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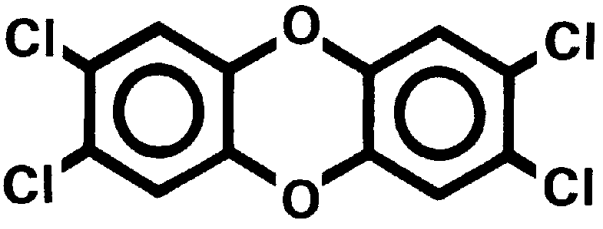
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, "dioxin")



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FOREWORD

Current Intelligence Bulletins are reports issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A Current Intelligence Bulletin may draw attention to a hazard previously unrecognized or may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

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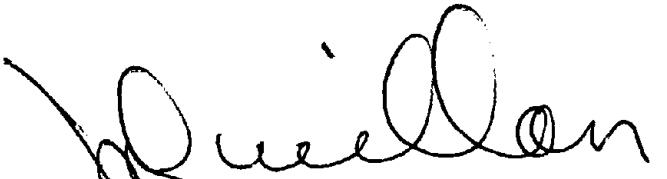
Because of the recent attention given to human exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, "dioxin") contaminated materials and published reports on the toxicity of TCDD, NIOSH staff consider it necessary to present a review of the pertinent data and a summary of findings related to the human hazard potential of TCDD. Because of the compression in this bulletin of the voluminous literature on TCDD, it is suggested that readers wanting to know more of the details of the reported studies consult the appended references.



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CURRENT INTELLIGENCE BULLETIN #40

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, "DIOXIN")

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ABSTRACT

In animals, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, "dioxin") causes various systemic effects at a wide range of exposure concentrations, including tumorigenesis, immunological dysfunction, and teratogenesis. Studies of humans exposed to TCDD-contaminated materials suggest that TCDD is the cause of observed chloracne, metabolic disorders (porphyria), and other systemic problems and are suggestive of TCDD's ability to cause cancer.

TCDD occurs as a contaminant of materials such as 2,4,5-trichlorophenol (TCP), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2-(2,4,5-trichlorophenoxy)propionic acid (silvex). Occupational exposure may occur through contact with these materials during use or from the past contamination of worksites.

The National Institute for Occupational Safety and Health (NIOSH) recommends that TCDD be regarded as a potential occupational carcinogen, that occupational exposure to TCDD be controlled to the fullest extent feasible, and that decontamination measures be used for TCDD-contaminated work environments. This recommendation is based on a number of reliable studies demonstrating TCDD carcinogenicity in rats and mice.

BACKGROUND

Physical and Chemical Properties of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

TCDD is one of a family of isomers known chemically as dibenzo-p-dioxins. The chemical and physical properties are summarized in Table I. TCDD is a colorless crystalline solid at room temperature. It is sparingly soluble in most organic solvents and essentially insoluble in water. TCDD is stable to heat, acids, and alkali and will decompose when exposed to ultraviolet light, including sunlight [1].

TABLE I

CHEMICAL AND PHYSICAL PROPERTIES OF TCDD [2,3]

CAS Registry No.:	1746-01-6	
Empirical formula		$C_{12}H_4Cl_4O_2$
Percent by weight	C	44.7
	O	9.95
	H	1.25
	Cl	44.1
Molecular weight		322
Vapor Pressure mm Hg at 25°C		1.7×10^{-6}
Melting point, °C		305
Decomposition temperature, °C		>700
Solubilities, g/liter		
o-Dichlorobenzene		1.4
Chlorobenzene		0.72
Benzene		0.57
Chloroform		0.37
n-Octanol		0.05
Methanol		0.01
Acetone		0.11
Water		2×10^{-7}

Formation and Use of TCDD

TCDD forms as a stable by-product or contaminant during the production of TCP. Run-away reactions at high temperature, in which excess TCDD was produced, have occurred at TCP production sites in the United States and elsewhere [4]. Normally, TCDD persists as a contaminant in TCP in relatively small, variable amounts (0.07-6.2 mg/kg) [5]. TCP has been utilized primarily as a feedstock for production of the phenoxy herbicides 2,4,5-T and silvex, resulting in the contamination of these products with TCDD. Production of 2,4,5-T and silvex ceased in the United States in 1979. However, stockpiles of both products are still being distributed and

used. TCP also is used in the production of hexachlorophene, a bactericide and fungicide.

The combustion of 2,4,5-T can result in its conversion to small amounts (0.6 ppt TCDD/1 ppm 2,4,5-T burned) of TCDD. Also, the burning or heating of commercial and purified chlorophenates and pyrolysis of polychlorinated biphenyls (PCBs) contaminated with trichlorobenzenes have resulted in the production of TCDD [6,7]. The formation of TCDD from trace chemical reactions in fires has been postulated but has not been verified [8,9].

Existing Regulations and Guides

No occupational exposure standard exists for TCDD. The United States Environmental Protection Agency (U.S. EPA) temporarily suspended or banned most uses of 2,4,5-T and silvex in 1979, although their use was allowed on sugarcane, orchards and for miscellaneous non-crop uses [10]. On October 18, 1983 EPA published its intent to cancel registration of pesticide products containing 2,4,5-T and silvex and to prohibit the transfer, distribution, sale or importation of any unregistered pesticide product containing 2,4,5-T or silvex or their derivatives [11].

Nature of Occupational Exposure to TCDD

It is not possible to estimate accurately the number of U.S. workers currently at risk of exposure to TCDD. Occupational exposure to TCDD may occur during production of TCP; in decontamination of worksites from prior production or use of TCP, 2,4,5-T, or silvex; from waste materials (such as reclaimed oil) contaminated with TCDD; or from cleanup after fires in transformers containing polychlorinated aromatics.

Dust or soil particles contaminated with TCDD can remain airborne or accumulate on indoor or outdoor work surfaces and may present a potential exposure hazard. Exposure to TCDD as a vapor will normally be negligible because of its low vapor pressure. Contact with TCDD-contaminated liquids is possible through the handling of drums or tanks containing the liquid or through dispersion of the liquid.

TOXICITY

Results of Studies of TCDD in Animals

Acute and Chronic Toxicity

There is wide variation in the dosage of TCDD required to cause death among animal species (oral LD_{50} 0.6-5,000 μg TCDD/kg body weight (bw)) [12,13]. Progressive weight loss with death several weeks later is reported to characterize the response in experimental animals after administration of a lethal dosage of TCDD [12,14,15]. Animals given single or repeated oral dosages of TCDD of 0.1 to 25 μg/kg bw demonstrated increased liver weights and lipid accumulation, thymic atrophy, and histopathological changes in liver and thymus [12,16-18].

TCDD is reported to be at least three times more potent than any other known compound in stimulating production of aminolevulinic acid synthetase (ALA), the rate-limiting enzyme in porphyrin and heme synthesis [19,20]. Varied effects on hematological functions have been reported in rats and mice dosed with TCDD: increased numbers of erythrocytes and leucocytes, increased hemoglobin concentration, decreased blood platelets in rats [21,22], and decreased hemoglobin concentration in mice [23].

Effects on Reproductive Function

TCDD administered at dosages of 0.125-3.0 μg TCDD/g bw to mice and rats induced fetotoxicity that included cleft palates and kidney anomalies [24-26], intestinal hemorrhages and excessive tissue/organ fluid (edema), and prenatal mortality [27,28].

Impairment of reproduction has been reported for rats ingesting 0.01 μg TCDD/kg bw/day. Significant decreased fertility, litter size, number of pups alive at birth, postnatal survival, and postnatal body weight of pups were evident in two successive generations delivered from male and female rats that ingested TCDD 90 days prior to first mating, during pregnancies, and for the durations of time between pregnancies [29]. No significant dose-related reproductive effects were observed in male mice treated with up to 2.4 μg TCDD/kg bw/day and mated with untreated female mice [30,31].

Immunological Effects

TCDD induced immunological function alterations, expressed by decreased thymus-to-body weight ratios, in nursing newborn rats exposed through dosing of the lactating mother [32]. Other reports have shown that pre- and post-natal maternal dosing of rats and mice with TCDD caused thymic atrophy

and suppression of cellular immunity in the offspring [33]. TCDD administered intraperitoneally or orally to mice induced a strong immunosuppressive effect on antibody production and cell-acquired immune responses [34].

Mutagenic Effects

Results of mutagenicity tests are inconclusive. In two studies TCDD was mutagenic in Salmonella typhimurium TA 1532 without activation [35,36]. In another study, which used a more sensitive mutant strain, Salmonella typhimurium TA 1537, TCDD was not a mutagen [37]. There is weak evidence of chromosomal aberrations in bone marrow of rats given dosages of 0.25 to 4 µg TCDD/kg bw [38,39].

Carcinogenic Effects

Male rats fed dosages of 0.001 µg TCDD/kg bw/week for 78 weeks and sacrificed at week 95 of the study showed a variety of neoplastic tumors (ear duct carcinoma; lymphocytic leukemia; kidney adenocarcinoma; malignant peritoneal histiocytoma; skin angiosarcoma; hard palate, tongue and nasal turbinate carcinoma) [40]. Female rats that had ingested TCDD for two years at a dosage of 0.1 µg/kg bw/day developed carcinomas of the liver and squamous cell carcinomas of the lung, hard palate, nasal turbinates, or tongue [41]. Male and female rats orally dosed with 0.5 µg TCDD/kg bw/week for two years demonstrated neoplastic nodules of the liver and thyroid adenomas [42].

Male mice fed dosages of TCDD of 0.05 or 0.5 µg/kg/week for two years developed liver cancer; female mice fed 0.2 or 2.0 µg/kg/week for the same duration developed liver cancer and thyroid follicular cell adenomas [42]. TCDD applied to the skin of female mice for two years (0.005 µg/kg bw/application; 3 days/week) resulted in a significantly higher incidence ($p=0.007$) of skin cancers (fibrosarcomas) when compared to untreated controls. An increase in the same tumor type, although not statistically significant ($p=0.084$), was also observed in the male mice that received a maximum dosage of 0.001 µg TCDD per application [43].

Human Health Effects

The only information on the health effects in humans from exposure to TCDD is from clinical or epidemiological studies of populations who were occupationally and non-occupationally exposed to 2,4,5-T and TCP contaminated with TCDD. Because of the coincidental exposure to 2,4,5-T and TCP and to other herbicides as well as to TCDD, it is not possible to

attribute the observed health effects solely to TCDD exposure. To date, no studies of humans include a quantitation of exposure to TCDD.

Chloracne and Other Systemic Effects

Chloracne is a chronic and sometimes disfiguring skin eruption caused by exposure to halogenated aromatic compounds including TCDD. Chloracne is possibly a result of systemic effects of these compounds, although it also may occur as a contact dermatitis [44,45].

There are numerous cases of chloracne reported following accidental exposure to chlorinated aromatic chemicals which were probably contaminated with TCDD [46-48]. The most notable recent exposure occurred in Seveso, Italy in 1976 [49]. In most incidences of chloracne, there are a variety of signs and symptoms (ranging from gastrointestinal disturbances to metabolic disorders) which accompany the appearance of the skin eruptions and persist for varying lengths of time [50-54].

Reproductive Effects In Humans

Reproductive effects resulting from possible human exposure to TCDD are inconclusive. Data on male workers who applied agricultural sprays of 2,4,5-T or who produced TCDD-contaminated materials are consistent with the animal data which suggest no reproductive effects in males from TCDD exposure [55-57]. To date, no study of reproductive effects in women or in offspring of males or females with defined exposure to TCDD has been reported.

Studies of birth defects in populations that may have been exposed non-occupationally to TCDD have been conducted in Australia where a correlation was observed between 2,4,5-T use and seasonal variation in the rate of spinal cord and spine formation defects; no causal association could be drawn [58]. In a similar study in Hungary, an increased incidence of congenital malformations including spine formation defects could not be correlated with increased use of 2,4,5-T [59]. A study based on incomplete fetal tissue samples from the Seveso, Italy population found no mutagenic, teratogenic, or fetotoxic effects in 30 interrupted pregnancies and four spontaneous abortions in women believed to have been exposed to TCDD [60]. A U.S. EPA study found a positive relationship between spontaneous abortions and 2,4,5-T use in the Alsea, Oregon area [61]. The study, however, has been severely criticized because of its numerous limitations: inaccurate comparisons of the study and control areas; inaccuracies in the collection of data on spontaneous abortions; incomplete and inaccurate data on 2,4,5-T usage; and failure to recognize that the rate of spontaneous abortions was not greater than would be expected [62].

Studies of Mortality and Carcinogenesis in Humans

Findings have been inconclusive in many mortality studies of workers with occupational exposure to TCDD-contaminated materials because of the small size of the study population and concomitant exposures to other substances.

No excess mortality or tumor incidence was observed among Swedish railroad workers exposed to unknown amounts of 2,4-D, 2,4,5-T, and other herbicides but believed to have been exposed primarily to phenoxy acid herbicides for at least 45 days [63]. In a subsequent analysis of mortality in this group of workers, 45 deaths (49 expected) were observed in the total population. A significant excess of tumors also was observed among those believed to be exposed primarily to Amitrol® (3-amino-1,2,4-triazole), a suspect carcinogen, as well as to phenoxy herbicides. Two cases of stomach cancer (0.33 expected) were observed among those exposed primarily to phenoxy herbicides [64].

Among Swedish forestry workers exposed to phenoxy herbicide preparations, supervisors, who had more extensive exposure to herbicides than the other forest workers, had a nonsignificant excess of deaths from all cancers. Mortality associated with the presence of tumors was, however, lower than expected for the total group of exposed workers [65].

In a group of 74 workers involved in an accident during TCP production in Germany, 21 deaths occurred during the following 27 years. Seven (7) malignant neoplasms vs. 4.2 expected and a significant excess of stomach cancer (3 observed vs. 0.61 expected) were observed [66].

Several case control studies of cancer patients have yielded data on the carcinogenicity of phenoxyacetic herbicides. Two studies were conducted in Sweden following a clinical observation of patients with soft tissue sarcoma who had previous occupational exposure to the herbicides [67]. The first study of 52 cases of soft tissue sarcoma concluded that the sarcoma cases were 5.3 times more likely than the 206 controls to have had occupational exposure to phenoxyacetic acids (primarily 2,4,5-T and 2,4-D) [68]. The second study of 110 cases of soft tissue sarcomas indicated that this population was 6.8 times more likely to have had exposure to phenoxyacetic acids than the 219 controls [69]. In neither study was it possible to demonstrate the relative risk related to exposure to TCDD-contaminated 2,4,5-T because of the presence of impurities such as chlorinated dibenzodioxins and dibenzofurans which were part of the phenoxyacetic herbicides.

In other reports from Sweden, 11 of 17 patients with malignant lymphoma reported occupational exposures to phenoxyacetic acids or chlorophenols

[70]; a case control study with 169 malignant lymphoma cases found a significantly higher occupational exposure to phenoxyacetic acids (primarily 2,4,5-T, and 2,4-D) associated with the sarcoma cases than did the 338 controls. Analysis by individual herbicide exposure was not possible [71].

Two additional studies conducted in Sweden for colon cancer and nasal and nasopharyngeal cancer did not demonstrate an elevated risk for occupational exposure to phenoxyacetic acids [72,73].

Among four small groups of U.S. production workers exposed to TCP and 2,4,5-T a total of 105 deaths were observed [74-76]. In these, three deaths were attributed to soft tissue sarcoma (43 times the number expected for this age group of U.S. white males) [77]. Later, four additional cases were reported to have soft tissue sarcomas [78-81]. However, a detailed review of work records and expert review of pathological tissue specimens have shown only two of the seven cases with both confirmed exposure to TCP or 2,4,5-T and diagnosis of soft tissue sarcoma [82].

Summary of Toxicity in Animals and Humans

TCDD causes a variety of systemic and immunological effects in animals with wide variation among species in the dosage required to cause death. Studies using rats and mice have demonstrated that TCDD is an animal teratogen and carcinogen. Results of tests for mutagenicity are inconclusive.

Humans exposed to materials reported to be contaminated with TCDD have developed chloracne and other signs of systemic poisoning. Soft tissue sarcoma has been observed in excess among workers exposed to phenoxy herbicides. These data are inconclusive regarding TCDD toxicity in humans because the populations studied had mixed exposures making causal relationships between exposure and effect unclear. The data are, however, suggestive of an association between exposure to phenoxyacetic herbicides contaminated with TCDD and excess lymphoma and stomach cancer. Attempts to associate reproductive effects with TCDD exposure are inconclusive because of the inadequately defined populations studied and the difficulties of defining exposure.

RECOMMENDATIONS

There are several classifications for identifying a substance as a carcinogen. Such classifications have been developed by the U.S. National Institute of Environmental Health Sciences, National Toxicology Program [83], the International Agency for Research on Cancer [84], and OSHA [85]. NIOSH considers the OSHA classification the most appropriate for use in identifying carcinogens in the workplace. This classification is outlined

in 29 CFR 1990.103.* Since TCDD has been shown to carcinogenic in experimental studies with rats and mice, and studies are suggestive of an association between human exposure to TCDD-contaminated materials and carcinogenicity, NIOSH recommends that TCDD be considered as a potential occupational carcinogen and exposure to TCDD in all occupational settings should be controlled to the fullest extent feasible. While observations to date do not confirm a causal relationship between TCDD exposure and soft tissue sarcoma, they suggest a need for continued investigations.

Because of the variety of situations likely to be encountered in TCDD-contaminated worksites, it is not possible to offer in this bulletin detailed procedures for assessing exposures or decontamination. Based on NIOSH hazard evaluations of TCDD-contaminated sites, the following general guidelines are recommended until more specific procedures can be developed [86,87].

Assessment of Exposure

Workers may be exposed to TCDD derived from a variety of sources: the production of TCP, residues from prior production or use of 2,4,5-T or silvex, waste materials contaminated by TCDD, or contamination resulting from transformer fires. The first step in assessing workplace contamination should be environmental sampling to determine the presence of TCDD contamination, keeping in mind the possible routes of exposure, with later sampling conducted to define the quantity of TCDD in the environment. The assessment may include sampling of soil and settled dust for TCDD, air sampling for TCDD-contaminated particles, and wipe sampling of surfaces [86,87].

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*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals."

Decontamination and Worker Protection Programs

In general, decontamination procedures must provide an organized process in which levels of contamination are reduced. This requires containment, collection, and disposal of contaminated solutions and residues generated during the cleanup. Separate facilities should be provided for decontamination of large equipment.

Each stage of decontamination, such as gross decontamination and repetitive wash/rinse cycles, should be conducted separately, either by using different locations or by spacing in time. Personnel decontamination locations used should be physically separated to prevent cross-contact and should be arranged in order of decreasing level of contamination. Separate entry/exit routes and locations should be provided for workers when it is necessary to isolate them from different contamination areas containing incompatible waste. Entry and exit points to these areas should be well marked and controlled. Access to the decontamination area should be separate from the path between the contaminated and clean areas. Dressing stations for entry should be separate from re-dressing areas for exit.

Protective Clothing and Equipment

All workers who may be exposed to TCDD should be equipped with adequate chemical protective clothing and equipment to ensure their protection. In the selection of protective clothing, consideration should be given to the utilization of disposable apparel due to the uncertainty of decontamination of clothing.

The protective apparel should consist of both outer and inner garments. The outer garments should consist of a zippered coverall with attached hood and draw string or elastic sleeves, gloves and closure boots. If exposure is to particulate or dust, the coveralls should be made of a non-woven fabric such as spunbonded polyethylene, Tyvek®. In cases of exposure to liquids, the coveralls, gloves and boots should be made of chemically resistant materials such as disposable laminates, e.g., Saranax® coated Tyvek®, or synthetic elastomers such as butyl, nitrile or neoprene rubber. The inner garments should consist of cotton coveralls, undershirts, undershorts, gloves, and socks and should be disposed of after use. The effectiveness of the protective clothing should be evaluated under simulated use conditions, regardless of the type of clothing used. All disposable clothing should be placed in marked and approved containers and disposed of appropriately. All reusable clothing and equipment should be thoroughly cleaned and checked for residual contamination before reuse or storage.

Respiratory Protection

The use of respiratory protection requires that a respiratory protection program be instituted according to the requirements of 29 CFR 1910.134 [88] and that the respirators have been approved by the Mine Safety and Health Administration (MSHA) and by NIOSH. This program should include training on proper fit testing and use and procedures for respirator maintenance, inspection, cleaning and evaluation.

For situations where TCDD contamination is low (e.g., exposure to dust contaminated with low levels of TCDD), air purifying respirators should provide sufficient protection until the extent and characterization of the exposure can be determined. Where quantities of materials highly contaminated with TCDD have been released and have contaminated an area (e.g., production accidents), all workers who may be exposed to TCDD should wear respirators that consist of a self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode. An alternate method utilizes a combination Type C supplied air respirator, with full facepiece, operated in pressure-demand mode and equipped with auxiliary positive pressure self-contained air supply.

Post-Decontamination Testing

The adequacy of the decontamination effort should be determined by conducting follow-up sampling and analysis of the contaminated areas and protective equipment. This testing should be conducted as each area is decontaminated and after the entire facility has been cleaned.

REFERENCES

1. Crosby DG, Moilanen KW, Wong AS: Environmental generation and degradation of dibenzodioxins and dibenzofurans. Environ Health Perspect 5:259-266 (1973).

2. Crummett WB, Stehl RH: Determination of chlorinated dibenzo-p-dioxins and dibenzofurans in various materials. Environ Health Perspect 5:17-25 (1973).

3. National Research Council of Canada: Polychlorinated Dibenzo-p-dioxins: Criteria for Their Effects on Man and His Environment. Pub. No. NRCC 18574: NRCC/CNRC Assoc. Comm. on Scientific Criteria for Environmental Quality, Ottawa, Canada (1981).

4. Hay A: Accidents in trichlorophenol plants: A need for realistic surveys to ascertain risks to health. Ann NY Acad Sci 320:321-324 (1979).

5. Firestone D, Ress J, Brown NL, et al.: Determination of polychlorodibenzo-p-dioxins and related compounds in commercial chlorophenols. J Assn Off Anal Chem 55(1):85-92 (1972).

6. Stehl RH, Lamparski LL: Combustion of several 2,5,5-trichlorophenoxy compounds: Formation of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Science 197:1008-1009 (1977).

7. Rappe C, Marklund S: Formation of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) by burning or heating chlorophenates. Chemosphere 3:269-281 (1978).

8. Bumb RR, Crummett WB, Cutie SS, et al.: Trace chemistries of fire: A source of chlorinated dioxins. Science 210(4468):385-389 (1980).

9. Kimble BJ, Gross ML: Tetrachlorodibenzo-p-dioxin quantitation in stack-collected coal fly ash. Science 207:59-61 (1980).

10. Federal Register, Environmental Protection Agency, Part III, 44(52):15874-15920 (March 15, 1979).

11. Federal Register, Environmental Protection Agency, Part X, 48(202):48434-48437 (October 18, 1983).

12. McConnell EE, Moore JA, Haseman JK, et al.: The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. Toxicol Appl Pharmacol 44:335-356 (1978).

13. Henck JM, New MA, Kociba RJ, et al.: 2,3,7,8-tetrachlorodibenzo-p-dioxin: Acute oral toxicity in hamsters. Toxicol Appl Pharmacol 59:405-407 (1981).

14. McConnell EE, Moore JA, Dalgard DW: Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Rhesus monkeys (Macaca mulatta) following a single oral dose. Toxicol Appl Pharmacol 43:175-187 (1978).

15. Kociba RJ, Keiler PA, Park CN, et al.: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD): Results of a 13-week oral toxicity study in rats. Toxicol Appl Pharmacol 35:553-574 (1976).

16. Gupta GN, Vos JG, Moore JA, et al.: Pathologic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Environ Health Perspect 5:125-140 (1973).

17. Kimbrough RD: Morphology of lesions produced by the dioxins and related compounds. In: Tucker RE, ed.: Human and Environmental Risks of Chlorinated Dioxins and Related Compounds. Proceedings of an international symposium on chlorinated dioxins and related compounds, held October 25-29, 1981, in Arlington, Virginia. pp. 527-538 (1983).

18. Matthiaschk G: Survey about toxicological data of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In: Paoletti R, ed.: Monographs of the Giovanni Lorenzini Foundation, Volume 1, Dioxin: Toxicological and Chemical Aspects. pp. 123-136 (1978).

19. Poland A, Glover E: 2,3,7,8-tetrachlorodibenzo-p-dioxin: A potent inducer of delta-aminolevulinic acid synthetase. Science 179:476-477 (1973).

20. Poland A, Glover E: Studies on the mechanism of toxicity of the chlorinated dibenzo-para-dioxins. Environ Health Perspect 5:245-251 (1973).

21. Weissberg JB, Zinkl JG: Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin upon hemostasis and hematologic function in the rat. Environ Health Perspect 5:119-123 (1973).

22. Zinkl JG, Vos JG, Moore JA, et al.: Hematologic and clinical chemistry effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Environ Health Perspect 5:111-118 (1973).

23. Vos JG, Moore JA, Zinkl JG: Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in C57B1/6 mice. Toxicol Appl Pharmacol 29:229-241 (1974).

24. Courtney KD, Moore JA: Teratology studies with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Appl Pharmacol 20:396-403 (1971).

25. Smith FA, Schwetz BA, Nitschke KD: Teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in CF-1 mice. Toxicol Appl Pharmacol 38:517-523 (1976).

26. Moore JA, Gupta BN, Zinkl JN, et al.: Postnatal effects of maternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Environ Health Perspect 5:81-85 (1973).

27. Sparschu GL, Dunn FL, Rowe VK: Study of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Fd Cosmet Toxicol 9:405-412 (1971).

28. Khera KS, Ruddick JA: Polychlorodibenzo-p-dioxins: Perinatal effects and the dominant lethal test in Wistar rats. Toxicology 120:70-84 (1973).

29. Murray FJ, Smith FA, Nitschke KO, et al.: Three generation reproduction study of rats given 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the diet. Toxicol Appl Pharmacol 50(2):241-252 (1979).

30. Lamb JC IV, Moore JA, Marks TA, et al.: Development and viability of offspring of male mice treated with chlorinated phenoxy acids and 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Toxicol Environ Health 8:835-844 (1981).

31. Lamb JC IV, Marks TA, Gladen BC, et al.: Male fertility, sister chromatid exchange, and germ cell toxicity following exposure to mixtures of chlorinated phenoxy acids containing 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Toxicol Environ Health 8:825-834 (1981).

32. Luster MI, Faith RE, Clark G: Laboratory studies on the immune effects of halogenated aromatics. Ann NY Acad Sci 320:473-486 (1979).

33. Vos JG, Moore JA: Suppression of cellular immunity in rats and mice by maternal treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Int Arch Allergy Appl Immunol 47:777-794 (1974).

34. Garattini S, Vecchi A, Sironi M, et al.: Immunosuppressant activity of TCDD in mice. In: Hutzinger O, ed.: Chlorinated Dioxins and Related Compounds: Impact on the Environment. Proceedings of a workshop, Institute Superiore di Sanita, Rome, Italy, held 22-24 October 1980. pp. 403-409 (1982).

35. Hussain S, Ehrenberg L, Lofroth G, et al.: Mutagenic effects of TCDD on bacterial systems. Ambio 1:32-33 (1972).

36. Seiler JP: A survey on the mutagenicity on various pesticides. Experimenta 15(5):622-623 (1973).

37. Geiger LE, Neal RA: Mutagenicity testing of 2,3,7,8-tetrachlorodibenzo-p-dioxin in histidine auxotrophs of Salmonella typhimurium. Toxicol Appl Pharmacol 59:125-129 (1981).

38. Green S, Moreland F, Sheu C: Cytogenic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on rat bone marrow cells. FDA By-Lines 6:242-294 (1977).

39. Loprieno N, Sbrana I, Rusciano D, et al.: In vivo cytogenic studies on mice and rats exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In: Hutzinger O, ed.: Chlorinated Dioxins and Related Compounds: Impact on the Environment. Proceedings of a workshop, Institute Superiore di Sanita, Rome, Italy, held 22-24 October 1980. pp. 419-428 (1982).

40. Van Miller JP, Lalich JJ, Allen JR: Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere 9:537-544 (1977).

41. Kociba RJ, et al.: Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol Appl Pharmacol 46:279-303 (1978).

42. National Toxicology Program: Technical Report Series No. 209. Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Osborn-Mendel Rats and B6C3F$_1$ Mice (Gavage Study). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health Publication No. 82-1765, (February 1982).

43. National Toxicology Program: Technical Report Series No. 201. Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Swiss-Webster Mice (Dermal Study). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health Publication No. 82-1757, (February 1982).

44. Crow KD: Chloracne. Semin Dermatol 1(4):305-313 (1982).

45. Jones EL, Krizek H: A technic for testing acnegenic potency in rabbits, applied to the potent acnegen, 2,3,7,8-tetrachlorodibenzo -p-dioxin. J Invest Dermatol 39:511-517 (1962).

46. May G: Chloracne from the accidental production of tetrachlorodibenzodioxin. Br J Ind Med 30:276-283 (1973).

47. Goldmann PJ: [Severe acute chloracne. A mass intoxication by 2,3,6,7-tetrachlorobenzodioxin]. Hautarzt 24:149-152 (1973) (Ger.).

48. Reggiani G: Acute human exposure to TCDD in Seveso, Italy. Toxicol Environ Health 6:27-43 (1980).

49. Pocchiari F, Silano V, Zampieri A: Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. Ann NY Acad Sci 320:311-320 (1979).

50. Pazderova-Vejlupkova J, Nemcova M, Pickova J, et al.: The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Arch Environ Health 36(1):5-11 (1981).

51. Singer R, Moses M, Valciukas J, et al.: Nerve conduction velocity studies of workers employed in the manufacture of phenoxy herbicides. Environ Res 29:297-311 (1982).

52. Oliver RM: Toxic effects of 2,3,7,8 tetrachlorodibenzo 1,4 dioxin in laboratory workers. Br J Ind Med 32:49-53 (1975).

53. Caramashi F, Del Corono G, Favaretti C, et al.: Chloracne following environmental contamination by TCDD in Seveso, Italy. Int J Epidemiol 10(2):135-143 (1981).

54. Kimbrough RD, Carter CD, Liddle JA, et al.: Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode. Arch Environ Health 32(2):77-85 (1977).

55. Smith AH, Matheson DP, Fisher DO: Preliminary report of reproductive outcomes among pesticide applicators using 2,4,5-T. NZ Med J 93(680):177-179 (1981).

56. Smith AH, Fisher DO, Pearce N, et al.: Congenital defects and miscarriages among New Zealand 2,4,5-T sprayers. Arch Environ Health 37(4):197-200 (1982).

57. Townsend JC, Bodner KM, Van Peenen PFD, et al.: Survey of reproductive events of wives of employees exposed to chlorinated dioxins. Amer J Epidemiol 115(5):695-713 (1982).

58. Field B, Kerr C: Herbicide use and incidence of neural tube defects. Lancet I (June 23):1341-1342 (1979).

59. Thomas HF: 2,4,5-T use and congenital malformation rates in Hungary. Lancet I (July 26):214-215 (1980).

60. Rehder H, Sanchoni L, Cefis F, et al.: [Pathologic-Embryologic studies in cases of abortion connected with the accident at Seveso]. Schweiz Med Wochenschr 108(42):1617-1625 (1978) (Ger.).

61. Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practices. Environmental Protection Agency. Prepared by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Benefits and Field Studies Division, OPP, OTS, EPA, (1979).

62. Wagner S, Witt JM, Norris LA, et al.: A Scientific Critique of the EPA ALSEA II Study and Report. Environmental Health Sciences Center, Oregon State University, Corvallis, (October 25, 1979).

63. Axelson O, Sundell L: Herbicide exposure, mortality, and tumor incidence: An epidemiological investigation on Swedish railroad workers. Work Environ Health 11:21-28 (1974).

64. Axelson O, Sundell L, Andersson K, et al.: Herbicide exposure and tumor mortality: An updated epidemiologic investigation on Swedish railroad workers. Scand J Work Environ Health 6:73-79 (1980).

65. Hogstedt C, Westerlund B: [Mortality of forest workers exposed and not exposed to phenoxy acid preparations.] Lakartidningen 77(19):1828-1831 (1980) (Swe.).

66. Thiess AM, Frentzel-Beyme R, Link R: Mortality study of persons exposed to dioxin in a trichlorophenol-process accident that occurred in the BASF AG on November 17, 1953. Am J Ind Med 3:179-189 (1982).

67. Hardell L: [Malignant mesenchymal tumors and exposure to phenoxy acids: A clinical observation.] Lakartidningen 74:2753-2754 (1977) (Swe.).

68. Hardell L, Sandstrom A: Case control study: Soft tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer 39:711-717 (1979).

69. Eriksson M, Hardell L, Berg NO, et al.: [Case-control study on malignant mesenchymal tumors of the soft parts and exposure to chemical substances.] Lakartidningen 76:3872-3875 (1979) (Swe.).

70. Hardell L: Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. Lancet I (January 6):55-56 (1979).

71. Hardell L, Eriksson M, Lenner P, et al.: Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. Br J Cancer 43:169-176 (1981).

72. Hardell L: Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. Scand J Work Environ Health 7:119-130 (1981).

73. Hardell L, Johansson B, Axelson O: Epidemiological study of nasal and nasopharyngeal cancer and their relation to phenoxy acid of chlorophenol exposure. Am J Ind Med 3:247-257 (1982).

74. Zack JA, Suskind RR: The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. J Occup Med 22(1):11-14 (1980).

75. Ott MG, Holder BB, Olson RD: A mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid. J Occup Med 22(1):47-50 (1980).

76. Cook RR, Townsend JC, Ott MG, et al.: Mortality experience of employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J Occup Med 22(8):530-532 (1980).

77. Honchar PA, Halperin WE: 2,4,5-trichlorophenol and soft tissue sarcoma. Lancet I (January 31):268-269 (1981).

78. Cook RR: Dioxin, chloracne, and soft tissue sarcoma. Lancet I (March 1):618-619 (1981).

79. Moses M, Selikoff IJ: Soft tissue sarcomas, phenoxy herbicides, and chlorinated phenols. Lancet I (June 20):1370 (1981).

80. Johnson FE, Kugler MA, Brown SM: Soft tissue sarcomas and chlorinated phenols. Lancet II (July 4):40 (1981).

81. Fingerhut MA, Halperin WE: Dioxin exposure and sarcomas. JAMA 249(23):3176 (1983).

82. Statement by J. Donald Millar, M.D., Assistant Surgeon General, Director, National Institute for Occupational Safety and Health, Centers for Disease Control, Public Health Service, Department of Health and Human Services, Before the United States House of Representatives Committee on Public Works and Transportation Subcommittee on Investigations and Oversight. (November 9, 1983).

83. Matthews HB: NTP Technical Report on the Toxicity and Carcinogenicity of Tris(2-ethylhexyl)phosphate (Cas. No. 78-42-2) in F344/N rats and B6C3F$_1$ mice (gavage study), National Toxicology Program, Research Triangle Park, North Carolina, p. 4, (unpublished report, September 8, 1983).

84. World Health Organization: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. IARC Monographs, Supplement 1 (1979).

85. Code of Federal Regulations, U.S. Department of Labor, Occupational Safety and Health Administration, 29 CFR 1990.103 (1982).

86. Health Hazard Evaluation - Determination Report No. 83-395, Overnight Transportation Company, St. Louis, Missouri. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio (1983).

87. Health Hazard Evaluation - Determination Report No. 83-394, P.J. Hamil Transfer Company, St. Louis, Missouri. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio (1983).

88. Code of Federal Regulations, U.S. Department of Labor, Occupational Safety and Health Administration, 29 CFR 1910.134 (1982).

CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS

1.	Chloroprene	- January 20, 1975
2.	Trichloroethylene (TCE)	- June 6, 1975
3.	Ethylene Dibromide (EDB)	- July 7, 1975
4.	Chrome Pigment	- June 24, 1975
		- October 7, 1975
		- October 8, 1976
5.	Asbestos - Asbestos Exposure during Servicing of Motor Vehicle Brake and Clutch Assemblies	- August 8, 1975
6.	Hexamethylphosphoric Triamide (HMPA)	- October 24, 1975
7.	Polychlorinated Biphenyls (PCB's)	- November 3, 1975
		- August 20, 1976
8.	4,4'-Diaminodiphenylmethane (DDM)	- January 30, 1976
9.	Chloroform	- March 15, 1976
10.	Radon Daughters	- May 11, 1976
11.	Dimethylcarbamoyl Chloride (DMCC) Revised	- July 7, 1976
12.	Diethylcarbamoyl Chloride (DECC)	- July 7, 1976
13.	Explosive Azide Hazard	- August 16, 1976
14.	Inorganic Arsenic - Respiratory Protection	- September 27, 1976
15.	Nitrosamines in Cutting Fluids	- October 6, 1976
16.	Metabolic Precursors of a Known Human Carcinogen, Beta-Naphthylamine	- December 17, 1976
17.	2-Nitropropane	- April 25, 1977
18.	Acrylonitrile	- July 1, 1977
19.	2,4-Diaminoanisole in Hair and Fur Dyes	- January 13, 1978
20.	Tetrachloroethylene (Perchloroethylene)	- January 20, 1978
21.	Trimellitic Anhydride (TMA)	- February 3, 1978
22.	Ethylene Thiourea (ETU)	- April 11, 1978
23.	Ethylene Dibromide and Disulfiram Toxic Interaction	- April 11, 1978
24.	Direct Black 38, Direct Blue 6, and Direct Brown 95 Benzidine Derived Dyes	- April 17, 1978
25.	Ethylene Dichloride (1,2-Dichloroethane)	- April 19, 1978
26.	NIAX Catalyst ESN	- May 22, 1978
27.	Chloroethanes - Review of Toxicity	- August 21, 1978
28.	Vinyl Halides - Carcinogenicity	- September 21, 1978
29.	Glycidyl Ethers	- October 12, 1978
30.	Epichlorohydrin	- October 12, 1978
31.	Adverse Health Effects of Smoking and the Occupational Environment	- February 5, 1979
32.	Arsine (Arsenic Hydride) Poisoning in the Workplace	- August 3, 1979
33.	Radiofrequency (RF) Sealers and Heaters: Potential Health Hazards and Their Prevention	- December 4, 1979
34.	Formaldehyde: Evidence of Carcinogenicity	- April 15, 1981

CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS (CONTINUED)

35.	Ethylene Oxide (EtO): Evidence of Carcinogenicity	- May 22, 1981
36.	Silica Flour: Silicosis	- June 30, 1981
37.	Ethylene Dibromide (EDB) Revised	- October 26, 1981
38.	Vibration Syndrome	- March 29, 1983
39.	The Glycol Ethers, with Particular Reference to 2-Methoxyethanol and 2-Ethoxyethanol: Evidence of Adverse Reproductive Effects	- May 2, 1983
40.	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, "Dioxin")	- January 23, 1984

NOTE: Bulletins #1 through #18 and #19 through #30 have been reprinted as NIOSH publications, #78-127 and #79-146 respectively, for the convenience of those that desire a complete series of Current Intelligence Bulletins. Distribution of these publications and single copies of Bulletins #31 and later are available from NIOSH Publications Dissemination, Division of Standards Development and Technology Transfer, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

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