necrotic pancreatitis and 1 from oesophageal hemorrhage. The 16 men who had retired and were still alive were well. No abortions or miscarriages were reported in the wives of exposed workers still employed at the factory.

A similar accident occurred at the 2,4,5-T-producing factory of the Philips Duphar Company in The Netherlands in 1963 (Dalderup, 1974; Hay, 1976). Of 50 people affected, at least 10 still had skin complaints in 1976; 4 workers died within 2 years of the accident.

Five cases of chloracne were reported following an industrial accident in an Italian TCP factory (Hofmann and Meneghini, 1962).

Dugois, et al. (1968) observed 21 cases of chloracne after an accident in 1966 in a French factory producing TCP in the Grenoble region. Pain in the right hypochondrium was recorded frequently in affected workers.

A further accident occurred at the TCP-producing factory of Coalite and Chemical Products at Bolsover, Derbyshire, UK, in April 1968 (Jensen and Walker, 1972; May, 1973). Of the 14 men who were in the building during or immediately after the explosion, 10 showed some abnormality in liver function tests (increase of zinc and/or thymol turbidity and/or serum glutamic-pyruvic transaminase); however, all tests were within normal limits 10 days later, and production was started again. Within the next 7 months, 79 workers developed chloracne, with younger men being affected first; most of these workers recovered within 4-6 months. Three years later, chloracne was observed in 2 outside employees who came into contact with a tank that had been subject to the most rigorous cleaning after the accident. Although they were exposed for only one or two days, their chloracne was very persistent. In addition, the son of one and the wife of the other developed chloracne some months later.

In July 1976, an accident at the TCP-producing ICMESA factory in Meda, Italy (Bert, et al. 1976; Hay, 1976) resulted in the contamination of a large, densely populated area including the towns of Seveso, Meda, Cesano Maderno and Desio. Five days after the accident, animals began to die. Over 700 people have been evacuated from the more heavily contamined area (evacuation began two-and-a-half weeks after the accident); some 4000-5000 people still live in areas that have been found to be less heavily contaminated. The total population of the four towns involved is about 100,000 people. Hundreds of people complained of acute skin lesions and symptoms of systemic poisoning, and, by the end of October 1976, 37 cases of chloracne had been reported among the evacuated persons, mostly in children and young people. Raised serum transaminase and γ-glutamyl transferase levels were found in about 20 percent of the people living in or near the affected areas.

Goldman, P.J. 1973. Schwerste akute chlorakne, eine massenintoxikation durch 2,3,6,7-tetrachlorodibenzodioxin. Der Hautarzt 24:149.

Green, S., and F.S. Moreland, 1975. Cytogenetic evaluation of several dioxins in the rat. Toxicol. Appl. Pharmacol. 33:161.

Green, S., et al. 1977. Cytogenetic effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on rat bone marrow cells. FDA By-Lines 7: 292. Food Drug Admin., Washington, D.C.

Greig, J.B. 1972. Effect of 2,3,7,8-tratrachlorodibenzo-1,4-dioxin on drug metabolism in the rat.Biochem. Pharmacol. 21:3198.

Greig, J.B., and F. DeMatteis. 1973. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on drug metabolism and hepatic microsomes of rats and mice. Environ. Health Perspect. 5: 211.

Greig, J.B., et al. 1973. Toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Food Cosmet. Toxicol. 11:585.

Gupta, B.N., et al. 1973. Pathological effects of TCDD in laboratory animals. Environ. Health Perspect. 5: 125.

Harris, M.W., et al. 1973. General biological effects of TCDD in laboratory animals. Environ. Health Perspect. 5: 101.

Harvey, C.G. 1973. Dioxin, a contaminant in 2,4,5-T. Presented at Wisconsin Pest Control Conference with Industry: January 17, 1973 (unpublished).

Hay,A. 1976. Toxic Cloud over Seveso. Nature (London) 262:636.

Helling, C.S. 1971. Pesticide mobility in soils. II. Applications of soil thin-layer chromatography. Soil. Sci. Am. Proc. 35: 737.

Helling, C.S., et al. 1973. Chlorodioxins in pesticides, soils and plants. Jour. Environ. Qual. 2: 171.

Hofmann, H.T. 1957. Neuere Erfahrunger mit hoch-toxischen chlorkohlenwasserstoffen. Naunyn-Schmideberg's Arch. exp. Path. Pharmako. 232:228.

Hofmann, M.F., and C.L. Meneghini, 1962. A proposito delle follicolosi da idrocarburi clorosostituiti (acne clorica). G. Ital. Derm. 103:427.

Hook, G.E.R., et al. 1975a. Induction and suppression of hepatic and extrahepatic microsomal foreign-compound-metabolizing enzyme systems by 2,3,7,8-TCDD. Chem. Biol. Interact. 10:199.

Hook, G.E.R., et al. 1975b. 2,3,7,8-tetrachlorodibenzo-p-dioxin induced changes in the hydroxylation of biphenyl by rat liver microsomes. Biochem. Pharmacol. 24:335.

Hussain, S., et al. 1972. Mutagenic effects of TCDD on bacterial systems. Ambico. 1:32.

International Agency for Research on Cancer, Chlorinated, 1977. Dibenzodioxins, IARC Monographs on The Evaulation of Carcinogenic Chemicals to Man, Vol. 15, Lyon, France.

Isensee, A.R., and G.E. Jones. 1971. Abosrption and translocation of root and foliage applied 2,4-dichlorophenol, 2,7-dichlorodibenzo-p-dioxin and TCDD. Jour. Agri. Food Chem. 19: 1210.

Isensee, A.R., and G.E. Jones. 1975. Distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in aquatic model ecosystems. Environ. Sci. Technol. 9: 668.

Jensen, N.E., and A.E. Walker. 1972. Chloracne: three cases. Proc. Soc. Med. 65: 687.

Jérasek, L., et al. 1973. Acne chlorina and porphyria cutanea tarda during the manufacture of herbicides. Cs. Dermatoe. 43:306.

Jírasek, L., et al. 1974. Acne chlorina, porphynia cutanea tarda and other manifestations of general intoxication during the manufacture of herbicides. Cs. Dermatol. 49:145.

Kearney, Philip C., et al. 1972. Persistence and metabolism of chlorodioxins in soils. Environmental Science & Technology 5:1017.

Khera, K.S., and J.A. Ruddick. 1973. Polychlorodibenzo-p-dioxins: Perinatal effects and the dominant lethal test in Wistar rats. E.D. Blair, ed., Chlorodioxins - origins and fate. Pages 70-84 In Adv. Chem. Ser., No. 120. Am. Chem. Soc., Washington, D.C.

Kimbrough, R.D., et al. 1977. Epidemiology and pathology of a tetrachlorodibenzo-p-dioxin poisoning episode. Arch. Environ. Health 32: 77.

Kimmig, J., and K.H. Schulz. 1957. Berufliche Ake (sog. chlorakne) durch chlorierte aromatische zyklische ather. Dermatologia 115:540.

King, M.E., and A.R. Roesler. 1974. Subacute intubation study on rats with the compound TCDD. PB-257. Natl. Tech. Info. Ser. Springfield, Va.

Kirsch, et al. 1975. Structural and functional studies of ligandin, a major renal organic anion-binding protein. Jour. Chin. Invet. 55: 1009.

Kocher, et al. 1978. A search for the presence of 2,3,7,8-tetrachlorodibenzo-p-dioxin in beef fat. Bull. Env. Cont. Toxicol. 19:229.

Kociba, et al. In press. Toxic. & App. Phar.

Kociba, R.J., et al. 1976. 2,3,7,8-tetrachlorodibenzo-p-dioxin results of a 13 week oral toxicity study in rats. Toxicol. Appl. Pharmacol. 35 (3). 1976.

Kondorosi, A., et al. 1973. Inactivation of QB RNA by electrophiles. Mutat. Res. 17: 149.

Kouri, R.E. 1976. Relationship between levels of aryl hydrocarbon hydroxylase activity and susceptibility to 3-methycholanthrene and benzo(a)pyrene induced cancers in inbred strains of mice. Page 139 In R.J. Freudenthal and P.W. Jones, eds. Polynuclear aromatic hydrocarbons: Chemistry, metabolism and carcinogenesis, Vol. 1, Raven Press, New York.

Kouri, R.E., and D.W. Nebert. 1977. Genetic regulation of susceptibility to polycyclic hydrocarbon-induced tumors in the mouse. In Proc. Symposium on origins of human cancer, Cold Springs Harbour, N.Y. 1976 (In Press).

Kouri, et al. 1974. Aryl hydrocarbon hydroxylase in human lymphocyte cultures by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Life Sci. 15:1585.

Lucier, G.W., et al. 1973. TCDD induced changes in rat liver microsomal enzymes. Environ. Health Perspect. 5: 199.

Lucier, G.W., et al. 1975a. Nature of the enhancement of hepatic uridine diphosphlate glucuronyltransferase activity by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Biochem. Pharmacol. 24: 325.

Lucier, G.W., et al. 1975b. Postnatal stimulation of hepatic microsomal enzymes following administration of TCDD in pregnant rats. Chem. Biol. Interact. 11:15.

Matsumura, F., and H.J. Benezet. 1973. Studies on the bioaccumulation and microbial degradation of TCDD. Environ. Health Perspect. 5: 253.

May, G. 1973. Chloracne from the accidental production of tetrachlorodibenzodioxin. Br. Jour. Ind. Med. 30: 276.

McConnell, E.E., et al. 1978. Toxicity of TCDD in rehesus monkeys (Macaca mulatta) following a single oral dose. Toxic. App. Pharm. 43:175.

Murray, F.J., et al. 1977. Three generations reproduction study of rats ingesting TCDD. Tox. Appl. Pharm. 41:200.

National Research Council, Safe Drinking Water Committee. 1977. Drinking water and health: Part II. Natl. Acad. Sci., Washington, D.C.

Nebert, D.W., et al. 1975. Genetic expression of aryl hydrocarbon hydroxylase activity in the mouse. Jour. Cell. Physiol. 85: 393.

Niwa, et al. 1975a. Genetic expression of aryl hydrocarbon hydroxylase activity in the mouse. Arch. Biochem. Biophys. 166:559.

Niwa, A. et al. 1975b. Induction of aryl hydroxlase activity in various cell cultures by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Mol. Pharma. 11:399.

Oliver, R.M. 1975. Toxic effects of TCDD in laboratory workers. Br. Jour. Ind. Med. 32: 49.

Piper, Walter N., et al. 1973. Excretion and tissue distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Environ. Health Pers. 5:241.

Poland, A., and E. Glover. 1973a. Chlorinated dibenzo-p-dioxins: Potent inducers of S-Amino levulinic acid synthetase and aryl hydrocarbon hydroxylase. II. A Study of the structure activity relationship. Molecular. Pharm. 9:736.

Poland, A., and E. Glover, 1973b. 2,3,7,8-Tetrachlorodibenzo-p-dioxin: A potent inducer of S-Aminolevulinic acid synthetase. Science 179:476.

Poland, A., and E. Glover. 1974. Comparison of 2,3,7,8-tetrachlorodibenzo-p-dioxin a potent inducer of aryl hydrocarbon hydroxylase with 3-methylcholanthrene. Mol. Pharmacol. 10: 349.

Poland, A.P., et al. 1971. A health survey of workers in a 2,4-D and 2,4,5-T plant. Arch. Environ. Health 22:316.

Poland, A.P., et al. 1974. Genetic expression of aryl hydrocarbon hydroxylase activity induction of mono-oxygenase activities and cytochrome P-1-450 formation by 2,3,7,8-TCDD in mice genetically. Jour. Biol. Chem. 249: 5599.

Poland, A.P., et al. 1976. Stereospecific high affinity binding of 2,3,7,8-TCDD by hepatic cytosol evidence that the binding species is receptor for induction of aryl hydrocarbon hydroxylase. Jour. Biol. Chem. 251: 4936.

Rose, J.Q., et al. 1976. The fate of 2,3,7,8-TCDD following single and repeated oral doses to the rat. Tox. Appl. Pharmacol. 36:209.

Schulz, K. H. 1957. Klinische und experimentelle untersuchungen zur atiologie der chloracne. Arch. Klin. exp. Dermatol. 206:589.

Schulz, K.H. 1968. Clinical picture and etiology of chloracne. 10/µg/kg oral LD_{50} rabbits. Arbeits-Medizen Sogialmedizin Arbeitshugiene 3:25.

Schwetz, B.A., et al. 1973. Toxicity of chlorinated dibenzo-p-dioxins. Environ. Health Perspect. 9: 81.

Seiler, J.P. 1973. A survey on the mutagenicity of various pesticides. Experientia 29:622.

Sidwell, V.D., et al. 1974. Composition of the edible portion of raw (fresh or frozen) crustacenas, finfish, and mollusks. I. Protein, fat, moisture, ash, carbohydrate, energy value, and cholesterol. Mar. Fish. Rev. 36: 21.

Smith, F.A., et al. 1976. Teratogenicity of TCDD in DF-1 Mice. Toxic. App. Pharm. 38:519.

Sparschu, G.L., et al. 1971. Study of the teratogenicity of TCDD in the rat. Food Cosmet. Tech. 9: 405.

Telegina, K.A., and L. I. Bikbulatova, 1970. Affection of the follicular apparatus of the skin in workers occupied in production of butyl ether of 2,4,5-trichlorophenoryacetic acid. Vestn. Dermatol. Veneral. 44:35.

Tenchini, M.L., et al. 1977. Approaches to examination of genetic damage after a major hazard in the chemical industry: Preliminary cytohenic findings on TCDD-exposed subjects after the Seveso accident. Presented at the Expert Conference on Genetic Damage Caused by Environmental Factors, Oslo, Norway, May 11-13, 1977.

Thiess, A.M., and P. Goldmann, 1977. Uber das trichlorphenol-dioxin-unfallgeschehen in der BASFAG vom 13. November 1953. In Vortrag, auf dem IV. Medichem-Kongress, Haifa, 1976 (in press).

Toth, K., et al. 1977. Carcinogenic bioassay of the herbicide 2,4,5 TCPE with eifferent TCDD content in Swiss mice. In Internation Conference on Ecological Perspectives on Carcinogens and Cancer Control, Cremona, 1976, Basel, Karger, A.G.

Van Miller, J.P., and J.R. Allen. 1977. Chronic toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Fed. Proc. 35: 396.

Van Miller, J.P., et al. 1976. Tissue distribution and excretion of tritiated tetrachlorodibenzo-p-dioxin in nonhuman primates and rats. Food Cosmet. Toxicol. 14: 31.

Van Miller, J.P., et al. 1977. Increased incidence of neoplasms in rats exposed to low levels of TCDD. Chemosphere 6:625.

Vos, J.G., et al. 1974. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in C-57BL-6 mice. Tox. Appl. Pharm. 29:229.

Woods, J.S. 1973. Studies of the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on mammalian hepatic S-Aminoleviclinic acid synthetase. Environ. Health Perspect. 5: 221.