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Is 2,3,7,8-TCDD (Dioxin) a Carcinogen for Humans?

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2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) has suddenly become the focal point of controversy over the relationship of chemical waste to human health. Specific concern exists regarding its potential association with human malignancy. Subcellular, cellular, and whole-animal experiments suggest that TCDD exerts much of its activity by inducing enzymes that protect the intact organism from the assault of environmental contamination. TCDD is a potent inducer of aryl hydrocarbon hydroxylase, although wide variations between species do exist. Conventional tests for mutagenicity have produced conflicting results. Animal experiments have shown the development of tumors following chronic low level ingestion of TCDD. The human evidence regarding the potential carcinogencity of TCDD comes from occupational, military and environmental exposures. Several studies have come out of Sweden suggesting an association between sarcoma and exposure to herbicides. Although there is little solid evidence that 2,3,7,8-TCDD produces substantial chronic disability or premature death in man, a significant body of experimental evidence for its carcinogenicity makes it likely that a small number of human malignancies may be due to its action. Since 2,3,7,8-TCDD is an unwanted contaminant it could be eliminated with little measurable consequence.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD or "dioxin"), an unwanted by-product resulting from the manufacture of the herbicide 2,4,5-trichlorphenoxyacetic acid (2,4,5-T) and the germicide hexachlorophene, has suddenly become the focal point of controversy over the relationship of chemical waste to human health. This isomer, one of 22 isomers of TCDD, was first identified by the German chemist Sorge in 1956, in an investigation into the cause of industrial chloracne (*1*). Reports published between 1949 and 1973 described a human syndrome that included chloracne, liver disease, peripheral neuropathy, porphyria cutanea tarda and psychological abnormalities but the possibility of malignancy was not considered. The use of Herbicide Orange in Vietnam, the accidental use of TCDD-contaminated waste oil for dust control in Missouri, and the spill of wood preservative containing about 30 ppb of TCDD in Sturgeon, Missouri, in 1979 have provoked a flurry of scientific, political, and legal activity. Forty-seven railroad employees who participated in the Sturgeon cleanup were awarded $58 million dollars in 1982 (the decision was later overturned in appellate action), and 15,000 veterans were awarded 180 million dollars in an out-of-court settlement in 1984. These large settlements mainly reflect concern for the present or future development of malignant disease and fetal transmission of germ cell mutations that might produce birth defects. This paper reviews the theoretical, experimental, and epidemiologic evidence for the carcinogenic potential of TCDD.

A number of animal studies performed over the past decade have shown that TCDD is not only the most toxic of the 22 isomers of TCDD but, based on an LD_{50} of 2 μg/kg in guinea pigs, is believed to be one of the most toxic substances ever synthesized (*2*). The toxicity of 2,3,7,8-TCDD, based on lethal doses for guinea pigs, is 2000 times greater than that of 1,3,6,8-TCDD and at least 20,000 times greater than that of other tetrachlorinated phenols. In this paper, the abbreviation TCDD refers to the 2,3,7,8 isomer; the same convention is usually followed in the literature.

Substantial species differences do exist. Guinea pigs and chickens appear most sensitive, rabbits and mice are least sensitive, while monkeys and rats have an intermediate sensitivity (*3*). Humans are probably on the less sensitive end of the spectrum.

TCDD is an extremely stable solid that is insoluble in water, slightly soluble in fat, and nonvolatile although airborne spread by adsorption to particulate material occurs. It is absorbed from the gastrointestinal tract, lungs, and skin and is distributed to the organs in relationship to their fat content. Half-lives in different

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species have ranged from 12 to 50 days, but clearance is almost certainly nonlinear, so that small concentrations may persist for prolonged periods of time.

Exposure of primates to TCDD produces progressive weight loss, alopecia, and edema (*4*). Chloracne, a hallmark of human exposure, and blepharitis due to impaction of Meibomian glands are due to metaplastic changes in sebaceous glands that lead to secretion of a viscous material which plugs and destroys glandular material. Loss of body fat, involution of the thymus gland, ascites, testicular degeneration restricted to the seminiferous components, bone marrow hypocellularity, and reduction in plasma albumin are all seen in the exposed primate. Hepatic lesions including necrosis and fatty infiltration are found in mice, rats, rabbits, and chickens but are minimal in primates. Liver porphyrins are markedly increased in mice and chickens exposed to low concentrations of TCDD, porphyrins are only minimally increased following exposure in primates. Fetotoxicity and decreased fertility has also been reported in mice and rats (*5*).

Cellular and Subcellular Actions of 2,3,7,8-TCDD

TCDD induces a number of enzymes, including aryl hyroxylase, glucuronyltransferase and δ-aminolevulinic acid (ALA) synthetase (*6*). The induction of ALA synthetase leads to an increased concentration of porphyrin precursors in liver and urine. An additional action inhibiting the activity of uroporphyrinogen decarboxylase leads to a significant increase in the uroporphyrin/coproporphyrin ratio. Hepatomegaly and a dose-related proliferation of the rough endoplasmic reticulum are morphologic correlates of these biochemical observations since the microsomal monooxygenase system is embedded in that structure.

The ability of chlorinated dibenzo-*p*-dioxins and polychlorinated biphenyls (PCBs) to induce the hepatic monooxygenase system hints at a potential role in carcinogenesis since that system is responsible for the oxidation of foreign chemicals and steroids (*7*). Two types of monooxygenase inducers have been identified. Phenobarbital, for example, induces the terminal oxidase cytochrome P-450 and increases the metabolism of a number of substrates, while 3-methylcholanthrene induces a closely related terminal oxidase, cytochrome P-448. The prototype of this monooxygenase inducer, 3-methylcholanthrene, has been widely used experimentally as a cancer-promoting agent. TCDD is 30,000 times more potent in inducing aryl hydrocarbon hydroxylase (AHH) than is 3-methylcholanthrene. Poland and Glover have shown that 2,3,7,8-TCDD binds to a specific cytosolic receptor which induces AHH (*8*). AHH inducibility is inherited by a simple autosomal trait in inbred mice and appears to be controlled by a single gene. This may explain the wide variations in sensitivity to TCDD exhibited by different species. Poland and Glover also demonstrated that covalent DNA binding by TCDD is much lower than that of most chemical carcinogens, raising the possibility that carcinogenicity is not related to somatic mutation (*9*).

Experimental Evidence for Carcinogenicity in Animals

Conventional tests for mutagenicity have provided conflicting results (*3*). TCDD is mutagenic in *Salmonella typhimurium* strain TA 1532 but not in strains TA 1535, TA 1537 and TA 1538. Mutagenicity has been demonstrated in *Escherichia coli* strain Sd-4. Similar conflicting findings were reported in two-stage tumorigenesis models.

Berry et al. (*10*) noted that TCDD inhibited tumor initiation by 3-methylcholanthrene, while Kouri (*11*) showed an enhancing effect on the formation of 3-methylcholanthrene-induced sarcomas at the site of subcutaneous injection. Poland et al. (*12*) and Pitot (*13*) have also reported that TCDD is a promoter of carcinogenesis in mice skin (Poland) and rat liver (Pitot).

A group of experimental studies has shown the development of tumors following chronic low level ingestion of TCDD. Van Miller et al. (*14*) administered 0.001 μg TCDD/kg body weight/week to male rats for 78 weeks and found a variety of tumors at 95 weeks (ear duct carcinoma, lymphocytic leukemia, kidney adenocarcinoma, malignant peritoneal histiocytoma, skin angiosarcoma and carcinomas of hard palate, tongue and nasal turbinates). The number of animals exposed was small and it was difficult to determine whether the incidence of these tumors was greater than those appearing spontaneously. Studies conducted by the National Toxicology Program demonstrated hepatic and thyroid tumors in male and female rats (*15,16*). Male mice developed liver cancer, female mice developed liver cancer and thyroid follicular cell adenomas. The application of TCDD to the skin of female mice produced an increased number of fibrosarcomas compared to untreated controls.

Kociba et al. administered daily oral doses to groups of rats over a two year period (*17*). Ingestion of feed containing 2.2 ppb TCDD (0.1 μg/kg body weight per day) caused an increased incidence of hepatocellular carcinomas and squamous cell carcinoma of the lung, hard palate/nasal turbinates, or tongue. There was a reduced incidence of tumors of the pituitary, uterus, mammary glands, pancreas and adrenal glands. This dose led to liver and fat concentrations of 24 and 8.1 ppb, and to increased mortality, decreased weight gain, proliferation of the rough endoplasmic reticulum of the liver and increased urinary excretion of porphyrins.

Rats fed a diet containing 0.2 ppb (0.01 μg/kg/day) accumulated TCDD concentrations of 5.1 and 1.7 ppb in liver and fat and had substantially less evidence of toxicity. The only tumors observed were benign hepatic nodules. Diets containing 0.022 ppb produced liver and fat concentrations of 0.54 ppb in liver and fat. Histological, biochemical or clinical abnormalities were not observed at this dose.

Human Evidence for Carcinogenicity

Occupational Exposures

Analysis of groups of workers accidentally exposed during the manufacture of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) provides a relatively complete view of the human syndrome and permits some insight into dose-response relationships. 2,4,5-T produced prior to 1965 contained more than 30,000 ppb of 2,3,7,8-TCDD. Control measures introduced sometime thereafter reduced maximum concentrations to below 1000 ppb and, ultimately, to below 100 ppb. These reports of accidental exposure are of importance in estimating the carcinogenic potential since exposure can be estimated both by the known concentration of contaminant in the finished product and by the severity of symptoms experienced by the exposed population.

The first reported cases of illness following explosive release of toxic material during the manufacture of 2,4,5-T occurred in Nitro, WV, in 1949. An acute syndrome characterized by skin, eye, and respiratory tract irritation, headache, dizziness, and nausea subsided in several weeks and was followed by chloracne, severe muscular aches, and pains, fatigue, nervousness and irritability, dyspnea, decreased libido, and intolerance to cold. Examination revealed liver enlargement, peripheral neuropathy, prolonged prothrombin time, and increased serum lipids.

In all, there were 122 individuals with chloracne. Most of these abnormalities had subsided by 1953 but chloracne persisted. In addition, 26 individuals with chloracne associated with exposure to the routine 2,4,5-T operation were observed between 1949 and 1953.

Three major clinical reports evaluating the health of individuals exposed during that period have appeared. Zack and Suskind (*18*) followed 122 individuals with chloracne attributable to the 1949 accident through 1978. There were 32 deaths observed, with 46.41 expected from age, race, and time-specific mortality rates for the U.S. population. There were nine deaths from malignant disease, with 9.04 expected (lung, 5; acute myelogenous leukemia, lymphatic leukemia, Hodgkin's disease, and malignant fibrous histiocytoma of soft tissue origin).

Zack and Gaffey, in an attempt to study the chronic effect of TCDD in the same factory, evaluated the vital status of 884 men who had been employed in the West Virginia plant (*19*). Those exposed to 2,4,5-T were identified from employment records. Of 163 deaths observed, 35 were from malignant disease. Standardized mortality ratios (SMRs) calculated by comparison with age, race, and time-specific rates for the U.S. population were 1.03 and 1.13, respectively; neither was statistically significant. The SMR for bladder cancer was 9.49 due to the known carcinogenicity of paraaminobiphenyl. Nine of fifty-eight deaths in the exposed group were from malignant diseases; one of these had previously been reported by Zack and Suskind. The eight malignancies included lung (6), bladder (2), and generalized liposarcoma later diagnosed by pathologists from the Armed Forces Institutes of Pathology as an undifferentiated carcinoma. The proportional mortality rate (PMR) for malignant disease was 0.82 in the exposed group, 1.22 in the unexposed group. There is inevitable overlap between the two mortality studies because different criteria for exposure were utilized; chloracne following the accident was considered evidence of acute exposure in the first study, employment in a 2,4,5-T manufacture department in the second. Attempts to change group composition by avoiding overlap did not change the overall results.

A morbidity study was undertaken in 1979, 30 years after the accidental release of large quantities of 2,3,7,8-TCDD. Between 1948 and 1969, 204 individuals who had worked in the plant and 163 control individuals were examined by Suskind and Hertzberg (*20*). Chloracne was present in 52.7% of the exposed group compared to none of the control group. A history of peptic ulcer and reduced lung function was more common in the exposed group although there was no evidence of increased prevalence of hepatic disease, renal abnormalities or either central or peripheral nervous system disease.

In 1953, 74 employees were exposed to TCDD-contaminated material after an explosion in a reaction vessel in a BASF plant in Ludwigshafen, Germany (*21*). Overall mortality did not differ from that in three external control groups (total population of Ludwigshafen, district of Rhinehessia-Palatinate, and entire Federal Republic of Germany) or from two matched groups selected from unexposed factory workers; however, seven of the deaths were from malignant disease (4.1 expected) and three of these were cancer of the stomach (0.61 expected).

Some 30 cases of chloracne were identified by Schultz in a chemical plant in Hamburg, Germany, during 1956 (*1*). Schulz and Sorge soon discovered that technical grade 2,4,5-T, but not the pure chemical, produced an acnelike lesion in the rabbit ear, and by 1957 it became clear that 2,3,7,8-TCDD was the toxic substance associated with the manufacture of 2,4,5-T.

In 1963, 145 workers were exposed to TCDD that escaped following a factory explosion in a factory in Amsterdam (*22*). Twenty years later, the status of 141 of these individuals was evaluated; chloracne was present in 69. Twenty-five had died, eight with malignant disease. Thirteen of those who died and three of those who died from cancer had chloracne. The eight tumors were mesothelioma (asbestos exposure), melanosarcoma, stomach, pancreas, rectosigmoid, lung, bladder/kidney, and brain. Standard mortality rates for all deaths and for deaths from malignant disease were 1.19 (0.78–1.70) and 1.15 (0.49–2.09), respectively. The nature of the comparison population was not stated.

An explosion in the Coalite 2,4,5-TCP factory in Derbyshire, England, in 1968, released toxic materials estimated to contain 30,000 to 40,000 ppb of TCDD (*23*).

Chloracne developed in 70 workers and 11 workers developed abnormal liver function studies and white blood cell counts. Both tests were normal in 10 days. Ten years later, May reported that chloracne was still present in 22 of the men but that other abnormalities were not present (*24*). Reproductive histories and biochemical studies were normal and none of the individuals had developed malignant disease.

Chronic occupational exposure to TCDD has also been studied. Bleiberg et al. reported in 1946 that 21 workers at a 2,4,5-T plant in Newark, NJ, developed chloracne and that 11 of these had increased urinary excretion of uroporphyrins consistent with the diagnosis of porphyhria cutanea tarda (*25*). By 1968, chemical process changes had reduced the concentration of TCDD from 10,000 to 25,000 ppb to less than 1000 ppb. Poland et al. later studied 73 workers and found them to be in good health, although 13 still had chloracne (*26*).

Pazderova et al. presented a 10-year follow-up of 55 workers who had been chronically exposed to TCDD during the manufacture of 2,4,5-T between 1965 and 1968 (*27*). Chloracne, porphyria cutanea tarda, liver involvement, fatigue, and weakness of the lower extremities were the most common findings. Two of six reported deaths during the 10-year period of observation were from malignant disease; both of these were bronchogenic carcinoma. Two of the deaths were from traffic accidents.

An outbreak of chloracne occurred during 1964 at a 2,4,5-T plant in Midland, MI. Fourteen years later, Cook et al. conducted a vital status study of the 61 individuals known to have worked in the TCP process building during that period (*28*). Three had died from malignant disease (1.6 deaths expected based on age-specific rates for U.S. white male population). One individual with recurrent acne described as "not typical of chloracne" died 8 years after exposure from metastatic adenocarcinoma of unknown primary site, another with a rash of the right ear and face but without definitive diagnosis of chloracne died 11 years later of a fibrosarcoma, and another with chloracne died 12 years after exposure from a glioma. Ott et al., in an analysis of another cohort from Midland, MI, observed four deaths in 204 employees working in the department responsible for the manufacture of 2,4,5-T (*29*). One death was from carcinoma of the lung which was not statistically significant when compared to the age-specific mortality for U.S. white males.

Military and Nonoccupational Exposures to 2,3,7,8-TCDD

Approximately 19 million gallons of herbicide containing 2,4,5-T were sprayed over Vietnam between 1962 and 1971 (*30*). The two missions of Operation Ranch Hand were defoliation and crop destruction. Herbicides Pink, Green and Purple contained up to 66,000 ppb of TCDD and were used prior to July 1, 1965. After that time, aerial spraying was limited to Herbicide Orange which contained 2,000 ppb. The airborne crews engaged in Operation Ranch Hand were selected for epidemiologic study because their almost daily occupational exposure gave them "1000 times more exposure to Herbicide Orange than would an average unclothed man, standing in an open field directly beneath a spraying aircraft." Mortality studies were done on 1247 exposed Ranch Handers and 16,174 unexposed controls who served in Vietnam. Matched controls for a morbidity analysis were selected from this larger group of unexposed servicemen. Overall mortality rates for the two groups were almost identical (Table 1).

Table 1.

	No. of malignancies
Types of malignancies in reported cohorts	
Lung	22
Stomach	4
Kidney	3
Soft-tissue sarcoma	2
Leukemia	2
Colon	2
Prostate	2
Glioma	2
Testicle	2
Melanoma	2
Hodgkins	1
Pancreas	1
Tongue	1
Adenocarcinoma site unknown	1
Poorly differentiated carcinoma	1
Ranch hand skin malignancies (controls)	
Basal cell	31 (21)
Melanoma	3 (02)
Squamous cell	1 (03)

There were four deaths from malignant disease in the Ranch Hand group (lung, unspecified, kidney, and mediastinal melanoma) compared to 39 in the 12,193 matched controls (odds ratio, 1.0). The morbidity study identified 13 malignancies each in the exposed and control groups. Malignancies in the exposed group included lung (2), kidney, lip (3), bladder (2), prostate, germ cell neoplasm of testicle (2), and glioma. Thirty-five skin cancers were found in the exposed group and 27 in the comparison group. One matched control had fibrosarcoma of the skin. Neither chloracne nor porphyria cutanea tarda were present in the Ranch Hand population. Minor birth defects, abnormal, peripheral pulses and decreased unstimulated lymphocyte proliferation were more common in the exposed group but other differences were not identified.

Much higher concentrations of TCDD than were contained in Agent Orange were contained in waste oil used for dust control in Missouri in 1971. Part of the waste oil was obtained from a company in southwestern Missouri that manufactured 2,4,5-TCP as an intermediate for the production of hexachlorophene. Shortly after the application of waste oil to a horse arena in Moscow Mills, 43 horses in that arena died and exhibited intestinal colic, oral ulcers, severe weight loss, and other abnor-

malities (*31*). There were 26 known abortions and many foals exposed in utero died. A six-year-old girl who had played in the area presented several months later with nosebleeds, headache, diarrhea, painful urination, and hematuria. Her symptoms disappeared within several weeks, and a subsequent examination of the girl, her sister, and her mother, performed by Beale et al. five years later was completely normal (*32*). Kimbrough et al. reported that the initial soil sample from the area where the girl was playing contained about 30,000 ppb of TCDD.

A pilot health effects study was performed in Times Beach and other areas in Missouri where the TCDD containing waste oil had been applied by the same individual who sprayed the horse arenas (*33*). A group of 68 individuals considered to have a high probability of exposure to TCDD were compared to 36 individuals who had no exposure. There was an apparent trend of increased urinary abnormalities (more self-reported problems, leukocyturia, and hematuria) and lower helper/suppressor-cytotoxic lymphocyte ratios in the exposed group. No cases of chloracne, porphyria cutanea tarda of soft tissue sarcomas were found.

A much publicized and well-studied industrial accident in a TCP factory in Seveso, Italy, has produced chloracne, although there were surprisingly few permanent health consequences (*34*). There has been no increase in morbidity or mortality from malignant disease, although the 8-year period of observation is too short to permit any conclusions to be drawn about malignant disease. Presumably, plugging of an exhaust pipe resulted in an exothermic reaction that created extremely high concentrations of TCDD that were released in a cloud over the area. Although concentrations as high as 15,000 ppb were found in grass samples, vegetation was rapidly cleared and soil samples were much less contaminated. People were exposed to as high as 90 to 5000 ppb during the first 2 weeks but were then evacuated.

Soft Tissue Sarcoma without Chloracne: The Swedish Experience

The 1977 clinical observations published by Hardell suggesting that soft tissue sarcomas appeared to be associated with exposure to phenoxyacetic acids added a new dimension to the question of herbicide carcinogenicity (*35*). A subsequent case-control study published by Hardell and Sandstrom in 1979 demonstrated that individuals with sarcomas had a sixfold greater history of exposure to phenoxyacetic acids or chlorophenols compared to matched controls (*36*).

A second study by Eriksson et al. reported similar increased risk for soft tissue sarcoma in another group of individuals from southern Sweden (*37*). A similar study design led Hardell to conclude that both Hodgkins Disease and non-Hodgkins lymphoma, but not carcinoma of the colon, were associated with phenoxyacetic acid and chlorophenol exposure (*38*).

Soft tissue sarcomas were not identified. However, in a study of Swedish railroad workers exposed to phenoxy acids and amitrol (3-amino-1,2,4 triazol) during the same time period (*39*), 45 deaths were observed in a cohort of 348 railroad workers (49 deaths expected). There were 17 tumors (11.85 expected from entire Swedish population). The distribution of tumor type was not unusual.

The two Swedish case-control studies demonstrating a sixfold increase in herbicide exposure among patients with soft tissue sarcoma have been widely interpreted as strong evidence for the carcinogenicity of TCDD. The case-control approach is ideal for the study of uncommon events but difficulties in selecting control subjects can produce major errors. Exposure history in the study was retrospectively determined by questionnaire at a time when herbicide exposure was receiving considerable media attention leading those with soft tissue sarcoma to overestimate herbicide contact. Concern among herbicide workers may have led to increased medical surveillance leading to a detection bias similar to that demonstrated by Horwitz and Feinstein for uterine carcinoma and estrogen usage (*40*). Mortality rates for soft tissue sarcoma were 60% in the initial study and 35% in the second study, suggesting early diagnosis of smaller lesions. In addition, documented evidence of exposure to TCDD is uncertain and dose-response relationships could not be identified. It is difficult to ascertain the relative risk of exposure to TCDD because of potential concurrent exposure to other toxic substances. In addition, chloracne or other health problems were not mentioned and the study in southern Sweden demonstrated that phenoxyacetic acids uncontaminated by dioxins or dibenzofurans were also risk factors for the development of soft tissue sarcoma.

Smith et al. conducted a similar case-control study with 98 cases reported to the New Zealand Cancer Registry between 1976 and 1980 (*41*): 21 of the cases and 19 of the controls had a definite exposure history to phenoxyacetic acids. None of the cases were found in the more than 2000 herbicide sprayers in New Zealand, even though a great deal of phenoxyacetic acid herbicides have been utilized. Two separate studies from Finland in workers in five companies who sprayed 2,4-D and 2,4,5-T failed to reveal any increase in deaths from malignant disease although headache, fatigue and a few instances of skin involvement were reported (*42*). Another negative study was recently reported by Milham (*43*), who reported that marine engineers, bankers, laundry workers, plumbers, teachers, and students had much higher mortality ratios for soft tissue sarcomas than workers exposed to herbicides; the mortality ratio for bankers is almost four times that for herbicide workers, for example.

Pooling Mortality Data from Reported Cohort Observations

It is tempting to force an answer to the carcinogenicity question by attempting a global integration of re-

ported studies. Honchar and Halperin (44) reviewed four studies of workers from two United States chemical companies and notes that 3 of the total 105 deaths were due to soft tissue sarcoma (2.9% of mortality compared to an expected 0.07% for U.S. males between the ages of 20 and 80). Three other cases were briefly reported in the medical literature and contributed to the growing belief that a relationship between soft tissue sarcoma and exposure to TCDD exists. Fingerhut et al. have re-evaluated the seven cases in an unpublished manuscript that included an independent review of tissue diagnoses by pathologists from the Armed Forces Institute of Pathology. Two of the seven pooled cases were found to have carcinoma rather than soft tissue sarcoma, and three others did not appear to have an adequate record of exposure to TCDD. Thus five of the seven cases were either not soft tissue sarcomas or did not have good evidence of exposure.

A total of 258 deaths in 1977 individuals occupationally exposed to concentrations of TCDD that probably ranged from 1000 to 30,000 ppb have been reported in the literature. Since the time of observation was between 10 and 20 years after exposure, 20,000 to 40,000 person-years of risk have been evaluated. Thirty-four (13%) of these deaths were from cancer. This is not an unusual proportion of deaths from malignant disease and the distribution of reported tumors does not appear particularly unusual (Table 1).

Conclusions

Although there is little solid evidence that 2,3,7,8-TCDD produces substantial chronic disability or premature death in man, a significant body of experimental evidence for its carcinogenicity makes it likely that a small number of human malignancies may be due to it action. Careful long-term follow-up of Missouri and Vietnam cohorts will be essential in determining the relative risk of cancer in those exposed to the substance. Subcellular, cellular, and whole-animal experiments suggest that TCDD exerts much of its activity by inducing enzymes that protect the intact organism from the assault of environmental contaminants. Administration of 2 ppb of TCDD daily for 2 years to rats caused liver and fat concentrations of 24 and 8.1 ppb, increased mortality, failure to gain weight, and damage to many organ systems. Statistically significant increases in some tumor frequencies but decreased frequencies for other tumors at this dose of TCDD emphasize its complex action on cell function.

Since tumors in animals are associated with other clinical evidence of TCDD exposure and most exposed workers who experience illnesses after exposure do not develop malignant disease, the diagnosis of dioxin-associated illness should require an exposure history and some other manifestations closely associated with TCDD exposure. Signs and symptoms useful in establishing the diagnosis of dioxin-associated illness in a person are any two or more of the following provided there is evidence of exposure to 500 to 1000 ppb 2,3,7,8-TCDD for more than 1 month in the preceding 5 years.

- Chloracne: severe acneform lesions temporally related to period of maximum exposure.
- Abnormal urinary excretion of uroporphyrin with hirsutism
- Liver function abnormalities: specifically an elevated SGPT, SGOT or GGT unexplained by other causes
- Neuropathy proven by nerve conduction studies in the lower extremities without other causes such as alcoholism, diabetes, or disc disease
- Hypercholesterolemia or hypertriglyceridemia associated with weight loss or at least the absence of obesity. The relationship is strengthened if hyperlipidemia is temporally related to exposure and was not present prior to exposure
- Documentable evidence of profound weakness and depression. Weakness may be documented by exercise tolerance testing or ergometry. Depression should be documented by use of psychometric testing and reliable psychiatric consultation

Soft tissue sarcoma in an exposed individual should raise suspicion of a relationship to 2,3,7,8-exposure if at least one other sign or symptom is present. Chloracne appears to be both sensitive and specific; abnormal porphyrin excretion with hirsutism is quite specific but not particularly sensitive; hypercholesterolemia is quite nonspecific. These abnormalities can be used to construct a set of criteria for the diagnosis of dioxin-associated illness (Webb, Ayres, Evans, and Mikes, in press).

Unlike many chemicals which have important and redeeming social value, 2,3,7,8-TCDD is an unwanted contaminant that could be eliminated with little measurable consequence. High national priority must be given to the disposal of TCDD from existing contaminated areas and to identification and compensation of those who have suffered serious health problems.

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