FINAL REPORT

EVALUATION OF THE PERIPHERAL NERVOUS SYSTEM AMONG WORKERS EMPLOYED IN THE PRODUCTION OF CHEMICALS CONTAMINATED WITH 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

Marie Haring Sweeney, Ph.D.
Marilyn A. Fingerhut, Ph.D.
L. Barbara Connally, B.S.
Richard Hornung, Dr. P.H.

Industrywide Study Branch
Division of Surveillance, Hazard Evaluations, and Field Studies
National Institute of Occupational Safety and Health

July, 1990

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3. PB92-206069

4. Title and Subtitle: Evaluation of the Peripheral Nervous System among Workers Employed in the Production of Chemicals Contaminated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin

5. Report Date: 1990/07/00

6.

7. Author(s): Sweeney, M. H., M. A. Fingerhut, L. B. Connally, and R. Hornung

8. Performing Organization Rept. No.

9. Performing Organization Name and Address: Industrywide Study Branch, Division of Surveillance, Hazard Evaluations and Field Studies, NIOSH

10. Project/Task/Work Unit No.

11. Contract (C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words): The long term effects on the peripheral nervous system in workers with past exposure to production products contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (1746016) (TCDD) were evaluated. The severity of the current neurologic status was compared to the levels of TCDD measured in the serum of study subjects. Workers who were employed at two chemical factories at which chemicals contaminated with TCDD were manufactured, and a group of unexposed referents were assessed in a cross sectional medical study in 1987 through 1988. Questionnaires were used to collect follow-up data. There were 281 workers and 260 referents who were interviewed and medically examined. Peripheral neuropathy was found in about 18% of workers and 19% of referents. Serum TCDD levels ranged from 2 to 3390 parts per trillion (ppt) for 272 workers and from 2 to 20ppt for 86 referents tested. No dose-response relationship was observed between TCDD levels present at the time of the examination and the occurrence of peripheral neuropathy in this previously exposed population. The authors conclude that exposure to TCDD caused no excess chronic peripheral neuropathy in a group of exposed workers compared to unexposed referents.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms: NIOSH-Publication, NIOSH-Author, Toxic-effects, Neurotoxic-effects, Environmental-pollution, Herbicides, Agricultural-chemicals, Chemical-industry-workers, Epidemiology, Occupational-exposure

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages 323
	22. Security Class (This Page)	22. Price

(See ANSI-Z39.18) *See Instructions on Reverse*

OPTIONAL FORM 272(4-77)
(Formerly NTIS-35)
Department of Commerce

ACKNOWLEDGEMENT

There are many individuals who have supported and contributed to this effort. I thank Joseph Arezzo for his guidance in the analysis of the neurologic data, and Julie Tolbert for final manuscript preparation and Geoffrey for his thoughtful input. I would also like to extend my appreciation to Richard Hornung and James Morris for statistical advice, to Frances Guerra, Kathy Masterson, Mary Torok and Mary Chung for typing assistance, to Jolene Schoettelkotte, Steve Adams, Brent Tompkins and Lance Cameron for data management and programming assistance, and to Becky Swartz for clerical support.

TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF APPENDICES

Appendix

CHAPTER I

INTRODUCTION

Summary Description of the Substance of Interest

Over the past several decades researchers have investigated the effects of exposure to materials contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). Dioxins constitute a class of 75 isomers of tricyclic chlorinated phenoxy compounds. Of 22 known tetrachlorodibenzodioxin isomers, 2,3,7,8-tetra chlorodibenzo-p-dioxin (2,3,7,8-TCDD) is most comprehensively studied and is considered to be the most toxic of the chlorinated phenoxy compounds (Kociba and Schwetz, 1982).

2,3,7,8-TCDD is a common environmental contaminant. Release of 2,3,7,8-TCDD into the environment has occurred due to use of contaminated herbicides, due to distribution of contaminated effluent from industrial production of 2,4,5-trichlorophenol (TCP) 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) and hexachlorophene,

and from accidents associated with such processes (Esposito, 1980). Pulp bleaching operations, scrap metal reclamation processes, magnesium and nickels refining operations, incineration of municipal and industrial wastes, combustion of fossil fuels and other materials containing chlorine are also responsible for occurrence of 2,3,7,8-TCDD and consequent environmental pollution (NATO, 1988).

Occupational exposure to 2,3,7,8-TCDD occurred during the production of TCP or 2,4,5-T or while handling contaminated waste products or during the clean-up of TCP reactor accidents. Other modes of exposure to dioxins and dibenzofurans not described in this study are illustrated in Table 1 (Dunigan, 1984).

Summary Description of the Health Effects of Exposure to 2,3,7,8-TCDD

Animal toxicologic evidence reveals a wide variation of effects due to exposure to 2,3,7,8-TCDD which are dependent upon animal species, dose and length of exposure. The general classes of effects include debilitation and wasting (Allen et al, 1977; Moore et al, 1979), hepatotoxicity (Greig et al, 1973), thymic atrophy (Vecchi et al, 1983; Luster et al, 1982) immunosuppression (Vecchi et al, 1983), hematologic changes (Weissberg and Zinkl et al, 1973), dermatologic effects (Jones and Kizek, 1962; Kimmig and Schulz, 1957), lipid (Poli et al, 1980; Schiller et al, 1986) and glucose alterations (Schiller et al, 1986), carcinogenesis (Pitot

et al, 1980; Toth et al, 1979; Kociba et al, 1978; National Toxicology Program, 1982b), teratogenesis, and fetotoxicity (Courtney and Moore, 1971; Moore et al, 1979). No neurologic effects have been noted in test animals as a result of exposure to 2,3,7,8-TCDD. A review of effects observed in animal toxicologic studies is in Appendix A and in Tables 36-50.

The most frequent condition described in humans involves the skin, and less frequently disturbances of the neurologic system, liver, gastrointestinal, genitourinary, cardiovascular, pulmonary and immunologic systems as well as increased incidence of some malignancies and adverse reproductive effects. These findings are described in detail below. The majority of effects were reported among occupationally exposed groups and among residents of communities contaminated with tainted waste oil (Missouri) and industrial effluent (Seveso, Italy).

Introduction to the Study

Effects of the peripheral nervous system (PNS) represent consistent findings of previous case reports and studies of workers and community residents exposed to 2,3,7,8-TCDD contaminated materials. The goal of this report is to evaluate the potential long-term effects on the peripheral nervous system in workers with past exposure to production products contaminated with 2,3,7,8-TCDD. A second goal is to relate the severity of the

current neurologic status to the levels of 2,3,7,8-TCDD measured in the serum of study subjects.

This analysis of neurologic effects was conducted as part of a comprehensive cross-sectional epidemiologic study of workers previously employed in the production of sodium-TCP, 2,4,5-T or hexachlorophene. The study was designed to evaluate the long-term health effects of occupational exposure to chemicals and materials contaminated with 2,3,7,8-TCDD.

CHAPTER II

LITERATURE REVIEW

Chemistry of 2,3,7,8-Tetrachlorodibenzo-p-dioxin

The dioxins are a class of 75 isomers of tricyclic chlorinated phenoxy compounds. There are 22 known tetrachlorodibenzodioxin isomers of which 2,3,7,8-tetra chlorodibenzo-p-dioxin (2,3,7,8-TCDD) has been most comprehensively studied. Based on animal toxicological studies, 2,3,7,8-TCDD is currently considered to be the most toxic of the chlorinated phenoxy compounds (McConnell et al, 1978b). 2,3,7,8-TCDD ($C_{12}H_4Cl_4O_4$; MW=321.9) is a lipophilic, chemically stable compound of low volatility (estimated vapor pressure 1.7×10^{6}) and high melting point (305-306° C) (Esposito et al, 1980). Environmental degradation of 2,3,7,8-TCDD is most likely through photolysis, perhaps volatilization. Based on data generated after the Seveso

accident, the half-life of 2,3,7,8-TCDD in soil is estimated to be 10-12 years (Young et al, 1983; Wipf et al, 1983). When exposed to UV light, as in surface soil, degradation is less than one year. The estimated half-life in non-human mammalian systems ranges from 10.8 days in the hamster to 365 days in the monkey (Olson at al, 1980; McNulty et al, 1977.) For humans, the data on the rate of elimination is sparse. To date, two studies have suggested the rate to be 5.1 and 7.2 years (Pirkle et al, 1989; Poiger and Schlatter, 1985); however, there is some speculation indicating that there maybe considerable inter-individual variation in the elimination rate of 2,3,7,8-TCDD in the human population (Pirkle et al, 1989).

The synthesis of chlorophenols and certain other halogenated aromatic hydrocarbons is a major source of dioxins. Specifically, the 2,3,7,8-TCDD isomer is generated as a contaminant during the production of a chemical feedstock 2,4,5-trichlorophenol, from the reaction of tetrachlorobenzene and caustic (NaOH) (Esposito et al., 1980). It is estimated that greater amounts of the contaminant were produced as the reactor temperatures were increased above 180°C and pressures increased above 7KPa (Kilo Pascals) (Rappe and Buser, 1980). Unless removed, the 2,3,7,8-TCDD is passed on to the end products such as 2,4,5 trichlorophenoxyacetic acid (2,4,5-T), 2,4,5-T esters, 2,4,5-T amines, 2-(2,4,5 trichlorophenoxy) proprionic acid (Silvex), Silvex esters and amines, and hexachlorophene. In the United States, from

the mid-1930's until 1979, when the US EPA restricted the use of 2,4,5-T, these dioxin-contaminated chemicals had widespread industrial and environmental applications as defoliants, herbicides, fungicides and miticides (Esposito et al, 1980). Other sources of dioxins are described in a review recently published by the North Atlantic Treaty Organization (NATO, 1988).

Animal Studies: Animal Toxicologic Studies of the Effects of 2,3,7,8-TCDD on the Peripheral Nervous System

The literature is replete with studies describing the toxicologic effects of exposure to 2,3,7,8-TCDD. In these studies, researchers have observed wide interspecies variation in the nature and severity of the observed effects. Despite these differences, common effects have been noted. The general classes of common effects include weight loss, liver cell changes and enzymatic alterations, thymic atrophy and immunologic disturbances, carcinogenesis, teratogenesis and fetotoxicity. To date, no neurologic effects due to exposure to 2,3,7,8-TCDD have been reported in any species.

Currently, there are many extensive reviews of the toxicologic properties of 2,3,7,8-TCDD (Esposito et al., 1980; Poland and Knutsen, 1982; Shu et al, 1988; McConnell, 1989; Goldstein and Safe, 1989; Holder and Menzel, 1989). Appendix A briefly describes some of the major outcomes observed in animal toxicology studies including lethality, weight loss, dermatologic, hepatic, immunologic and reproductive effects. Details of the studies including species, dose and effects are also described in tables IIB.1 through IIB.14.

Human Studies: Effects of Exposure to Substances Contaminated with 2,3,7,8-TCDD on the Peripheral Nervous System

Several comprehensive reviews describing the health effects of exposure to 2,3,7,8-TCDD have been recently published (Kimbrough et al, 1980; IARC, 1986: Fingerhut et al, 1987. The information describing human health effects attributed to exposure to 2,3,7,8-TCDD contaminated materials is derived from wide variety of sources including clinical assessments (case reports) of exposed individuals and analytic epidemiologic studies using case-control, cross-sectional and cohort mortality designs. The case reports describe the acute outcomes of exposure to

2,3,7,8-TCDD and provide the bases for hypothesis generation for controlled epidemiologic studies, but they are not suitable for testing causal relationships between exposure and related health effects (Ashe and Suskind, 1950; Suskind et al, 1953; Bauer et al, 1961; Goldman, 1973). Several cross-sectional studies which included a medical examination of potentially exposed workers attempted to quantify the long-term risk of exposure (Suskind and Hertzberg, 1984; Lathrop et al, 1984; Lathrop et al, 1987; Singer et al, 1984). These three studies used unexposed control groups for comparison and have attempted to quantify exposure. However, they have been unable to relate exposure to materials contaminated with 2,3,7,8-TCDD with specific diseases or causes of death. This inability to define an exposure-outcome relationship is due to a variety of shortcomings in the studies, including small sample size, poor participation, short latency periods, selection of inappropriate controls, and the inability to quantify exposure to 2,3,7,8-TCDD or to identify confounding exposures. A thorough review of the limitations of the available epidemiologic literature relating to exposure to 2,3,7,8-TCDD was recently published by Fingerhut et al (Fingerhut et al, 1987).

The most frequently described 2,3,7,8-TCDD exposure-associated conditions in humans involve the skin, liver, and neurologic systems, and less frequently, disturbances of the gastrointestinal, genitourinary, cardiovascular, pulmonary and immunologic systems as well as increased incidence of some malignancies. The majority of

effects were reported among occupationally exposed groups, including chemical production workers, pesticide users and individuals handling or exposed to materials which have been treated with 2,3,7,8-TCDD contaminated pesticides, and among residents of communities contaminated with tainted waste oil (Missouri) and industrial effluent (Seveso, Italy).

The following section contains a review of the case reports and epidemiologic studies which document occurrences of impairment of the peripheral nervous system after occupational exposure to materials contaminated with 2,3,7,8-TCDD. A description of studies documenting health effects other than peripheral nervous system disorders is included as Appendix B.

Effects of 2,3,7,8-TCDD on the Peripheral Nervous System: Case reports

Although there are no studies reporting neurologic abnormalities related to 2,3,7,8-TCDD exposure in animal models, neurological effects are reported to have occurred shortly after exposure occupationally exposed individuals (Ashe and Suskind, 1950; Baader and Bauer, 1951; Bauer et al, 1961; Goldman, 1973; Jirasek et al, 1974; Oliver, 1975; Pocchiari et al, 1979) and in residents of one community following an industrial accident which released substances into the atmosphere (Filippini et al, 1981) (Table 2).

Among worker populations, symptoms and conditions reported immediately after exposure include fatigue (Ashe and Suskind, 1950; Suskind et al, 1953; Kimmig and Schulz, 1957; Bauer et al, 1961; Goldman, 1973; Jirasek et al, 1974), pain (Ashe and Suskind, 1950; Baader and Bauer, 1951; Jirasek et al, 1974; Oliver, 1975), weakness (Baader and Bauer, 1951; Bauer et al, 1961) or reduction in muscle coordination in upper and lower extremities (Ashe and Suskind, 1950; Baader and Bauer, 1951; Bauer et al, 1961; Goldman, 1973; Jirasek et al, 1974; Oliver, 1975; Poland et al, 1971), absence (Ashe and Suskind, 1950), reduction, or alteration in sensory function (Baader and Bauer, 1951; Bauer et al, 1961; Goldman, 1973) or motor function (Goldman, 1973; Oliver, 1975), decreased deep tendon reflex (Kimmig and Schulz, 1957; Poland et al, 1971), hyperactive deep tendon reflex (Ashe and Suskind, 1950; Goldman, 1973) and degeneration of distal axons (Ashe and Suskind, 1950). Several authors also observed altered sense of taste (Goldman, 1973; Oliver, 1975), hearing (Goldman, 1973; Kimmig and Schulz, 1957; Poland et al, 1971) and smell (Goldman, 1973; Poland et al, 1971). Two individuals reported changes in the visual field; however, there is no clinical evidence to support this information (Oliver, 1975).

A few reports indicate that signs and symptoms of peripheral nerve diseases may persist in some exposed individuals and may last for as long as 25 years post-exposure (Suskind et al, 1953; Poland et al 1971; Moses et al, 1984; Jirasek et al, 1974; Pazderova-

Vejlupkova et al, 1981). In 1953, Suskind reported a variety of neurologically related symptoms in 36 workers from a plant in Nitro, West Virginia, who had developed chloracne and other symptoms after exposure to contaminants subsequent to a TCP reactor explosion in March, 1949 (N=11), or during normal production process of TCP and 2,4,5-T (N=25) between 1948 and 1953 (Suskind et al, 1953). The most frequently reported post-exposure symptoms in this relatively young group (average age=36 years; range = 22-63 years) included frequent pain or aches in upper and lower extremities (N=19), abnormal fatigue (N=17), and nervousness (N=8). Whether these symptoms also occurred among other exposed individuals with or without chloracne or among the nonexposed plant population was not investigated.

In 1971, Poland and colleagues (1971) found some evidence of neurologic damage in a medical assessment of 73 male employees, who at the time of the assessment were working with TCP, 2,4,5-T, 2,4-D and other chemicals. The findings included unexplained leg fatigue (2.7%), nonspecific headaches (11%), decreased auditory acuity (13.6%), and decreased proprioception, absent Achilles tendon reflexes or hand tremors (10.9%). However, this analysis is limited by the absence of an unexposed control group. In addition, there was no control of potential confounders of peripheral nerve disease.

Between 1968 and 1969, Jirasek et al (1974) examined 55 workers who were engaged in the production of sodium 2,4,5-trichloro-phenoxyacetate and butyl ester of 2,4,5-trichlorophenoxyacetate acid and who were described as "suffering from chronic TCDD intoxication". The length of time these workers were exposed to 2,3,7,8-TCDD contaminated chemicals, their job duties and frequency of exposure were not described. All workers were administered repeated neurological examinations (the number was not specified). The examinations included electromyographic (EMG) evaluation of sensory and motor fibers of upper and lower extremities (tested nerves were not specified). Other components of the neurologic examination were not described. Onset of neurologic symptoms which included a "feeling of sickness", fatigue, weakness in the lower extremities were gradual, appearing in 10 workers several months after completion of work in 2,3,7,8-TCDD contaminated processes. The appearance of clinical signs of neuropathies continued over a period of three to four years post-exposure. Sixty-two percent of the workers had normal neurological examinations, 23% (N=13) were diagnosed with polyneuropathy of the lower limbs, 7% suffered from encephalopathy and 8% experienced unspecified pathologic changes which the authors suggested were not due to exposure.

Ten years after the initial examination, Pazderova-Vejlupkova et al (1981) reevaluated the health status of 44 of the original 55 workers and found that although three workers showed improvement, 31% (N=14) had evidence of polyneuropathy.

The published reports summarized above describe neurologic dysfunction among individuals who were exposed to 2,3,7,8-TCDD during the production of TCP and 2,4,5-T. None of the reports were designed as studies with unexposed control groups for comparison. In addition, the reports did not (and perhaps, could not) assess extent of exposure in relation to health outcomes. Other limitations include the absence of a standard procedure for conducting clinical examinations and little or no evaluation of potential confounders of peripheral neuropathy. However, the reports play an important role in the identification of potential hazards of exposure to materials contaminated with 2,3,7,8-TCDD and generate the hypotheses required for epidemiologic investigations.

Cross-sectional studies

Occupational exposure

In 1979, many years after the 1949 TCP reactor explosion in Nitro, W.V. and the 1950 and 1953 investigations by Suskind, a neurological assessment was conducted on a volunteer sample of workers from the same plant in Nitro, West Virginia (Moses et al, 1984) (Table 3). Whether any of the 36 workers examined by Suskind in 1950 and 1953 was included in the Moses study was not stated. Moses found a statistically significant ($p < 0.01$) reduction in sensory function measured by sensitivity to pinprick among those with current cases of chloracne. This group also included one

individual involved in the clean-up of the 1949 accident, who presented with absent deep tendon reflexes of the lower limb, accompanied by reduced sensation to pain and vibration and motor weakness.

The Moses study was designed as a cross-sectional epidemiologic study to assess the effect of past exposure to dioxin-contaminated products on current health. Despite the intent of the design to evaluate the differences between exposed and unexposed workers, there are methodological limitations which reduce the reliability of the results. No details of the neurologic exam were published and it is not clear that subjects were examined by physicians blinded to the subjects' past medical history or exposure. The single sensory abnormality found significantly in excess among those with current cases of chloracne was determined by the more subjective pinprick test rather than by an objective measure of nerve function, such as neurophysiologic tests. In addition, exposure to 2,3,7,8-TCDD was not able to be estimated due to irreconcilable inconsistencies in self-reported work histories and the lack of good company records to estimate and confirm the likelihood of exposure. Although the authors recognized that the absence of chloracne did not preclude exposure, nevertheless, they compared the results of the group with chloracne to those without chloracne. Thus, the study design was revised to explore the differences in health status in individuals with and without chloracne. Because exposed workers may have been included in the

group diagnosed without chloracne, the usefulness of the data to quantify exposure-disease relationships is extremely limited.

Another independent study of TCP workers from the plant in West Virginia, conducted in 1979, found no significant changes in the nerve conduction velocities of the sural and peroneal nerves (Suskind and Hertzberg, 1984). No details of the neurologic exam were published. However, as described by the authors, the NCV measurements were not conducted in a well controlled environment; therefore, the findings should be interpreted cautiously.

In 1979, nerve conduction velocities (NCV) of the median motor, median sensory and sural sensory nerves were obtained from 55 of 190 active, retired and former workers of a plant which produced 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-T from 1957-1979 (Singer et al, 1982). The comparison group consisted of 17 employees of Mt. Sinai School of Medicine and 8 subjects of another study. History of any exposure to neurotoxic agents, alcohol use, diabetes, neurologic diseases or disk disease or injury was obtained. One or more NCV's were slowed in 46% of the exposed group and in 5% of the control group due to a significant reduction of mean conduction velocities of the median motor and sural sensory nerves. This reduction in velocities remained significantly different from control groups after removing 8 subjects who drank more than 28 alcoholic beverages per week and 9 subjects who had past exposure to neurotoxic agents.

This study suffers from many shortcomings which limit its interpretability. It is difficult to determine from the text what criteria were used to select the study subjects which included only 45% of the eligible subjects. In addition, the selection of the comparison group is inappropriate and appears to be an afterthought. Controls were not age-matched to the study group, necessitating the use of a formula to correct for these variations; controls were selected among a group of Mt. Sinai employees from New York City, and may not be appropriate for this study of industrial chemical workers in Arkansas, due to differences in lifestyle, or socioeconomic status. The exposed and unexposed groups were not tested concurrently nor in the same test environment, thus introducing an unquantifiable observation bias into the analysis. Examiners were not blinded to the exposure status of the study participants. If the exposed subjects were self-selected due to the presence of pre-existing symptoms of undiagnosed neurologic disease, the prevalence rate in the exposed will be spuriously elevated. Finally, 2,4-D has been described as a peripheral neurotoxin. Its effect and that of other potentially neurotoxic chemicals was not considered in the analysis. The results of this study should be interpreted with these limitations in mind.

In July 1976, 2,3,7,8-TCDD contaminated effluent from a runaway TCP reaction at the ICMESA plant in Meda, Italy, was vented into the atmosphere and dispersed over neighboring communities (Pocchiari et al, 1979). The most heavily contaminated town was downwind of the

plant in Seveso. In an effort to quantify exposure-related neurologic disorders, two governmentally sponsored screenings were conducted in 1977 and 1978, on 308 residents of Seveso and nearby nonexposed communities. Two hundred workers from the ICMESA plant were also included in one of the screenings. The report of the results of the screening does not describe the extent of the exposure of these workers to 2,3,7,8-TCDD contaminated chemicals and whether or not they, too, were exposed to the effluent of the reactor explosion. Among these workers, approximately 4% (N=8) were found to have damage to peripheral nerve fibers of multiple (unspecified) nerves, controlling for confounding factors such as alcohol abuse, diabetes, kidney disease, and neurotoxic medication use. Other potential neurotoxic occupational exposures do not appear to have been considered. Three of these workers were described as having polyneuropathies of the lower limbs. The authors did not examine an unexposed control population to obtain comparable data on neurologic function. Thus, it is not possible to determine whether or not the observed effects are in excess in this group of workers.

Residential exposure

In general, the findings of neurologic abnormalities among exposed community residents are less striking than those among occupational groups. In 1979, a preliminary report of the two neurologic

screenings conducted in 1977 and 1978 on residents of Seveso and other communities was released by Pocchiari et al (Pocchiari, 1979) (Table 4). The exposed population consisted of 446 of 733 (61%) residents living in an area with soil contamination averaging 15.5 ug/m3 to 580.4 ug/m3 TCDD (Zone A). The unexposed group was comprised of 255 of 26,800 (0.95%) residents living in areas outside of Seveso with soil contamination averaging less than 3.0 ug/m3 (Zone B+R) (Pocchiari et al, 1979). In the 1977 screening, 6.7% of the tested residents from Zone A and 1.2% of the residents in Zone B+R exhibited evidence of clinical neurological damage; and 3.1% of the Zone A residents and 1.2% of the Zone B+R residents exhibited subclinical neurologic damage as demonstrated by nerve conduction velocity. No data were provided to support the reported findings. In 1978, 205 Zone A residents were screened; no residents from Zone B+R were screened. The proportion of individuals with clinical neurologic damage in Zone A residents increased to 11.7% and the proportion of subclinical findings increased to 4.9% of the group.

Although the findings are consistent with previous reports of neurologic abnormalities in exposed groups, the study is limited by low participation in both exposure groups; by nonspecific methods of evaluating individual exposures (soil samples); by the lack of evidence that examiners were blinded to the exposure status of study participants; by the lack of evidence that confounders such as age, disease status, or other neurotoxic exposures were

considered in the evaluation; and, by the possible self-selection into the 1978 screening of Zone A residents who tested positively in 1977.

In 1981, Filippini published a cross-sectional study of a total of 308 Seveso residents who participated in all parts of the 1978 neurologic screening program sponsored by Italian Government (Filippini et al, 1981). This study includes a more thorough description of the data collection and analysis of the data presented by Pocchiari et al (1979). Presence of neuropathy was assessed through nerve conduction velocity, clinical examination and symptom questionnaire. Normal values for conduction velocities, distal latency and amplitude were calculated based on age-specific data gathered from the unexposed referent group excluding individuals who were alcoholic, occupationally exposed to neurotoxic agents or had diseases predisposing to peripheral neuropathy. Prevalence risk ratios (PRR) for peripheral neuropathy were determined separately for all Seveso residents and for those who exhibited clinical indication of 2,3,7,8-TCDD exposure, defined as the presence of elevated liver enzyme levels (GGT, SGOT, SGPT) (which are also indicative of non-specific insults to the liver), or chloracne. PRRs for peripheral neuropathy were also determined for residents exhibiting conditions which are risk factors for neuropathy, e.g., alcoholism, inflammatory disease, diabetes, or potential occupational exposure to neurotoxins, etc.

Seveso residents who had clinical indication of exposure or who had risk factors for neuropathy were found to have significantly greater prevalence of peripheral neuropathy than residents without either manifestation (PRR (indicator of exposure) = 2.8, 95% CI=1.2-6.5; PRR (predisposing factors) = 2.6%, 95% CI=1.2-5.6) (Filippini et al, 1981). Additional analysis identified further that individuals who met the definition for chloracne or abnormal levels of hepatic enzymes were significantly more at risk than residents without either condition.

The strengths of the study are the use of a comparison population from an 'uncontaminated' region of Italy from which baseline conduction velocities and other neurologic parameters were calculated; the completeness of the screening exam, as described, and; the use of a definition of peripheral neuropathy to define disease status. On the other hand, the study suffers from a variety of limitations. The generalizability of the study results is compromised by the low participation rate (45%) of the exposed in the 1978 screening. Finally, the design of the study does not permit the investigators to determine if the observed neurologic condition occurred prior to or subsequent to exposure to 2,3,7,8-TCDD contaminated materials.

Unlike the findings among Seveso residents, no neurological or other abnormalities were found in a self-selected group of Missouri residents who lived in communities at the time the areas were

sprayed with 2,3,7,8-TCDD contaminated waste oil (Webb et al, 1987). In this study high risk of exposure was defined as 'potential exposure to between 20 and 100 parts per billion (ppb) of TCDD for at least two years or levels greater than 100 ppb for at least six months'. Low risk of exposure included individuals with little or no reported exposure to 2,3,7,8-TCDD. At the time of this pilot study, the analytic techniques to measure adipose or serum levels of 2,3,7,8-TCDD were not available. However, in a second study of Missouri residents conducted approximately 13 years after exposure, adipose tissue levels of 2,3,7,8-TCDD were obtained for 51 individuals with high risk of exposure and 128 with low risk of exposure (Andrews et al, 1989). Additionally, 41 of the 51 subjects who met the criteria for exposure participated in a medical examination. In the exposed group, adipose tissue levels ranged from 3.7 ppt - 750 ppt on a whole weight bases. In the unexposed participants, adipose tissue 2,3,7,8-TCDD levels ranged from nondetectable to 20.2 ppt on a whole weight basis. No health effects related to exposure to 2,3,7,8-TCDD contaminated wastes were noted in this exposed group (Webb et al., submitted for publication). The negative results of this study are not surprising given that only a small proportion of the individuals in the study considered to have been exposed to 2,3,7,8-TCDD had serum 2,3,7,8-TCDD levels above the normal range of 20 ppt. With the exception of this small group of TCP production workers and users of a heavily contaminated horse arena, given their overall low serum 2,3,7,8-TCDD levels, the exposure status of the remainder of the 'exposed' group was misclassified.

Studies in Vietnam Veterans

A number of cross-sectional studies have been conducted to elucidate the effects of possible exposure to the herbicide Agent Orange on U.S. military personnel stationed in Vietnam between 1962 and 1972. Agent Orange was composed of a 1:1 mixture of the butyl esters of 2,4-D and 2,4,5-T which was contaminated with 2,3,7,8-TCDD.

Two of the largest epidemiologic investigations of United States military personnel stationed in Vietnam during the use of Agent Orange were conducted independently by the Air Force (Lathrop et al, 1984, 1987) and the Centers for Disease Control (CDC) (Centers for Disease Control Vietnam Experience Study, 1988) (Table 5). The U.S. Air Force studied personnel called Ranch Handers, who were involved in the aerial spraying of herbicides and insecticides in Vietnam from 1962 through 1971. The comparison group was composed of Air Force personnel stationed in Vietnam outside the sprayed zone. The CDC study included a sample of ground troops who had enlisted in the Army for one term between January, 1965, and December, 1971, and who were stationed in Vietnam or other areas outside of Vietnam (Vietnam era veterans).

Both studies used cross-sectional designs, composed of comprehensive medical and psychological assessments. The Air Force Study includes plans to repeat the health assessments every 5 years

over a 20 year period from 1982 to 2002; the CDC study was to be conducted once.

Air Force Ranch Hand Study - Neurologic Assessment

In the first of the examination series published in 1984 (baseline), the neurologic assessment included a review of neurologic injuries and disease, examination of cranial nerve function, peripheral nerve function (sensory, motor, vibration and deep tendon reflex) and CNS function (tremor, coordination, stance and gait), and nerve conduction velocities (Lathrop et al, 1984). In the second examination series published in 1987 (follow-up), the nerve conduction velocities were omitted while the other exams remained the same (Lathrop et al, 1987).

The results of both the baseline and follow-up exams showed little or no difference between the Ranch Hand group and their controls, or within the six exposure groups. With the exception of a statistically significantly increase in abnormal Babinski reflex among Ranch Hand personnel in the baseline study only, no other outcomes differed between Ranch Handers and controls in either study.

In a separate study conducted after analyses of the above studies had been completed, serum 2,3,7,8-TCDD levels were examined for a sample of 147 Ranch Handers who participated in the follow-up study

(Wolfe et al., 1988). The average lipid adjusted serum 2,3,7,8-TCDD level was 49.9 ppt, ranging from 0-313 ppt. Although the current serum 2,3,7,8-TCDD levels among the Ranch Hand group were much higher than average population levels, there is little evidence from the two medical studies of adverse neurologic consequences. However, it is possible that when the medical data are reanalyzed using serum levels as the exposure index, the result of "no effect" maybe altered.

CDC Vietnam Experience Study

Of the 2490 Army Vietnam veterans and 1972 non-Vietnam, Army veterans who participated in the examination, few had evidence of peripheral neuropathy as determined from a neurological physical examination, nerve conduction velocity amplitude tests or vibration and thermal thresholds. Vietnam veterans reported slightly more symptoms related to peripheral nerve disease but this result was not borne out by the more objective measures of the examination (Centers for Disease Control Vietnam Experience Study, 1988).

The results of this study are not surprising because it appears that the Army ground troops in Vietnam were not exposed to substantial levels of 2,3,7,8-TCDD contaminated chemicals. In a recent study, the mean serum 2,3,7,8-TCDD levels of a sample of Army Vietnam veterans and the control group of non-Vietnam veterans

were found to be equivalent at 4 ppt (CDC Veterans Health Studies, 1988). Therefore, no differences in neurologic health would have been expected.

Effects of exposure to chemicals contaminated with 2,3,7,8-TCDD on the central nervous system

The reports which have been described in this review have concentrated on descriptions of effects on the peripheral nervous system. However, reports of workers exposed to 2,3,7,8-TCDD contaminated chemicals have noted symptoms reflecting central nervous system (CNS) involvement. For completeness, it is necessary to describe in this report effects ascribed to the CNS because the human nervous system is a complex network of interconnected fibers, chemical mediators and regulators and the activities of the various components of the nervous system are interrelated. Some reports document possible CNS effects related to exposure to 2,3,7,8-TCDD contaminated processes. These include decreased coordination (Oliver, 1975), headaches (Ashe and Suskind, 1950; Bauer et al, 1961; Jirasek et al, 1974; Poland et al, 1971;Oliver, 1975), nervousness (Ashe and Suskind, 1950; Suskind et al, 1953), sleeping disturbances (Bauer et al, 1961; Oliver, 1975), mood changes (Oliver, 1975), loss of concentration (Oliver, 1975), depression (Bauer et al, 1961), abnormal EEG (Bauer et al, 1961; Jirasek et al, 1974) and suggestions of hypomania as indicated by scores of a personality inventory (Poland et al, 1971). As previously noted,

these data were reported without comparison to an unexposed control population and presumably collected without benefit of standard questionnaires or administration procedures. Yet, the data suggest that some unquantified effect may have occurred both to acutely (Suskind and Ashe, 1950; Suskind et al, 1953; Bauer et al, 1961; Oliver, 1975) and chronically (Poland et al, 1971; Jirasek et al, 1974) exposed workers.

Limitations of Epidemiologic Studies and Case Reports Describing Effects of the Peripheral Nervous System

The overall results of these case reports and epidemiologic studies of occupational and environmental exposure to 2,3,7,8-TCDD contaminated materials demonstrate that exposure produced symptoms consistent with peripheral nerve damage occurring shortly after exposure, which, in some cases lasted many years. However, the case reports are not controlled investigations and the designed epidemiologic studies are limited by inadequate control selection, limited exposure assessment, and inappropriately standardized examinations.

This study of New Jersey and Missouri workers employed in the production of chemicals contaminated with 2,3,7,8-TCDD, conducted by NIOSH and described in the Methods Section, was designed to correct the limitations of past investigations by incorporating into the study a population with high potential for exposure, an

unexposed control group matched for key confounders, a set of standardized interview and examination procedures, and the measurement of serum levels of 2,3,7,8-TCDD of workers and referents at the time of the examination. The data generated by the study should provide clear information about the relationship between exposure to 2,3,7,8-TCDD contaminated chemicals and long-term health effects of the peripheral nervous system as well as other systems.

Tissue Levels of 2,3,7,8-TCDD in Human Populations

Serum levels in workers and exposed community residents

The highly lipophilic nature of the dioxins prompted a number of researchers to develop methods to measure specific dioxin isomers in human adipose tissue and serum. These analytic methods are useful in identifying populations who were suspected of having exposure to 2,3,7,8- TCDD through contaminated materials. Recently, Patterson et al (1989) summarized the published adipose and serum 2,3,7,8-TCDD levels in exposed and unexposed populations (Table 6). He illustrated that there is clear evidence that exposure occurred in selected groups, in particular workers employed in the manufacture of TCP and 2,4,5-T. The findings are striking. The tissue concentrations of 2,3,7,8-TCDD among individuals living in industrialized nations with no known exposure

to 2,3,7,8-TCDD ranges from non-detectable to 33 parts per trillion (ppt), with a mean of approximately 7 ppt. In contrast, the tissue concentration of individuals exposed to 2,3,7,8-TCDD in the production or maintenance of contaminated chemicals ranged from 5.9 ppt to 3,389 ppt among 2,4,5-T workers in the United States and West Germany (Beck et al, 1989; Sweeney et al, 1989; Patterson et al, 1989). Among individuals with known exposure to 2,3,7,8-TCDD were 16 individuals who used a horse arena after it was sprayed with 2,3,7,8-TCDD-contaminated waste oils (Andrews et al, 1989). Their tissue concentrations approached that of the industrial workers with a range of 55-577 ppt.

Individuals residing in Seveso, Italy, at the time of the TCP reactor accident have also been shown to have markedly elevated serum 2,3,7,8-TCDD levels in samples collected within a year after the accident (Mocarelli et al, 1988). Serum samples of 13 residents were analyzed in 1988. Nine of the residents inhabited the most heavily contaminated area of Seveso, five were diagnosed with severe chloracne and four had no evidence of chloracne. Four individuals who resided in an uncontaminated area were used as controls. The controls had serum 2,3,7,8-TCDD levels of 13 ppt, 15 ppt, 17 ppt and 59 ppt. In contrast, the levels in the chloracne cases ranged from 828 to 27821 ppt, while the levels of those who lived in the contaminated area but were without chloracne, ranged from 1,772 to 10,439 ppt.

The levels of the exposed Seveso residents appear much higher than those of the chemical workers and Missouri horse riders. However, it is important to note that the serum 2,3,7,8-TCDD levels of the Seveso residents were measured within one year of their exposure, while the serum 2,3,7,8-TCDD levels of the workers and riders were measured from 15-37 years after exposure ceased. To compare these groups, the elimination rate of 2,3,7,8-TCDD from the body must be considered. To do this Sweeney et al. (1989) estimated serum 2,3,7,8-TCDD levels at the determination of occupational exposure for a sample of 135 former TCP and 2,4,5-T production workers. The estimated levels ranged from 3.7 ppt to 30,927 ppt based on a standard half-life equation ($Ct=Co\ e^{-Ket}$), assuming a standard half-life rate of 7 years. The highest half-life extrapolated level of 30,927 ppt is consistent with those of Seveso residents tested shortly after the reactor accident and suggests that some workers had equally high levels while employed in NaTCP and 2,4,5-T production processes.

Serum 2,3,7,8-TCDD levels among participants of the Air Force Ranch Hand Study and the CDC Validation Study

During the course of both the Air Force and CDC studies, the opportunity to measure serum levels of 2,3,7,8-TCDD became available. In 1988, the CDC published results of a sub-study conducted to correlate serum 2,3,7,8-TCDD levels with record-based and interview-based methods used to identify veterans with the highest likelihood of exposure, and the health of veterans who may

have had potentially high exposures (Centers for Disease Control Veterans Health Studies, 1988). The study found no difference in the current 2,3,7,8-TCDD levels or in neurological status between 646 Vietnam veterans and 97 veterans who did not serve in Vietnam. Both groups had mean levels of 4 ppt, which fall within the normal range of 0-20 ppt in adipose tissue for residents of industrialized countries (Patterson et al, 1989). (Serum and adipose tissue 2,3,7,8-TCDD levels correlate in an approximately 1:1 ratio (Patterson et al, 1986)). These results suggest that the record-based and interview-based methods used to estimate exposure were not predictive of exposure to 2,3,7,8-TCDD in Vietnam. More importantly, the study found that the exposure to 2,3,7,8-TCDD contaminated herbicides of U.S. Army ground troops stationed in Vietnam was limited.

Wolfe et al (1988), measured serum 2,3,7,8-TCDD levels in a sample of 196 participants of the Ranch Hand study. In the 147 Ranch Handers, lipid-adjusted levels ranged from 0-313 ppt, with an average of 49.9 and in the controls, the lipid-adjusted levels ranged from non-detectable to 26 ppt, with an average of 5 ppt (Wolfe et al, 1988).

Metabolism and Half-life of 2,3,7,8-TCDD in Humans

With the exception of the serum 2,3,7,8-TCDD levels measured in Seveso residents, quantitation of levels of 2,3,7,8-TCDD provide a

good method for assessing current body-burden but it does not shed light on the levels encountered by workers and other exposed individuals at the time of exposure. Currently, information about the metabolic mechanism and elimination rate of 2,3,7,8-TCDD in humans is sketchy. The available data to date concerning the elimination rate and biologic half-life of 2,3,7,8-TCDD in humans was generated in two studies, one which included 36 Vietnam veterans who participated in the 1982 and 1987 Air Force Ranch Hand Studies (Pirkle et al, 1989). In the other study, a scientist ingested radiolabelled 2,3,7,8-TCDD and measured the elimination rate in urine and feces (Poiger and Schlatter et al, 1985). In the Ranch Hand Study, the median half-life was calculated to be 7.1 years with a 95% confidence limit of 5.8-9.6 years, assuming the elimination rate followed first order kinetics and no additional exposure above background level (Pirkle et al, 1989). The half-lives ranged from 2.91 to 743 years, implying that perhaps there is considerable inter-individual variability in the half-life for the human population.

The most recent findings of the ingestion study of a single male scientist indicate that the elimination of 2,3,7,8-TCDD may follow a two-compartment model with an overall half-life of approximately 9-10 years (Poiger et al, 1989). Another important finding was that a weight drop of approximately 20 kilograms did not increase the elimination rate and that the concentration of 2,3,7,8-TCDD in the remaining adipose tissue increased fractionally. While these data shed some light on the possible kinetics of 2,3,7,8-TCDD

metabolism in humans, they are derived from a small sample. Samples of larger groups exposed to 2,3,7,8-TCDD would be the most useful means of determining the metabolic parameters in human populations.

The Peripheral Nervous System

Introduction

The mammalian nervous system is composed of a network of nerve cells and their associated projections, chemical mediators and related connective tissues. The nervous system is designed to conduct impulses between segments of the nervous system and from the nervous system to tissues outside the system. Theoretically, the nervous system is divided into two functional units, the central (CNS) and peripheral (PNS) nervous systems. Although often described as independent units because of differing anatomic structures, areas of control and susceptibility to certain toxins, the central and peripheral nervous systems interact in concert to control most activities of the organism.

Much of the available information suggests that in humans exposure to 2,3,7,8-TCDD may be related to disturbances of peripheral nerves. A brief description of the PNS follows. This description includes a review of the components and functions of the PNS, causes of peripheral nerve dysfunction and possible mechanisms of

peripheral nerve damage. More comprehensive descriptions of the peripheral nervous system and pathological changes may be found elsewhere (Dyck et al, 1984).

Description

The PNS is the part of the nervous system (motor, sensory and autonomic neurons) extending outside the central nervous system (brain and spinal cord) and associated with Schwann cells or ganglionic satellite cells (Schaumburg et al, 1983). Anatomically, the PNS is composed of the peripheral branches of the autonomic nervous system, spinal and cranial nerves (except the second cranial nerve), the dorsal and ventral nerve roots, dorsal root ganglia, and sensory and motor terminal ramifications (Barr, 1979).

A characteristic of peripheral nerves is the presence of axons. Axons are extensions of the peripheral nerve cell which project outward from the cell body (neuron). Axons conduct impulses from the cell body to the viscera and limbs (efferent, motor) or from the peripheral region to the central nervous system (afferent, sensory). Axons consist of the axolemma or axon membrane and the axoplasm. The axolemma is thought to contain sodium channels which play a role in the release of sodium ions during membrane depolarization resulting in impulse propagation. Axoplasm is the cytoplasm of the axon and contains mitochondria and protein structures called microtubules and neurofilaments. The latter two

organelles are responsible for transport of nutrients along the axon and for axon growth after injury. Axonic metabolism is maintained by cellular functions in the cell body which is located at the spinal cord.

A nerve is composed of a number of axons or fibers which are grouped in bundles or fascicles and ensheathed in three layers of connective tissue: epineurium, which encapsulates the entire nerve; perineurium, which surrounds bundles of nerve fibers; endoneurium, which covers individual fibers. These sheaths of connective tissue provide a barrier to external chemical insult and serve as structural support for each nerve fiber. Nerve tissue is vascularized by a capillary system which passes through the perineurium to the endoneurium. Vessels in the endoneurium are characterized by tight junctions between endothelial cells. These tight junctions are designed to prevent entrance of unwanted blood-borne materials into the endoneurial space (blood-nerve barrier) (Olsson, 1984).

Schwann cells are uniquely associated with the peripheral system, providing the myelin sheath which envelopes the peripheral nerves. Oligodendrocytes perform an analogous function in the central nervous system. Myelinated peripheral axons are covered by a series of Schwann cells, connected end-to-end, beginning at approximately the nerve root, and extending continuously along the length of the nerve to its end. One Schwann cell invests a unique

segment of the axon by wrapping multiple layers of myelin around the fiber. Composed of lipids and proteins, myelin insulates the nerve and increases as well as maintains the conduction velocity of impulses along the axons. Together with the endoneurium, myelin also prevents interference of impulses between one nerve and another. Nodes of Ranvier mark the region along the nerve fiber where one Schwann cell ends and where another Schwann cell commences. Nodes function as the region of impulse propagation along the myelinated fibers.

Schwann cells are also associated with unmyelinated peripheral nerve fibers. Although myelin may not invest the axon as in the myelinated nerves, the Schwann cell may, within the nerve, separate one unmyelinated axon from another. A single nerve may contain a mixture of myelinated and unmyelinated fibers which have afferent and efferent functions.

Components of the PNS

The cranial nerves innervate much of the facial area and are responsible for activities of the special senses - vision, hearing, taste and smell, as well as sensory and motor function of the face, neck and oral cavity. Cranial nerve II or the optic nerve is an extension of the central nervous system. The autonomic fibers of cranial nerves IX, X and XI are also involved in the regulation of cardiac and respiratory function, and sensory and motor activities

of the abdominal viscera. Cranial nerves may carry efferent as well as afferent impulses, their functions may overlap or innervate different parts of the same organ or act in concert with other nerve fibers to compose a single functional unit.

The remaining components of the peripheral nervous system include the nerves derived from the brachial, lumbar and sacral plexus and the autonomic system. With the exception of sensory neurons in the dorsal root ganglia and some cranial root ganglia, the autonomic nerves constitute neurons outside the central nervous system which innervate the viscera (Appenzeller and Atkinson, 1984). Nerves from the brachial, lumbar and sacral plexus provide sensory and motor innervation to the arms, hands, legs, feet and lower trunk. These nerves are most often the primary targets of many industrial neurotoxins and are the primary focus of this study of workers exposed to materials contaminated with 2,3,7,8-TCDD.

Assessment of PNS function

Peripheral nerve function and status may be assessed using a combination of techniques. The procedures used for this study included: medical history; clinical examination; quantitative sensory tests; and, electrophysiology tests.

In this study, a history of nerve injuries and disorders as well as symptoms consistent with neurological disorders were obtained as

part of the medical history. The clinical examination documented signs indicative of functional loss attributable to damage to a nerve or group of nerves. The examination conducted in this study is described in the methods.

The ability of nerves to conduct impulses from one point to another is characterized by measurement of the functional status of the nerves including conduction velocity, amplitude, and latency (electrophysiology tests). The methods used for measuring these parameters are as described in the methods. Amplitude of the wave measures the coherence with which the tested nerve fibers respond to an electrical stimulus of a predefined intensity (Ma and Liveson, 1983). Amplitude drops as nerve fibers in the axons are damaged or destroyed. Latency is defined as the time from the beginning of stimulus to the intitiation of the response or the rate at which the largest fibers of the nerve propogate action potentials along the axon (Daube, et al., 1978; Ma and Liveson, 1983). Conduction velocity represents the speed of depolarization between two points on the nerve and is calculated using the nerve fiber-specific latency values and the distance between the electrodes. In the laboratory situation, the length of the nerve is the distance between the stimulating and recording electrodes. Conduction velocity is reduced or absent due to disorders which damage or destroy axon or myelin.

The quantitative sensory tests used in this study measured vibration and thermal sensitivity of specific sensory nerve fibers. Vibration sensitivity was assessed to examine the integrity of the distal portion of the long, large diameter myelinated axons innervating the Pacinian and Meissner corpuscles in the hands and feet (Light and Edward, 1984). These nerves which also regulate proprioception are particularly sensitive to the effects of exogenous neurotoxins (Bove et al., 1986). Thermal sensitivity was assessed to examine the integrity of the smaller diameter, A-delta and unmyelinated c fibers of the peripheral nerves which detect temperature and pain stimuli (Bove et al., 1986). Loss of unmyelinated c fibers also leads to absent corneal and deep tendon reflexes in autonomic nerve disease (Appenzeller and Atkinson, 1984).

Damage to the PNS

Physical trauma, chemical insults, and systemic disease processes are the major causes of damage to the PNS. While the morphologic, pharmacologic and electrophysiologic changes and severity of effect varies with the type of insult, the deterioration of sensory or motor function is a consistent end result. Sensory disorders may be accompanied by pain, tingling, numbness, loss of temperature and vibration sensitivity or enhanced temperature sensitivity. Motor nerve dysfunction may include weakness, atrophy of muscle, fasciculations (muscle twitching), and loss of proprioception and

deep tendon reflexes. Some conditions may cause both sensory and motor dysfunction reflected in clinical signs and symptoms consistent with both types of nerve fiber loss.

Trauma

Physical trauma to the peripheral nerves may be due to full or partial transection, chronic stretching, compression, or entrapment of the nerve. The effects of acute or chronic trauma to the nerve are usually exhibited in the regions distal to the injury and recovery and restoration of function is dependent upon the extent and type of damage incurred (Schaumburg et al., 1983). The mechanisms causing nerve damage after traumatic injury are not well known, but factors such as mechanical stress on the nerve, e.g., rubbing against a bone, tendon or ligament, prolongued axonal compression, and the resulting edema or ischemia, may contribute to axonal damage (Bove et al., 1986). In more severe cases, the axon and myelin undergo irreparable damage, termed Wallerian degeneration.

Systemic disorders

A number of systemic diseases, including infectious, metabolic and nutritional disorders, adversely effect the integrity of the PNS (Dyck et al, 1984). The neurotoxic mechanism varies depending upon the specific disease process as does the severity of the

dysfunction. Peripheral nerve disease may also be a manifestation of genetic disorders (Dyck et al, 1984; Schaumburg et al, 1983; Asbury and Gilliatt, 1984).

Effects of toxic exposures

Axonopathies

A host of occupational and environmental exposures as well as iatrogenic compounds are known peripheral neurotoxins (Schaumburg et al, 1983; Spencer, 1980; Seppalainen and Haltia, 1980; LeQuesne, 1980; Schaumburg and Spencer, 1980; Politis et al, 1980; Windebank et al, 1984; O'Donoghue, 1986; LeQuesne, 1984; Sterman and Schaumburg, 1980).

Histopathologically, toxic disorders of the PNS are characterized by damage to the axon, myelin or neuron and may distribute symmetrically or cause disturbances at a single site (focal) or a number of localized sites (multifocal) along the nerve process (Schaumburg et al, 1983). Physical signs and symptoms of toxic axonopathies usually appear after long-term exposure. Axonopathies are usually first manifested in the lower limb. It is believed that this characteristic is due to fact that in the mammalian body, the nerves in the lower limb are the largest and longest in the system. The axon as well as the myelin usually degenerate symmetrically from the distal ends of the nerves causing sensory

loss in a "stocking and glove" distribution (feet, ankles and calves to knees; hands, wrist to mid-forearm) accompanied by mild motor nerve conduction slowing and loss of ankle jerks (Schaumburg et al, 1983). Once the exposure is removed, regeneration of the axon and myelin is possible.

Myelinopathies

Exposures damaging to myelin cause rapid degeneration of the myelin tissue, resulting in mild sensory loss and severe slowing of nerve conduction, loss of tendon reflexes, impairment of vibratory and proprioceptive ability, general weakness and paralysis due to demyelination of large diameter motor axon (Schaumburg et al, 1983). The axon is often spared and remyelination is possible after discontinuation of exposure.

Neuronopathies

Neuronopathies are rare phenonmena and their etiologies are not well understood (Schaumburg et al, 1983). They have rapid onset and no chance of recovery due to the destruction of both the nerve cell body and the axon. Sensory and tendon reflex loss is severe, while motor function is left intact.

Autonomic dysfunction

Autonomic disturbances are most often manifested when small diameter myelinated, unmyelinated afferent and efferent nerves are affected or when demyelination occurs to myelinated autonomic fibers of the vagus nerve and nerves innervating smooth muscles (McLeod, 1988). Major clinical signs and symptoms manifested by autonomic system disorders include orthostatic postural hypotension, impaired heart rate control, sweating abnormalities of the extremities, bladder and sexual dysfunction and reduced or absent pupillary reflex (Appenzeller and Atkinson, 1984). Autonomic nerve dysfunction is caused by a variety of systemic diseases, genetic neuropathies, cancer and toxic exposure.

Biochemical Alterations

In addition to morphologically altering the structure of the peripheral nerve, some chemical and biologic neurotoxins interrupt the biochemical requirements of impulse propogation (Price and Griffin, 1980). The action of these types of neurotoxins range from binding with neurotransmittor inhibitors e.g. organophosphates, to alteration of the anatomy of the synapse (Price and Griffin, 1980).

Mechanisms of Neurotoxicity

A great deal more is known about the pathologic consequences of neurotoxic damage than is known about the manner in which toxins reach the axon or neuron or about the mechanisms by which neurotoxic effects occur after contact with the nerve components. In a review of peripheral nervous system toxicity, Cavannah (1985) described several methods by which toxins may enter the nerve environment (Cavannagh, 1985). A hypothesized, but not well tested route of entry may be the node of Ranvier. Although Cavannagh explains that the lipophilic nature of the nodal region would not allow many chemicals to penetrate the area, it may be a mechanism which would explain the way some drugs directly enter the peripheral nerve (Cavannagh, 1985). Protein molecules have been shown to ascend along both motor and sensory fibers after entry through axon terminals (Kristensson and Olsson, 1971). This mechanism has not been tested using chemical neurotoxins.

The permeability of vascular walls has been shown to be increasingly important as a mechanism in neurotoxic damage. Natural fenestrations or openings in the endothelial lining of blood vessels innervating the dorsal root ganglia and the autonomic ganglia, have been shown to permit entry of certain chemicals to the endoneurial space. For example, methyl mercury selectively attacks the dorsal root and autonomic ganglion by entering through naturally occurring openings in the capillary endothelial lining,

causing degredation of neuronal rough endoplasmic reticulum and loss of protein synthesizing (Jacobs, 1980).

Rather than entering through the juncture between endothelial cells, some chemicals cause severe damage to the endothelial lining. This damage permits infiltration of the toxin and other blood components into the endoneurial space (Jacobs, 1980). Lead and cadmium reach the nerve after destroying vascular endothelial cells. Compression of the nerve by resulting edema, disturbance of the axonal microenvironment and damage to the Schwann cell are some of the disruptions thought to occur.

The anatomy of the peripheral nerves may also play a role in the mechanism of toxic neuropathies. Two noted characteristics of toxic neuropathies are: that the sensitivity of axons to neurotoxins is proportionate to axonal length and diameter; and, that for most situations, distal areas are affected before the more proximal regions. These two characteristics are most likely related. The susceptibility of the longer nerves may be increased because the longer the nerve, the farther the distal end lies from the source of metabolic energy at the neuron. Therefore, with continual or repeated insult, the more distal components of the peripheral nerves may not be able to be repaired as rapidly as the more proximal regions and, therefore, sustain damage first (Cavannagh, 1985).

Neurotoxic effects of 2,3,7,8-TCDD

As detailed previously, a variety of signs and symptoms including pain, numbness in the upper and lower extremities and reduced pinprick sensation, weakness and abnormal levels of fatigue have been reported in individuals potentially exposed to materials contaminated with 2,3,7,8-TCDD (Ashe and Suskind, 1950; Baader and Bauer, 1951; Suskind, 1953; Bauer et al, 1961; Poland et al, 1971; Goldman, 1973; Jirasek et al, 1972; Oliver, 1975; Pocchiari et al, 1979; Pazderova-Vejulpkova et al,1981; Singer et al, 1984; Moses et al, 1984). A single cross-sectional study of residents from Seveso, Italy, found abnormal conduction velocites among residents of the highly contaminated regions of Seveso compared to residents of unexposed communities (Filippini et al, 1981).

Unfortunately, there are no animal toxicologic data describing the neuropathologic consequences of exposure to 2,3,7,8-TCDD. The absence of animal studies on the neurotoxicity of 2,3,7,8-TCDD is puzzling because the aggregate of human data from the various case series and studies suggests that exposure to chemicals contaminated with 2,3,7,8-TCDD may cause pathology in both motor and sensory nerves. Whether the dysfunction is due to axon or myelin destruction, or a combination of effects in both structures, remains unconfirmed. Currently, there is a single report of a TCP production worker who was employed in a West Virginia plant with a

distal axonopathy confirmed by nerve biopsy (Moses et al, 1984). No other reports have provided additional cases of myelin or axon destruction related to 2,3,7,8-TCDD exposure.

Because 2,3,7,8-TCDD is produced as a contaminant during the production of TCP and is passed on to the end product, 2,4,5-T, it is possible that the effects may also be due to either dioxin contaminated TCP or other substance(s) in the products. There are no animal data to support or reject the hypotheses that either TCP or 2,4,5-T uncontaminated by 2,3,7,8-TCDD are neurotoxins. There is only one case series which reported human health effects after exposure to pure 2,3,7,8-TCDD (Oliver, 1975). No symptoms of sensory or motor effects were noted among three laboratory workers who were exposed during the synthesis of pure 2,3,7,8-TCDD, although other symptoms consistent with exposure, such as chloracne and elevated lipid levels were present (Oliver, 1975).

Occupational Exposure of the Study Population to Neurotoxins Other than 2,3,7,8-TCDD

Workers from both the New Jersey and Missouri plants may also have been exposed at the worksite to other suspected neurotoxins besides 2,3,7,8-TCDD, notably 2,4-D in the New Jersey plant and hexachlorophene in the Missouri plant. At the New Jersey facility, 2,4-D was produced from the plant opening through 1968. 2,4-D is not contaminated with the 2,3,7,8-TCDD isomer. Hexachlorophene was

produced for approximately 2 years in Missouri and because it is a pharmaceutical product, little if any 2,3,7,8-TCDD would have been present in the end product.

2,4-Dichlorophenoxyacetic acid has been associated with clinical evidence of peripheral neuropathy reported in two men exposed while spraying the herbicide (Goldstein et al., 1959; Berkley and Magee, 1963). Neither case report discussed the possibility of simultaneous exposure to other neurotoxic herbicides. The results of animal studies are quite mixed. Early animal toxicologic studies report symptoms of asthenia, lethargy and ataxia after exposure to 2,4,D (Hill and Carlisle, 1947; Bjorklund and Erne, 1966). But more recent studies have found little evidence to suggest that 2,4-D causes neuropathic changes (Mattsson et al., 1986; Hansen et al., 1971; Mattsson et al, 1986; Squibb et al, 1983; Toyoshima et al., 1985).

Between 1970 and 1972, TCP and hexachlorophene were produced at the Missouri plant. Hexachlorophene is readily absorbed through the skin, and has been shown to cause demyelination of peripheral nerves (Pleasure et al, 1974) and to affect the central nervous system adversely (Kimbrough, 1971). In a review of the toxicity of hexachlorophene by Kimbrough (1971), signs and symptoms resulting from hexachlorophene exposure included diplopia and other

functional abnormalities of the eye, weakness of the lower limbs, nausea, vomiting, irritability, convulsions, cerebral edema and coma. In most cases, withdrawal of exposure relieved the symptoms.

It is not possible to determine all the other potential neurotoxins to which the New Jersey or Missouri workers were exposed. In addition, employment in other environments may have also provided unreported opportunity for exposure to peripheral neurotoxins. Yet, if 2,3,7,8-TCDD is the primary cause of chronic peripheral neuropathy in this population, a dose-response relationship between serum 2,3,7,8-TCDD should be evident given the very wide range of serum levels.

CHAPTER III

METHODS

Introduction

The following section describes the design, the population, the data collection and the analytic methods used to evaluate the long-term health effects of 2,3,7,8-TCDD on the peripheral nervous system.

Generally, the study design followed a cross-sectional approach whereby the health of the study population was assessed once during the period 1987-1988. The study population consisted of workers who were employed at two different chemical plants at which chemicals contaminated with 2,3,7,8-TCDD were manufactured, and a group of unexposed referents. A detailed description of the selection of the worker and referent study populations follows.

The overall objectives of this analysis, the evaluation of peripheral neuropathy, are two-fold: to determine whether workers exposed in the past to chemicals contaminated with 2,3,7,8-TCDD have a higher rate of peripheral neuropathy than unexposed referents, and to determine whether the observed peripheral neuropathy is related to the extent of exposure to 2,3,7,8-TCDD contaminated processes based upon serum 2,3,7,8-TCDD levels obtained at the time of the examinations. If there is an increased risk for peripheral neuropathy among workers, then an additional objective of the study is to determine whether severity of the disease or dysfunction is related to serum 2,3,7,8-TCDD levels.

Study Design

The study design combined the characteristics of two types of observational studies: cross-sectional and follow-up. Cross-sectional data were collected during a single comprehensive medical examination which was conducted between March, 1987, and March, 1988, under contract with the Lovelace Medical Clinic in Albuquerque, New Mexico. The medical examination included an assessment of the current physical and mental health of the study participants. Follow-up data were collected through questionnaires and record review of past events and included details of work experiences, dates of diagnosis of medical conditions of interest and other exposures and medical conditions which may be related to the occurrence of peripheral neuropathy.

Power of the study

The overall power of the study to detect peripheral nerve disease was calculated based on the data from the study by Moses et al. (1984) which found pinprick sensation to be reduced significantly in individuals with chloracne compared to those without chloracne. Based on data from this study, the likelihood of finding at least a 2-fold excess of peripheral nerve disease in our study population of an estimated 448 workers was 100%, if such an excess existed. Results of the neurologic examination of another study of the TCP workers in the West Virginia plant (Suskind and Hertzberg, 1984) could not be used to estimate power because of reservations cited by the authors.

Study population

Description and Selection Process

NIOSH Dioxin Registry

The worker population eligible for participation in the cross-sectional medical study were selected from among 6583 male workers who were included in the NIOSH Dioxin Registry. This registry, established in 1979, contains demographic and work history information on workers who were assigned to the production or to

the maintenance of operations in any of 14 U.S. plants where dioxin-contaminated chemicals were manufactured. The purpose of the Dioxin Registry was a basis for research on this population of 2,3,7,8-TCDD exposed workers. A mortality study and a cross-sectional medical study, described in this paper, were conducted on the workers in the registry.

Workers eligible for participation in the cross-sectional study included all living workers from a total of 586 who were ever employed in the manufacture of products contaminated with 2,3,7,8-TCDD at either one of two plants, located in Newark, New Jersey and in Verona, Missouri. The selection of these two plants for inclusion in the study was motivated, in part, by requests to NIOSH from the states of Missouri and New Jersey to assist in the investigation of the effects on workers exposed to "dioxin" in their respective states. While the motivation for selection of these facilities was, in part, a public health response, there are scientific bases as well, and these are described below.

New Jersey plant study population

Four hundred ninety (490) workers were employed at the New Jersey facility from 1951 through 1969. From August, 1951, through August, 1969, sodium 2,4,5-trichlorophenol (NaTCP), 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), 2,4-dichlorophenoxy acetic acid (2,4-D) were produced at the New Jersey facility. Chlorinated benzene and other chemicals were also produced until

1960. Because many of the production operations at this facility occurred in the same building and maintenance workers and operators were assigned to most operations, all employees at this facility were considered exposed and therefore included in the cross-sectional medical study.

There are considerable advantages to studying this worker population. The health of workers from the New Jersey plant has been the subject of two case reports which described high incidence of chloracne and other dermatologic abnormalities (Bleiberg et al, 1964; Poland et al, 1971), possible cases of porphyria (Bleiberg et al, 1964) and hypomania (Poland et al, 1971). Both reports used volunteers and neither used control groups. Additionally, there is evidence that this plant produced some of the most heavily 2,3,7,8-TCDD contaminated NaTCP and 2,4,5-T among those plants whose products were surveyed (Fee, 1975). Thus, the advantages for studying this plant are: 1) a population which has documented evidence of exposure-related disorders; 2) a heavily exposed workforce, which would increase the likelihood of detecting an exposure related outcome. Recent data also confirm the high level of exposure in this population. Sweeney, et al (1989) found an average serum 2,3,7,8-TCDD level of 293 parts per trillion (ppt) in a sample of 111 workers from this plant as compared with a mean of 8 ppt in 54 unexposed controls.; and, 3) long-term exposure, with a wide range of exposure periods (up to 19 years), which increases the likelihood and frequency of exposure of all the study subjects, thus increasing the potential for exposure.

Missouri plant study population

For four months between May, 1968, and January, 1969, NaTCP and 2,4,5-T were produced at the Missouri plant. After a short hiatus, production of NaTCP for the manufacture of hexachlorophene began in April, 1970, and continued through January, 1972. Ninety-six (96) individuals were involved in the production of NaTCP, 2,4,5-T or hexachlorophene and were eligible for participation in this cross-sectional medical study.

The Missouri plant population has never been previously studied. The primary advantage to studying this plant is that some of the workforce experienced short-term but heavy exposure. Based on the fact that production of hexachlorophene requires the redistillation of NaTCP which yields heavily contaminated effluent (stillbottoms), researchers suspected, and later confirmed (Patterson et al, 1989), that workers in this plant were at high risk of exposure to chemicals contaminated with 2,3,7,8-TCDD, particularly, the individuals who handled the stillbottoms. These wastes were shown to contain levels of 2,3,7,8-TCDD exceeding 300 parts per million (ppm) (Marlow et al, 1987). Recent evidence indicates that adipose tissue levels measured on a whole weight basis of 2,3,7,8-TCDD from production workers assigned to the NaTCP and 2,4,5-T production process greatly exceed the adipose tissue levels in other workers at this plant not assigned to the processes (Patterson et al, 1989). In addition, the mean serum 2,3,7,8-TCDD level of 171 ppt

in a sample of 32 workers from this plant was statistically significantly increased compared with 7.1 ppt for unexposed referents (Sweeney et al, 1989).

Location and tracing of living workers

All workers from both plants who were alive and located at the time of the study were eligible to participate in both an in-home interview and a comprehensive medical examination. With the assistance of a contractor, workers were traced using company personnel records, federal agency records (Social Security Administration, Internal Revenue Service, Health Care Finance Administration, National Death Index), credit bureau searches, U.S. Postal Service, telephone directory assistance, city directories and personal field visits.

Referent selection

For comparison, one individual with no prior history of employment in facilities which produced phenoxy herbicides was sought from within the current community of the worker, who matched the worker by age, (within 5 years), race and sex. Community-based referents were chosen to control for the possible confounding effects of socioeconomic status and other environmental exposures. The sampling algorithm specified a systematic enumeration of households within the census blocks closest to the home of the worker.

Beginning in the census block of the worker, a minimum of 4 individuals who met the matching criteria were identified. (For approximately 10% of the workers, it was necessary to identify 6-10 individuals who met the matching criteria.) Once the 4 matches were found, they were approached in a predefined order and requested to participate in the study. The goal of this procedure was to limit the number of individuals requested to participate and, ideally, to convince the first person in the random sequence to participate. In general, the individual who was first in the sequence participated in the study 48.2% of the time; 74.8% of the participating referents were obtained within the first three requests.

Data Collection

Information on worker and referent health status was collected through a comprehensive set of interviews and medical examinations. Trained interviewers administered a questionnaire in the home of each study participant, which elicited lifetime medical and reproductive history, demographic and lifestyle information including smoking habits, alcohol consumption, education, religion, income and residential history, and a detailed occupational history. Medical records were obtained to verify selected, self-reported health outcomes previously associated with 2,3,7,8-TCDD exposure.

Each subject participated in a thorough medical examination designed to evaluate the current status of those conditions previously reported in the literature as related to exposure to 2,3,7,8-TCDD contaminated materials. The medical examination included a general physical, dermatologic and neurologic evaluations, psychological and neurobehavioral tests, pulmonary function tests, chest x-ray and blood and urine chemistries. Serum was also obtained to measure personal serum 2,3,7,8-TCDD levels. To reduce observer bias, all examiners conducted the medical examination or tests blind to the exposure status (worker or referent) of the participant.

Clinical Assessment of Peripheral Nerve Function

The components of the neurological evaluation were selected to identify abnormalities caused by exposure to toxins affecting peripheral nerves. To assess peripheral nerve dysfunction in this study, four classes of data were collected: respondent reported symptoms, clinical signs evaluated during the neurologic examination, quantitative sensory testing of thermal and vibratory sensitivity and hearing and visual acuity, and electrophysiology tests including conduction velocity, amplitude, and latency to measure the functional status of the peripheral nerves (Bove et al, 1986; Moody et al, 1986).

Clinical neurologic evaluation

The clinical neurologic evaluation of the peripheral nervous system was conducted by nine board certified neurologists. Prior to performing neurologic evaluations on study participants, the neurologists were trained to conduct a standardized neurologic examination. The standardized neurologic examination was constructed by Herbert Schaumburg, M.D., of Albert Einstein College of Medicine, an expert in the field of occupational neurology and toxicology.

The neurologic examination included an evaluation of the motor, sensory or mixed fibers of the twelve cranial nerves, assessment of muscle strength in the upper and lower limbs, activity of deep tendon reflexes (brachial, patellar, achilles), sensory perception of pain (pinprick), light touch (cotton puff), vibration (tuning fork), and position of digits. Other peripheral nerve and central nervous system (CNS) functions were assessed in a more limited manner, by the evaluation of stance, gait, coordination of hand and foot movements, and signs of intentional or unintentional tremor.

Periodic review of examination techniques was conducted to ensure adherence to the standardized protocol. In addition, a random sample of five percent of the neurologic examinations were repeated on the same day by a second neurologist who was blind to the findings of the first examining neurologist.

Electrophysiology tests

Electrophysiologic tests including conduction velocities, amplitudes and latencies were conducted on sensory fibers of the median (distal and proximal), ulnar and sural nerves, and motor fibers of the median and peroneal nerves. Joseph C. Arezzo, Ph.D., of the Albert Einstein College of Medicine, an expert in testing of the peripheral nervous system, assisted in test design, conducted technician training and certification and quality assurance, and was consulted during data analysis. One hundred percent of the tracings for the electrophysiology tests were reviewed by Dr. Arezzo.

Electrophysiologic measurements were taken by technicians who used standard test techniques and who were certified in the administration of the NCV and quantitative sensory tests specified in the study protocol (Kimura, 1984). All electrophysiologic procedures were performed with a TECA TD 10 MK1 EMG. Two instruments were used daily; a third was used as a backup. The instruments were calibrated daily.

Surface electrodes were used to stimulate the nerve and were placed at standard points with reference to bony landmarks. Distance between the electrodes was measured for each nerve tested. In instances when the standard distance did not produce an acceptable response (particularly for the peroneal and sural nerves) placement

of the stimulating electrode was changed to obtain the best response recording. Before a response was considered 'absent' several alternative placements were attempted to obtain consistent responses after averaging.

All measurements were usually conducted unilaterally for upper and lower limbs on the dominant side. However, the limb on the non-dominant side was tested if the participant reported injury or surgery to the dominant limb, a history of an entrapment syndrome or if the dominant limb was absent. The tests were conducted in a quiet environment at a controlled ambient temperature. Because conduction velocities vary directly with limb temperature, skin temperature on the upper and lower limb was measured before testing. If the limb temperature was below 31°C, it was adjusted using a heating pad to 33.0°C for the upper limb and to 32.0°C for the lower limb ($\pm$ 1.0°C) (Dorfman and Bosley, 1979).

All recorded stimuli were supramaximal, i.e., above the stimulus level at which the highest response could be evoked. Sensory nerve fiber stimulation was antidromic (opposite the direction of normal stimulus) and motor nerve fiber stimulation was orthodromic (in the direction of normal stimuli). Parameters measured during electrophysiologic tests included latencies, which were used to calculate nerve conduction velocities, and amplitudes. Latency was measured in milliseconds as the time from the beginning of stimulus to the initiation of the response or the speed at which the largest

fibers of the nerve propagate action potentials along the axon (Daube et al, 1978; Ma and Liveson, 1983). To obtain a latency measurement, the nerve was stimulated at two different points, one closer to the center of the body (proximal) and one farther from the center (distal). The relative position of the active and recording electrodes remained constant for both measurements. The difference between the two latency measurements represented the time for the impulse to travel between the two points (Kimura, 1984). Amplitude of the wave defined the number of fibers tested and the coherence with which they responded to the stimulus (Ma and Liveson 1983). Amplitude was measured in microvolts. It was defined as the maximum distance between the baseline or resting phase to the peak of the M-wave response induced by stimulation.

Conduction velocity represented the speed of propagation over the length of the nerve between the stimulating and recording electrodes. Conduction velocities, expressed as distance per unit time (meters/second), were calculated by dividing the distance between the distal and proximal electrodes (centimeters) by the latency (milliseconds). Motor conduction velocities (MCV), proximal sensory conduction velocities (PSCV) and distal conduction velocities (DCV) were calculated using the formulas described below.

$$MCV = \frac{\text{Distance between distal \& proximal electrodes}}{\text{Proximal latency - Distal latency}}$$

$$PSCV = \frac{\text{Distance between distal \& proximal electrodes}}{\text{Proximal latency - Distal latency}}$$

$$DCV = \frac{\text{Distance}}{\text{Distal latency}}$$

Quantitative sensory tests

Quantitative sensory tests of thermal and vibratory sensitivity and auditory and visual acuity were conducted in this study. Only the analysis of quantitative sensory tests of thermal and vibratory sensitivity will be described in this report.

Vibration thresholds

Vibration sensitivity was tested to evaluate the integrity of the distal portion of the long, large diameter myelinated axons innervating the Pacinian and Meissner corpuscles in the hands and feet (Light and Edward, 1984). These nerves regulate vibratory sensations and proprioception and are particularly sensitive to the effects of exogenous neurotoxins (Bove et al, 1986). Vibratory thresholds were measured in volts on the Vibratron II manufactured by Sensortek (Arezzo et al, 1986). Thresholds were measured for the distal volar surface of the index finger and plantar surface of the great toe on the same side of the body, usually the dominant. The Vibratron II contains two identical vibrating rods connected to

a variable voltage source that controls the vibration intensity of the two rods. The test required the subject to touch each rod and determine which of the two rods was vibrating. The rods were turned off and on by the examiner in a predefined sequence. The vibration intensity was also controlled by the examiner. The on-off sequence was based on an algorithm which started the vibration intensity at a level which was easy for the subject to detect (above threshold). The vibration intensity was reduced by approximately 10% for each correct selection of the vibrating rod. When the vibrating rod was not selected (error), the misidentified vibration intensity was repeated twice. If the vibrating rod was not selected after two attempts at the same intensity, the intensity was increased by 10%. The test ended after the subject could not correctly select the vibrating rod 5 times. Thresholds were calculated by first dropping the measurements of the last correct and last incorrect responses then averaging the remaining 4 incorrect intensities and the 4 lowest correct intensities. The lower the threshold the greater the ability to detect vibratory stimuli.

Thermal thresholds

Thermal sensitivity was tested to evaluate the integrity of the smaller diameter, A-delta and unmyelinated c fibers of the nerves in the index finger and great toe. These fibers detect temperature and pain stimuli (Bove et al, 1986). Loss of unmyelinated c fibers

is also consistent with absent corneal and axon reflexes (Appenzeller and Atkinson, 1984). Thermal thresholds were measured for the distal volar surface of the index finger and the volar surface of the great toe on the same side of the body, usually the dominant. Thresholds were measured on the Sensortek Thermal Tester-NTE-2 manufactured by Sensortek, Inc. (Arezzo et al, 1986). This instrument has two identical thermal plates, the temperature of which may be controlled over a 50.0° temperature range (± 0.1°C). During the test, one plate was maintained at 25.0° C, while the temperature of the other was adjusted by the examiner according to the same on-off algorithm used in the vibratory test. The test was administered by requiring the subject to touch each of two plates for a maximum of 2 seconds and determine which was colder.

Thermal threshold sensitivity was calculated in degrees Centigrade. The lower the threshold the greater the sensitivity to temperature differences and pain producing stimuli. In the case of thermal thresholds only, the absence of a response indicated that the subject was unable to detect the maximum difference in temperature of 25°C between the two thermal plates. This inability to sense this great change is suggestive of peripheral nerve dysfunction. When a participant could not detect the maximum difference in at least five trials, the technician recorded the measurement as 20.

Medical history: self-reported symptoms

Disorders of the peripheral nervous system are associated with a variety of systemic disease processes, personal habits, environmental, occupational and iatrogenic exposures and trauma. Appendix C enumerates some of the major disease processes, medications, and extrinsic exposures associated in previous research with peripheral nerve dysfunction and assessed in the analysis as covariates. This information was obtained from the study participants during the demographic and occupational history interview and the medical history.

To take into account the presence of these neuropathic processes and exposures, a history of past and current neurologic conditions and symptoms consistent with peripheral nerve disease or degeneration was obtained during the examination as part of the medical history questionnaire. Questions pertaining to symptoms relating to nerve function are contained in Appendix D. A history was obtained on disorders of the peripheral and central nervous systems and on exposure to factors which may have adversely affected the PNS or CNS. These included diabetes, uremia, peripheral vascular disease, medication or alcohol use, occupational or environmental exposure to neurotoxins such as solvents, heavy metal or to neurologically damaging physical factors such as vibrating tools, repetitive hand movements or heavy

lifting. Symptoms related to autonomic nervous system dysfunction are also included in Appendix D.

Case Definition of Peripheral Neuropathy

Prior to the analysis of the neurologic data, an operational definition of distal peripheral neuropathy was developed to compare the prevalence of peripheral neuropathy in the examined workers with the examined referents. The case definition encompassed elements from the medical history (symptoms), neurological examination (signs), the electrophysiologic tests and the quantitative sensory tests. These data were specifically included in the case definition of peripheral neuropathy because, although there is no widely accepted single definition, there is a concensus that these four factors should be considered in the diagnosis of peripheral neuropathy (Dyck et al, 1985; American Diabetes Association, 1989).

Information collected from the medical history relevant to peripheral neuropathy included symptoms of tingling, burning, numbness, weakness or twitching or rippling in arms and legs. Results of the medical history were coded as positive if the participant responded affirmatively to the presence of a symptom or as negative if participant reported the absence of the symptom, since first exposure to 2,3,7,8-TCDD-contaminated processes.

Data from the neurologic examination which were incorporated into the case definition included: decreased strength in upper and lower limb muscles, absent or decreased tendon reflexes (ankle, patellar, biceps), pinprick, vibratory or position sensation, abnormalities of gait, station or coordination. Results of the neurological examination were coded as normal or abnormal by the examining neurologist who followed the standard study examination procedures.

For development of the case definition of peripheral neuropathy, each electrophysiology measure and thermal and vibration thresholds was dichotomized based on limits developed from the distribution of electrophysiologic measurements and thermal and vibration thresholds of the referent population. For nerve conduction velocities and amplitudes, measurements below the 5th percentile of the referent distribution were included as part of the case defintion for peripheral neuropathy. Likewise, latencies, quantitative sensory tests, and vibration and thermal sensitivity thresholds above the 95th percentile of the referent distribution were also included (Dyck et al, 1985).

Some referents were excluded <u>a priori</u> from the calculation of case limits because they had preexisting conditions which are strongly associated with peripheral neuropathy in the absence of exposure to 2,3,7,8-TCDD. Two different groups of exclusions were considered:

those with conditions which had not previously been associated with exposure to 2,3,7,8-TCDD and those with conditions which were putatively related to 2,3,7,8-TCDD exposure. Five referents were excluded because they had conditions which are associated with peripheral nerve disease but not related to exposure to 2,3,7,8-TCDD: two reported a history of genetically acquired neuropathy such as Charcot-Marie-Tooth syndrome; three reported use of medication at the time of the examination associated with peripheral neuropathy (LeQuesne, 1984; Schaumburg et al, 1983; D'Amour, 1979); one had a history of a deforming leg injury; and, one refused to participate in the electrophysiologic tests. Twenty-two referents in the second group were also excluded from the calculation of the case limit: twelve had diabetes; nine reported a history of stroke; and, one reported a history of multiple myeloma. Diabetes was defined as a fasting blood glucose 140mg/dl (7.8 nmol/L) measured in two successive tests, or current use of glucose-regulating medication or diet, or a history of physician diagnosed diabetes. The medical conditions leading to exclusion from the calculation of the case limits were diagnosed either before the study by the referent's personal physician, and reported in the medical history, or the condition had not been known to the referent and was first identified during the study examination. Based on these criteria, 29 referents were excluded from the calculation of case limits for lower limbs and 28 referents were excluded from calculation of case limits for upper

limbs. Data from the remaining referents were used to develop the case definition and are described in Table 7. A description of the exclusion of workers and referents from the analysis of peripheral neuropathy is included in this chapter in the section titled Statistical Analysis.

In this study a case of peripheral neuropathy was defined by the following criteria:

1. Clinical criterion:
   a. The presence of a latency, amplitude or conduction velocity outside the reference limit, plus

   b. At least one abnormal clinical sign diagnosed during the neurologic exam, or

   c. An out-of-range quantitative sensory test, or

   d. At least two positive neurologically related symptoms reported in the medical history.

2. Anatomic criterion:

Evidence from the neurological examination, quantitative sensory tests and symptoms must have been diagnosed or reported in the same part of the body (upper or lower) as the out-of-range electrophysiologic measurement.

Upper body measurements included: electrophysiologic measurements of the median motor and median sensory and ulnar sensory nerves; thermal and vibratory sensory test of the index finger; clinical assessment of the strength of the deltoid, tricep, bicep, brachioradialis, wrist extensor, wrist flexor, opponens pollicis, interossei, and finger extensor muscles; activity of the brachial tendon; sensory perception of pain and light touch of the index fingers, wrists, midforearm, biceps tendon, sensory perception of vibration of the index fingers and head of the radius, and sensory perception of position of the index fingers; abnormalities in rapid hand rotation and index finger-to-thumb manipulations.

Lower body measurements included: electrophysiologic measurements of the peroneal motor and sural sensory nerves; thermal and vibratory sensory test of the great toe; clinical assessment of the strength of the hip, knee, feet and toe flexor muscles, knee, feet and toe extensor

muscles; activity of the patellar and achilles tendons; sensory perception of pain and of light touch of the great toes, mid-dorsal section of feet, lateral malleoli, mid-shins and knees, vibration perception of the great toes and lateral malleoli, and sensory perception of position of the great toes; abnormalities in station, gait and toe tapping.

Assessment of the Severity of Peripheral Neuropathy

The severity of a case of peripheral neuropathy was based on the total number of out-of-range electrophysiologic or quantitative sensory test values, or abnormal signs from the neurologic examination, or positive symptoms reported in the medical history. Each out-of-range value, abnormal sign or greater than two symptoms was assigned a value of one, such that the greater the number of out-of-range, abnormal signs and positive symptoms, the more severe the condition.

Assessment of exposure to 2,3,7,8-TCDD contaminated chemicals

Duration of exposure to 2,3,7,8-TCDD contaminated chemicals at the New Jersey and Missouri plants

The NIOSH Dioxin Registry contains demographic and work history records for each qualifying individual. Work histories of

employment at companies where 2,3,7,8-TCDD contaminated chemicals were manufactured were reconstructed from personnel and payroll records. Work histories were abstracted and coded into a computer file. Data coded into the work history included first and last date of hire and, each job potentially contaminated with 2,3,7,8-TCDD and the associated department and operation. Duration of exposure in 2,3,7,8-TCDD contaminated processes was calculated in days of exposure by summing the calendar period of assignment to 2,3,7,8-TCDD contaminated processes as described previously (Sweeney et al, 1989).

Serum 2,3,7,8-TCDD levels

Serum 2,3,7,8-TCDD levels were used as a surrogate for exposure in this analysis because they were found to be highly correlated with length of exposure in an interim analysis of the serum levels of 135 production workers (Sweeney et al, 1989). Each participant of the medical examination donated 10-50 milliliters of serum for determination of serum 2,3,7,8-TCDD levels. Collection and preparation of these samples for analysis is described elsewhere (Fingerhut et al, 1989; Patterson et al, 1986).

All serum samples collected from examined workers were analysed for 2,3,7,8-TCDD content. However, only 35% of the serum collected from the examined referents was measured for 2,3,7,8-TCDD level. The referents whose serum was measured for 2,3,7,8-TCDD were

selected from a random sample of the examined referents. Each referent was randomly assigned a number from 1-260; then, every third referent sample was selected for analysis. The decision to measure only a sample of referent serum 2,3,7,8-TCDD levels was made early in the study, after each of the first 20 referent samples were found to contain less that 20 ppt of 2,3,7,8-TCDD. The mean level of these 20 samples was 8 ppt (Fingerhut et al, 1989), a level which was consistent with levels observed in other individuals from industrialized countries (Patterson et al, 1989). In contrast, the mean level of workers whose samples were analyzed concurrently, was 208 ppt, suggesting that exposure to chemicals contaminated with 2,3,7,8-TCDD was the cause of the high levels in the workers and that the rest of the referent samples would, likewise, be below 20 ppt. Because of the high per sample cost for analysis of 2,3,7,8-TCDD, and because the referent group had consistently low 2,3,7,8-TCDD levels, the analysis of only a random selection of the referent serum was conducted.

The serum 2,3,7,8- TCDD levels in this population follow a log-normal distribution (Sweeney et al., 1989). Unadjusted means of the natural logarithm of serum 2,3,7,8-TCDD were compared for workers and referents using a two sample Student's t-test (SAS, 1987). However, the untransformed serum 2,3,7,8-TCDD levels were used in the multiple logistic regression models because the magnitude of the coefficient of the exposure variable did not differ when the log transformed levels were used in the model.

Other exposures to 2,3,7,8-TCDD

During the administration of the study questionnaires, each participant was asked to report situations other than employment at the chemical manufacturing plant in Newark, New Jersey or Verona, Missouri where they may have been exposed to 2,3,7,8-TCDD contaminated substances. The demographic and occupational interview obtained information specifically on sources reported to have 2,3,7,8-TCDD contamination: residence on a farm or work in agriculture where 2,4,5-T may have been applied; and, service in Vietnam. Employment in metal recovery operations, paper and pulp mills or municipal incineration plants was also obtained if the participant reported it as part of his or her occupational history.

Analysis

Unmatched analysis

This analysis of peripheral neuropathy included all examined workers and referents. Although the intent of the study design was to conduct a matched analysis of examined workers and referents, contractual difficulties resulted in the examination of 65 (23.1%) workers without a corresponding examined matched referent, and in the examination of 44 (16.9%) referents without corresponding examined matched workers.

The advantage to a matched analysis is that the precision of the point estimate is better than in the unmatched analysis. However, the unmatched analysis would have greater power to detect an effect because the unmatched workers and referents represent approximately one-quarter of the total examined study population. In addition, because 78% of the remaining examined participants were matched, the analysis was strongly influenced by the matching effect of the larger proportion of examination participants. To evaluate the effect of including unmatched workers and referents in the analysis, comparisons were made between matched and unmatched workers and between matched and unmatched referents for selected demographic characteristics, cases of peripheral neuropathy and serum 2,3,7,8-TCDD levels.

Description of the examined study population

Selected demographic data were analyzed to compare the socioeconomic status of all workers and referents who participated in the examination and to describe personal habits relevant to the development of peripheral neuropathy. For the categorical variables, the statistical significance of the difference in the proportion of workers and referents was compared by chi-square test. The categorical variables were classified as: race (white, black, Asian), sex (male,female), income (less than $10,000, $10,000- $19,999, $20,000-$29,000, $30,000-$39,999, $40,000-$49,999, $50,000 or more, refused to answer the question),

education (1-8 yrs., 9-12 yrs., vocational training, some college and post-graduate training), and current alcohol status (current drinker: reported drinking within the past year; former drinker: denied drinking within the past year; never: never drank alcohol). For the continuous variables, age, height and lifetime alcohol consumption, the means for workers and referents were compared in a two-sample Student's t-test. The variable, lifetime alcohol consumption, was log-normally distribution; thus, the natural log of the variable was used in the two-sample Student's t-test.

Exclusion of workers and referents from the analysis of peripheral neuropathy

It was necessary to exclude a priori from the analysis workers and referents with certain conditions which are strongly associated with disorders or dysfunction of the peripheral nervous system. Inclusion of these individuals in the analysis may have severely confounded the results and potentially masked, perhaps subtle effects, produced by exposure to 2,3,7,8-TCDD from the peripheral nerve disease produced by the predisposing condition.

As in the case of the referents who were excluded from the development of the case limits, conditions which excluded workers and referents from the analysis of peripheral neuropathy were divided into two groups: those which would have no relationship to

exposure to 2,3,7,8-TCDD including individuals who were taking of neurotoxic medications, individuals with hereditary peripheral nerve disease, individuals who had peripheral nerve damage due to a traumatic injury, and individuals who would not cooperate with the examining physician, or refused to complete a part of the neurologic assessment. In the case of the workers and referents in the latter category, the validity of the neurologic assessment may have been compromised by the refusal to perform the tests correctly and, thus, they were excluded from the analysis. The second group of workers and referents who were excluded from the analysis were those whose conditions may have been associated with exposure to 2,3,7,8-TCDD. This class of workers and referents included diabetics, individuals who reported a past history of stroke, or a history of multiple myeloma.

Although it is unlikely that exclusion of workers and referents having conditions putatively associated with exposure to 2,3,7,8-TCDD would have differentially excluded cases of peripheral neuropathy from the analysis, logistic regression models were constructed to evaluate the effect of removing these workers and referents from the analysis. Two different models were created, one which included all of the a priori exclusions and one which included diabetics as a covariate in the model. The change in the coefficient of the exposure variable in each of the models was compared. The models were constructed only for diabetics because

the number of cases of strokes and multiple myeloma were too small to obtain meaningful models.

Hypothesis testing - Cases of peripheral neuropathy

The statistical analysis of this study followed a general approach in which all relevant examination data for each study participant were reviewed but in which a single hypothesis was tested. The primary hypothesis of the study was that workers exposed to chemicals contaminated with 2,3,7,8-TCDD experienced an increased prevalence of peripheral neuropathy of the upper or lower limbs compared to an unexposed referent group. A single primary hypothesis was constructed from the combination of the neurologic data, because the diagnosis of peripheral neuropathy is generally made from the integration of information from the neurologic examination, electrophysiologic and quantitative sensory tests and the medical history. With this in mind, operational definitions of peripheral neuropathy of the upper and lower body were constructed. A second reason for development of one primary hypothesis was to avoid introduction of Type I Errors (incorrectly concluding that an association exists when it does not) which occur more often when many statistical tests are conducted on the same data set.

In evaluating the statistical significance of the primary hypothesis, a one-tailed 95% test of significance were used for the

analyses of peripheral neuropathy. This approach was used because the a priori hypothesis assumed that exposure to 2,3,7,8- TCDD increases the proportion of individuals with peripheral neuropathy.

Unadjusted odds ratios (OR) and chi-square tests were calculated to compare the proportion of workers and referents who met the case definition for peripheral neuropathy of the upper or lower limbs. To determine the severity of peripheral neuropathy in workers and referents, mean severity scores were calculated for cases of the upper and lower limbs. Two-sample t-tests were used to assess the statistical significance of the mean severity scores.

To evaluate the effect of potential confounders, a stratified analysis was conducted for cases of peripheral neuropathy. The variables considered as potential confounders include age at the time of the examination, race, sex, location of employment (at the New Jersey or Missouri plants) and alcohol consumption. The continuous variables of age at examination, lifetime alcohol consumption and serum 2,3,7,8-TCDD were stratified into categories with approximately equal numbers of worker cases. Because there are differing numbers of individuals who met the definition for peripheral neuropathy of the upper and lower limbs, the strata for age, alcohol consumption and serum 2,3,7,8-TCDD are slightly different for the two types of cases. Age at examination was stratified into the categories: upper limb: 30-49, 50-55, 56-62,

63-69 and 70 or higher; lower limb: 30-48; 49-52, 53-57, 58-62 and 63 or higher. Alcohol consumption was divided into the following strata: for the upper limb: less than 1-1.9, 2-16, 17-48, 49-202 and 202 or higher; for the lower limb: less than 1-2, 3-16, 17-43, 44-86 and 87 or higher. The following categories were used for serum 2,3,7,8-TCDD levels: for the upper limb, 0-19, 20-57, 58-123, 124-307 and 308 or higher; and, for the lower limb, 0-19, 20-34, 35-72, 73-152, 153 or higher. The Cochran-Mantel-Haenszel procedure (SAS, 1987) was used to combine the odds ratios of the separate strata into a summary odds ratio.

Multiple logistic regression models for cases of peripheral neuropathy

Multiple logistic regression analysis was performed to control simultaneously for potential confounders and to assess possible interactions between exposure and potential confounders (SAS, 1987). Exposure was kept in the model as one of three variables: a dichotomous variable of worker and referent; categories of serum 2,3,7,8-TCDD for the upper limb, 0-19, 20-57, 58-123, 124-308 and 308 or higher; for the lower limb, 0-19, 20-34, 35-72, 73-152, 153 or higher; and, a continuous measure of serum 2,3,7,8-TCDD. The categories were statified into categories with approximately equal numbers of worker cases and were used to assess possible dose response effects of increasingly higher levels of exposure. Potential confounders (covariates) evaluated in the regression

model included age at the time of the examination, lifetime alcohol consumption, race, sex, and a composite variable of musculoskeletal disorders or traumatic events which may have contributed to peripheral nerve dysfunction. If a subject reported having any one of the factors he or she was considered a positive response for the composite variable. Each of the following factors was considered in the composite variable for cases of both the upper and lower limbs: occurrences of head injury with loss of consciousness, sciatica, surgery on the spine, slipped disc, arthritis, and rheumatoid arthritis. Self-reported occurrences of carpal tunnel syndrome were added to the composite variable only for models of upper limb peripheral neuropathy and self-reported occurrences of gout were added to the composite variable only for models of lower limb peripheral neuropathy. To determine the covariates placed in the final regression, a modified stepwise regression (backward and forward) procedure was employed. Any covariate found to achieve a statistical significance of 0.1 or less was retained in the model.

In the modeling procedure, confounding was assessed by comparing the change in the coefficient of the exposure variable when the potential confounder was in and out of the model. Two-way interactions between the exposure variable and the dichotomous covariates were also examined.

Data from the neurologic examination, electrophysiologic tests and quantitative sensory tests

Although the case definition of peripheral neuropathy was used for the purpose of testing the primary study hypothesis, additional comparisons were made between workers and referents to evaluate the performance of all tests of the neurologic examination, the electrophysiologic, and the thermal and vibration sensitivity tests. This detailed review of all of the individual measurements of the neurologic data was conducted to identify possible trends or other effects which may have been masked by the use of a case definition of peripheral neuropathy.

Prior to analysis, the distribution of the electrophysiologic and quantitative sensory tests were examined for normality. Of the 22 variables, 14 required natural log transformation to meet the requirements of normality of the statistical tests. No adjustments for multiple statistical tests were made. Two sample t-tests were used to assess statistical significance of means of these continuous data. Because the results of the t-tests comparing the log-normalized and untransformed data were the same, the untransformed data are shown in the tables, except where noted.

Unadjusted odds ratios (OR) and chi-square tests were calculated to compare the proportion of workers and referents with abnormal findings in the neurologic examination, the proportion of workers

and referents with electrophysiologic and quantitative sensory tests which fell outside the case limit, and the proportion of workers and referents with positive neurologic symptoms reported in the medical history. Unadjusted means and two-sided 95% confidence intervals for the continuous values of the electrophysiologic and quantitative sensory tests were calculated separately for workers and referents.

CHAPTER IV

RESULTS

Descriptive Statistics

The population of New Jersey and Missouri workers eligible for participation in the cross-sectional study totaled 586. Of these, 142 (24.2%) were determined to be deceased and 44 (7.5%) could not be located for vital status determination (Table 8). All 400 remaining workers who were known to be alive at the start of the study were invited to participate in the study; 360 (90%) were interviewed and 281 (70%) were examined (Table 9). For each of the 360 interviewed workers, at least 4 referents who fit the matching criteria were identified according to the prescribed algorithm. A total of 938 potential referents was identified from among community residents who fit the matching criteria and who were invited to participate in both the in-home interview and the

medical examination (Table 10). Of these, 325 (34.6%) were interviewed and 260 (27.5%) were examined. The analyses presented in this report include only the 281 workers and the 260 referents who participated in the in-home interview and the two-day medical examination.

Table 11 provides descriptive information on the study cohort. No statistically significant differences were found between examined workers and referents for age, race, gender, current family income, highest grade achieved, current alcohol status or lifetime alcohol consumption. A separate report will examine the differences between these study participants and the workers and potential referents who were unable to participate (deceased or disabled) or who refused to participate in both the in-home interview and the examination, or who were interviewed but refused to be examined.

Because workers and referents were excluded a priori from the analysis due to diabetes, stroke and other factors, 241 (85.8%) of the 281 examined workers and 232 (89.2%) of the 260 examined referents were eligible for inclusion in the analysis of neurologic outcomes. A total of 41 (14.6%) workers and 28 (10.7%) referents were excluded from the analyses of the upper body and 41 (14.6%) workers and 29 (11.2%) referents were excluded from the analyses of the lower body. The proportions of workers excluded from the analysis due to diabetes, stroke, current prescription of medications known to be neurotoxic or inherited neurologic disease,

are not statistically significantly different than the proportion of referents excluded from the analysis for the same conditions (Table 12).

Cases of Peripheral Neuropathy

Approximately 18% of examined workers and 19% of examined referents met the study case definition for peripheral neuropathy for either the upper or lower body (Table 13). The unadjusted OR of 0.93 (90% Lower confidence limit=0.63) for peripheral neuropathy of the upper body was similar to that of the lower body (OR=0.95, 90% Lower confidence limit=0.65).

Table 14 illustrates the mean and range of severity scores of workers and referents with peripheral neuropathy of the upper and lower limbs. In general, the sum of the number of abnormal findings from the neurologic examination, and the values outside the case limit for the electrophysiologic measures or thermal and vibration thresholds were not different between workers and referents for either case definition. The mean score of 5.1 for the upper limb for workers was not statistically significantly different than the mean of 6.4 for the upper limb in referents. Similarly, the means of 8.6 and 8.7 for the lower limb were not statistically significantly different for workers and referents, respectively.

Tables 15 and 16 illustrate the odds ratio for cases of peripheral neuropathy of the upper and lower limb adjusted for selected demographic characteristics. In the stratified analysis, age at examination among both workers and referents was statistically significantly associated with having peripheral nerve dysfunction in either the upper or lower limbs. Over eighty percent of the cases of the upper limb and seventy percent of the cases of the lower limb occurred in workers and referents over 50 years old. One hundred percent of the worker cases and 95% of the referent cases occurred in males and over 85% occurred in white workers and referents. While over 75% of the cases of peripheral neuropathy of the upper and lower limbs occurred among New Jersey workers, the proportion of cases of either the upper or lower limb was approximately the same for those with employment in the 2,3,7,8-TCDD contaminated processes at the Missouri plant (17.5%) and those who worked at the New Jersey facility (18.0%). The difference did not achieve statistical significance.

Serum 2,3,7,8-TCDD Levels

Serum 2,3,7,8-TCDD levels were obtained from 272 of the 281 examined workers and from 99 of the 260 examined referents (Table 17). Levels for 9 workers were not obtained. Blood could not be drawn from one worker because of the poor patency of his veins, and the analyzed samples did not meet the quality control standards of the laboratory for eight workers (Patterson et al, 1989; Turner et al, 1989). In addition, measurements for 161 referents were not

obtained. One sample did not pass the laboratory quality control specifications. The remaining samples were not analyzed.

Serum levels for 10 workers and 24 referents could not be determined because the levels fell below the limit of detection. To avoid exclusion of these observations from the regression models and avoid an upward bias in the mean 2,3,7,8-TCDD levels, an estimation of the actual levels was calculated (Hornung and Reed, 1990). (A missing value for any variable added to the regression model will cause exclusion of the entire observation). For each sample below the limit of detection, the estimated level was calculated by dividing the detection limit of the sample (which differed for each sample) by the square root of 2 and then was compared to the median 2,3,7,8-TCDD level for workers (74 ppt) or for referents (6 ppt), whichever was appropriate. If the estimated level fell below the corresponding median, the value was kept for analysis. Using this method, 10 estimated worker levels and 12 estimated referent levels were added to the analysis. The addition of these 22 levels did not cause statistically significant decreases in the mean for workers or for referents (Table 18).

To build the logistic regression models, referents whose serum 2,3,7,8-TCDD levels were not measured, were assigned a value of 6.0 ppt, the median level for the referents after inclusion of the samples which fell below the limit of detection. This adjustment was necessary to prevent elimination of referents from the model who lacked a value for the serum 2,3,7,8-TCDD level.

The serum level for 272 workers ranged from 2 to 3390 parts per trillion (ppt), with a mean of 211 (ppt) (Table 19). Serum 2,3,7,8-TCDD levels from 86 referents and ranged from 2 to 20 ppt. The mean of 7 ppt differed significantly from the mean level of the workers ($p<.0001$). When stratified by cohort, the mean serum level was 233 ppt for the New Jersey workers and 135 ppt for the Missouri workers. A comparison of the log-transformed mean levels for New Jersey and Missouri workers were not statistically significantly different.

Table 20 describes serum 2,3,7,8-TCDD levels among workers who met the case definition for peripheral neuropathy and workers who did not meet the case definition. The difference between worker cases and noncases did not achieve statistical significance.

A comparison of the proportion of workers with peripheral neuropathy in each of the serum 2,3,7,8-TCDD categories showed that there was approximately even distribution of cases of both the upper and lower limbs in each stratum, suggesting that there is little relationship between serum 2,3,7,8-TCDD level and peripheral neuropathy (Table 21).

Logistic Regression Models

Tables 22, 23 and 24 illustrate the covariates which remained in the final multiple logistic regression models. In the final models both for cases of peripheral neuropathy of the upper and lower

limbs, none of the three exposure variables (worker or referent, categories or continuous level of serum 2,3,7,8-TCDD) was statistically significantly related to case status. That is, after controlling for other factors related to peripheral neuropathy, serum levels of 2,3,7,8-TCDD were not associated with the presence of peripheral neuropathy. However, factors other than exposure were statistically significantly related to peripheral nerve dysfunction. For cases of peripheral neuropathy of the upper limb, age at examination, lifetime alcohol consumption, and other conditions, such as past history of carpal tunnel, sciatica and spinal surgery, remained in the final model as statistically significant covariates when the exposure measure was serum 2,3,7,8-TCDD. For cases of peripheral neuropathy of the lower limb, the final model, age at examination, and sex were statistically significant and remained in the model. No confounding and no interaction was observed in either model.

Finally, models were constructed to evaluate the effect of excluding individuals from the analysis of peripheral neuropathy due to diabetes (Table 25). When diabetes was added to the model as an independent variable, it remained as a statistically significant contributor of the overall model. However, the magnitude of the coefficient of the exposure variable and its statistical significance did not change from the model in which diabetes was excluded from the analysis. These data indicate that diabetes is a strong factor in the development of peripheral neuropathy of the upper and lower limbs; however, it has no

relationship to exposure to 2,3,7,8-TCDD. Thus, the final models were constructed without diabetics.

Individual Measures from the Neurologic Examination, Electrophysiologic Tests and Thermal and Vibration Sensitivity Tests

Neurologic examination

Tables 26, 27 and 28 describe the comparison of the proportion of abnormal clinical findings (signs) identified during the medical examination. For workers and referents, there are no statistically significant increased unadjusted odds ratios for any clinical signs evaluated in the examination of the cranial nerves (Table 26), of the upper limbs (Table 27) or the lower limbs (Table 28).

Electrophysiologic and Quantitative Sensory Tests

Table 29 and 30 describe the comparison of the unadjusted means for the electrophysiologic and quantitative sensory measurements. These data indicate few consistent differences between workers and referents for these parameters in upper limbs (Table 29) or in lower limbs (Table 30). For each measurement, the 95% two-sided confidence intervals of the mean values for workers and referents overlap, suggesting that the neurologic function of workers varies little from that observed in the unexposed referents. No

difference between the workers and referents achieved statistical significance based on a two-sample t-test.

The proportions of workers and referents with electrophysiologic and quantitative sensory tests which fell outside the case limit values for measurements of the upper limb (Table 31) or of the lower limbs (Table 32) are not statistically significantly different. Slight but statistically nonsignificant increases in the proportion of workers with out of range conduction velocities for the peroneal and sural nerves, and thermal and vibratory thresholds for the great toe weakly suggest some minor dysfunction in the nerves of the lower limb of workers compared to the referents.

Self-reported symptoms and conditions related to peripheral neuropathy

Of the symptoms related to peripheral neuropathy, workers reported approximately the same proportion of symptoms for the upper body as the referents (Table 33). In the lower limbs, workers report statistically significantly more trouble with cramping of the legs ($p < 0.05$) and difficulty balancing ($p < 0.05$). During the medical examination, participants were also asked to report on their history of injuries or conditions which may cause peripheral nerve dysfunction (Table 34). The workers reported the occurrence of these injuries and conditions with the same frequency as the referents.

CHAPTER V

DISCUSSION

Overview

The purpose of this analysis was to test the hypothesis that there is no difference in the prevalence of peripheral neuropathy in a group of workers who were occupationally exposed to 2,3,7,8-TCDD contaminated chemicals and in a group of unexposed referents. The signs and symptoms used to examine a number of the peripheral neuropathy were collected as part of a comprehensive cross-sectional medical study designed to examine many health effects associated with human exposure to 2,3,7,8-TCDD (Sweeney et al, 1989).

A case definition of peripheral neuropathy was constructed from data collected in the neurologic examination, the electrophysiologic and quantitative sensory tests and medical history interview. Based on this case definition, the prevalence

of peripheral neuropathy for either the upper limbs or the lower limbs in the workers did not significantly differ from that in the referent population. In addition, there was no relationship between increasing levels of serum 2,3,7,8-TCDD and cases of peripheral neuropathy, nor were the cases more severe in the workers. Similarly, no significant differences were observed between workers and referents when the individual measurements of the neurologic examination, electrophysiologic tests and quantitative sensory tests were evaluated.

Based on the results of the logistic regression analysis, cases of peripheral neuropathy of the upper limb appear to be related to lifetime alcohol consumption and history of physical conditions or injuries associated with peripheral nerve dysfunction. Neither of these variables achieved a statistical significance at the 0.05 level; however, they were retained in the model because they achieved a significance level of 0.07.

Neither lifetime alcohol consumption nor a positive history of physical injury contributed significantly to the model for cases of peripheral neuropathy of the lower limb. It appears that in this group, male workers are at higher risk for developing lower limb peripheral neuropathy than females. This finding is reasonable given that, in this group, the males were laborers, who were more likely to be subjected to a variety of musculoskeletal stressors of

the back or lower limbs, which may have increased their risk of developing neuropathy of the lower limb.

Neurologic Effects Observed in Other Cross-sectional Studies of 2,3,7,8-TCDD Exposed Populations

Peripheral Neuropathy

In addition to our study, seven cross-sectional studies have systematically evaluated the neurologic system in five different populations (Ranch Handers, Vietnam Army Veterans, TCP workers in Nitro, W.V., Missouri residents, Seveso, Italy residents) with potential for exposure to 2,3,7,8-TCDD contaminated chemicals. The results of our study are consistent with those of four of these studies which also found no effects related to the peripheral nervous system. A brief review of the studies follows. A study of TCP and 2,4,5-T workers from Nitro, West Virginia, found an 18% increase in reduced pin prick sensation among workers who reported a history of chloracne compared to exposed workers without a history of chloracne (Moses et al, 1984). No other neurologic deficits were found in excess. In our study, the proportion of workers and referents with decreased pin prick sensations (as determined by neurologic examination) was not statistically significantly different.

Investigators of another study of workers from the same plant in West Virginia did not report their results due to problems encountered during the administration of the neurologic evaluation (Suskind and Hertzberg, 1984). No statistically significant differences were found between exposed Ranch Handers and unexposed comparisons for the neurologic examination or the electrophysiologic tests, after controlling for fasting glucose level (diabetes) and alcohol use (Lathrop et al, 1984).

A statistically nonsignificant increase in the proportion of symptoms consistent with peripheral neuropathy were reported by U.S. Army Vietnam Veterans. However, there was no increase in the number of cases of peripheral neuropathy among Vietnam Veterans compared to the Vietnam-era Veterans or an increase in abnormalities observed during the neurologic examination, electrophysiologic tests or quantitative sensory tests (Centers for Disease Control Vietnam Experience Study, 1988).
Among populations exposed to environmental contamination by 2,3,7,8-TCDD, the results differ. Among Missouri residents who had a potential for exposure to 2,3,7,8-TCDD contaminated soil, the results of neurologic evaluations were generally negative (Webb et al, 1987). Statistically nonsignificant sensory loss was observed in the group defined as 'exposed'. No other neurologic effects were in excess.

On the other hand, a statistically significantly higher prevalence of peripheral neuropathy was identified among Seveso residents who exhibited other clinical signs of exposure to 2,3,7,8-TCDD (Filippini et al, 1981). The other clinical signs were elevated liver enzymes and chloracne, in the absence of conditions or exposures known to cause such pathologic changes.

There is probably no single explanation for the disparity in the findings among the noted epidemiologic studies and case reports. The differences may be ascribed to a number of factors, the most important being the amount of exposure to chemicals contaminated with 2,3,7,8-TCDD, the length of time between exposure to 2,3,7,8-TCDD contaminated chemicals and evaluation of peripheral nerve dysfunction and the unique limitations of each study.

Serum 2,3,7,8-TCDD Levels

Among the study of workers and residents exposed to 2,3,7,8-TCDD contaminated materials, an important factor is the amount of exposure to materials contaminated with 2,3,7,8-TCDD. Our study of workers from New Jersey and Missouri is the only study in which the relationship between serum 2,3,7,8-TCDD and neurologic endpoints was examined in a cohort of occupationally exposed individuals. As described previously in this report, the workers in our study had a mean lipid-adjusted serum 2,3,7,8-TCDD level of 211.3 ppt obtained

at the time of the examination. The highest level was 3390 ppt. A half-life extrapolation of these levels, assuming a 7 year half-life, estimated that the serum levels may have been as high as 34,000 ppt in at least one worker at the time he was last exposed. In this population, the serum 2,3,7,8-TCDD levels measured at the time of the examination and the half-life extrapolated levels were also found to be highly correlated (r=.8) with the number of days of exposure in production or in maintenance operations contaminated with 2,3,7,8- TCDD (Sweeney et al, 1989). If peripheral nerve dysfunction was related to serum level of 2,3,7,8-TCDD, a strong positive relationship between serum 2,3,7,8-TCDD level and the proportion of cases of peripheral neuropathy should have been observed. Even after controlling for other covariates, no such relationship was found.

Of the non-occupational populations in which neurologic evaluations were conducted, three studies reported serum or adipose tissue 2,3,7,8-TCDD levels (Wolfe et al, 1988; Centers for Disease Control, 1988; Moccarelli et al, 1988). However, only one of the studies used the levels in the analysis of neurologic outcomes. The U.S. Air Force Ranch Handers had a range of current serum levels which were much lower than those of the workers in our study (3.2 - 313 ppt), but which were significantly higher than those of unexposed populations. However, the relationships between serum 2,3,7,8-TCDD levels and neurologic endpoints were not examined

because the serum levels were not available for analysis of data from either the baseline study or the first follow-up study.

The U.S. Army Vietnam Veterans had a mean level of 4.2 ppt which was comparable to the mean serum 2,3,7,8-TCDD level in the unexposed Vietnam-era veteran controls (Centers for Disease Control, 1987). This population of Army Vietnam Veterans experienced minimal or no exposure to 2,3,7,8-TCDD contaminated chemicals above background level. Therefore, no adverse health effects related to 2,3,7,8-TCDD would have been expected.

The range of adipose tissue 2,3,7,8-TCDD levels in Missouri residents with potential for exposure to 2,3,7,8-TCDD was 3.7 - 750 ppt (Andrews et al, 1989). The highest levels were observed in 9 workers involved in NaTCP production in the Missouri plant who were also included in our study (mean = 245 ppt), and in 16 residents who used a horse arena shortly after it was sprayed with 2,3,7,8-TCDD contaminated waste oils (mean = 145 ppt). The remaining 156 examined residents had adipose 2,3,7,8-TCDD levels consistent with levels found in the general U.S. population (0-20 ppt), including those who were selected for study because they met the a priori criteria for environmental exposure to 2,3,7,8-TCDD. No exposure-related peripheral neuropathies were found in either the workers or horse arena users (Webb et al, 1987).

At the time the Seveso residents participated in the neurologic evaluation conducted by Filippini, exposure to 2,3,7,8-TCDD was estimated by the level of 2,3,7,8-TCDD in the soil of residential areas. Areas determined to be highly contaminated had levels of 2,3,7,8-TCDD ranging from 15.5 ug/m^3 to 580.4 ug/m^3 (Pocchiari, 1979). The soils in the unexposed regions averaged less than 3.0 ug/m^3. In 1988, serum levels of individuals residing in the 2,3,7,8-TCDD contaminated areas of Seveso and uncontaminated areas of Seveso and other nearby communities were measured from serum samples acquired within a year after the TCP reactor release. The serum levels in 5 residents from the most highly contaminated areas and diagnosed with chloracne ranged from 828 ppt to 27,821 ppt (Mocarelli et al, 1988); the levels in 5 residents from the same contaminated region but without chloracne had levels ranging from 1,772 ppt to 10,439 ppt; the levels in 5 residents from uncontaminated regions ranged from non-detectable to 137 ppt. It is not possible to ascertain if the exposed residents who had serum 2,3,7,8-TCDD levels measured were also participants in the evaluation of peripheral neuropathy. However, because the population studied by Filippini was selected from among the 735 individuals who lived in the most highly contaminated region of Seveso, it is realistic to assume that at least some of the participants in the study had exposures which were comparable to those whose serum 2,3,7,8-TCDD level was measured. The data from this study suggest that the high serum 2,3,7,8-TCDD levels in at

least the residents with chloracne are related to the elevated prevalence rate for peripheral neuropathy.

Length of time between exposure to 2,3,7,8-TCDD and evaluation of peripheral neuropathy

The period between initial exposure to 2,3,7,8-TCDD and the neurologic assessment varies considerably among the studies and case reports. The workers in our study, the West Virginian workers (Moses et al, 1984), the Ranch Handers (Lathrop et al, 1985; Lathrop et al, 1987), the U.S. Army Veterans (Centers for Disease Control Vietnam Experience Study, 1988), and the Missouri residents (Webb et al, 1987) were examined from 15 to 37 years after exposure terminated. In contrast, the Seveso residents were examined in 1978 and 1979, 2-3 years after the TCP reactor release (Filippini et al, 1981). Similarly, the case reports of adverse health effects in TCP workers generally described effects which occurred while the exposure continued (Suskind et al, 1953; Bauer, Schultz, Speigelberg, 1961; Goldman, 1973; Jirasek et al, 1974) or within a short time after exposure ended (Baader and Bauer, 1951; Jirasek et al, 1974). The consistency in the findings of the Filippini study and in the case reports suggest that the reported neurologic effects may occur shortly after exposure. Because the other epidemiologic studies (including our study) were conducted many years after the termination of exposure, it is not possible to determine whether or not neurologic effects occurred due to

2,3,7,8-TCDD in these exposed populations and resolved over time. However, with the exception of the Army Vietnam veterans, even the proportion of self-reported symptoms related to peripheral nerve dysfunction were not in excess among the exposed groups, suggesting that either the exposed individuals forgot they had the symptoms or that they never had them. Given the consistency of the results, the latter speculation is probably correct.

Study Limitations

The selection of the exposed and unexposed study populations, the study design and limitations and biases introduced into the study may affect the study results and interpretation. Cross-sectional studies are inherently limited by a variety of factors including survivor and participation biases, respondent recall bias, inter-observer variability, exposure and disease misclassification bias and insufficient power to detect an effect. Each of these factors are described below in reference to our study of NaTCP workers from New Jersey and Missouri.

Nonparticipation

The cross-sectional medical study of NaTCP production workers from New Jersey and Missouri was designed to obtain completed demographic and occupational history interviews from at least 80 percent of the surviving worker population and completed medical

examinations from at least 70 percent of the total surviving worker population. These levels of participation were set to achieve two objectives: to conduct a scientifically valid study which would permit generalizations of the results to similarly exposed populations, and to permit the contractor to attain a reasonable minimum level of performances. The planned level of participation was achieved; however, thirty percent of the surviving workers did not participate in the medical examination and 24 percent of the total group of workers was deceased.

Nonparticipation of a segment of the study population may have introduced bias into the study if the outcome of interest was differentially distributed among those who participated in the study and those who did not. If the outcome was significantly more (or less) prevalent in the nonparticipating workers than in the participating workers, the overall risk estimate for the outcome in the participating group would have been lower (or higher). In this study, nonparticipation in the two-day medical examination was of concern because of the inability to evaluate asymptomatic and undiagnosed medical conditions in the nonparticipating workers and referents. Five categories of nonparticipants emerged: deceased and unlocatable workers, workers and referents who completed the in-home interview but refused the examination, and workers and referents who refused to participate in any study related activity. Although it was impossible to obtain comparable clinical data for workers or referents who could not or would not

participate in the study examination, a medical history of outcomes hypothesized as associated with exposure to 2,3,7,8-TCDD contaminated materials was obtained through a telephone interview of the nonparticipating worker or referent. Next-of-kin or suitable proxy respondents were interviewed as surrogates for the deceased workers. The telephone interviews were collected to compare the prevalence of conditions related to exposure to 2,3,7,8-TCDD in nonparticipants with the prevalence of the same conditions reported by the examination participants. No further analysis was conducted on the workers who were lost to follow-up. The results of the analysis of the nonparticipant study will not be completed for some time but it will provide information to estimate the amount of bias introduced by nonparticipation. It will be the subject of a separate report.

During referent selection, considerable effort was made to recruit the first eligible referent (i.e., who matched a specific worker by age, race, sex and community) into the study. Of the 938 eligible referents invited to participate in the study, 260 (27.5%) completed in both the interview and the medical examination. Although the examination participation rate of the eligible referents is less than that of the workers, based on comparison of demographic data collected during the study (Table 11), the lower participation rate does not appear to have influenced the outcome of the study by including referents who were any sicker or

healthier, more or less educated, or wealthier or poorer than the participating workers.

There are few studies which invite participation from the general public and or which required the extensive commitment of this study. One study which invites participation of the U.S. populace is the National Health and Nutrition Survey (NHANES). In general, participation rates in the NHANES range from 60-80 percent depending on the target population; however, the examinations are usually limited to several hours and are conducted in the home town of the participants. Due to the higher demands placed on the participants of our study, a lower participation rate would have been expected.

Recall bias

To obtain information about past occupational and other confounding exposures, medical history, hospitalizations and other facts pertinent to the study, the respondents' memory was relied upon to reconstruct events which may have occurred many years in the past. In rare instances, the respondents called upon their own records to reconstruct their past history. However, in most cases, the respondents attempted this exercise without the benefit of written documents. Some have suggested that recall may be enhanced by an individual's exposure or disease status. Consequently, because of their known exposure to 2,3,7,8-TCDD contaminated chemicals, the a

priori assumption was made that workers may have been more likely to report the occurrence of exposure-related diseases and symptoms than their unexposed referents.

In this analysis of peripheral nerve dysfunction, the potential effect of recall bias was limited by the use of a test-based case definition for peripheral neuropathy. With the exception of the symptoms reported by participants in the medical history, the case definition for peripheral neuropathy was based primarily upon objective data from the neurologic, electrophysiologic, and quantitative sensory tests. Reported symptoms related to peripheral nerve dysfunction were not systematically validated with medical records. Therefore, to ensure consistency of responses, the case definition required that at least two positive symptoms must have been corroborated with an electrophysiologic measurement outside the case limit range in the same part of the body.

Of the eight symptoms, workers reported statistically significantly more cramping in the legs and difficulty balancing than the referents. However, the increase in the two symptoms did not appear be corroborated by other neurologic deficits because there was no increase in the proportion of cases of peripheral neuropathy in the lower limbs in the workers.

Observation bias

Due to the large number of physicians and technicians performing examinations and tests, the opportunity for the introduction of observer bias into the study data collection process was substantial. To limit this potential bias, the following steps were taken: 1) development of, and adherence to, protocols for the administration of interviews; 2) development of, and adherence to, standard examination procedures, and to standard test protocols; 3) blinding of clinicians and technicians who conducted the neurologic examination to the exposure status of the workers and referents, and, likewise, blinding of interviewers who conducted the medical history interviews to the exposure status of participants; 4) repetition of the neurologic examination on a 5% sample of the participants; and 5) continual onsite observation of examinations and test administration techniques.

A review of results of the neurologic examinations performed by the nine neurologists revealed large disparities in the proportion of abnormal findings for face pain and for gag reflex. Of the nine examiners, one neurologist reported 90 percent of the abnormal evaluations for face pain and 85 percent of the abnormal evaluations for gag reflex. Due to the large inconsistency between examiners, and the fact that there is little evidence in the literature that exposure to 2,3,7,8-TCDD specifically affects the

cranial nerves, the measures for face pain and gag reflex were omitted from the analysis.

A total of seven technicians conducted the electrophysiologic tests. One measure of success of the technician is the ability to obtain satisfactory reading (tracings on the recording paper) for the electrophysiologic measurements. All of the tracings were reviewed and certified as correct by our consultant. An unsatisfactory tracing was represented in the data as a missing reading. The percentage of missing data for the technicians ranged from 0.64% to 5.35% based on the total number of electrophysiologic tests conducted by each technician. Because the electrophysiologic measurements were the starting criteria for inclusion as a case of peripheral neuropathy, the absence of all measurements from either the upper or lower limbs would have excluded participants from consideration as a case. A review of the participants with missing electrophysiologic data revealed that only one subject was missing data from both the peroneal and sural nerves (lower limb). No participants were missing all data from the median sensory, median motor or ulnar nerves. Therefore, only one potential case was missed due to absent electrophysiologic data.

Misclassification bias

Misclassification bias may be introduced into the study in two areas: exposure status and disease status. Exposure status may be

misclassified if any of the referents experienced significant exposure to 2,3,7,8-TCDD and exhibited exposure-related disease. This would lead to the reduction of the exposure risk estimate for workers.

To avoid exposure misclassification, potential referents were excluded from consideration if they reported employment in facilities which manufactured TCP, 2,4,5-T or phenoxy herbicides. In addition, exposure was assessed by measuring serum 2,3,7,8-TCDD for all examined workers and a sample of referents. The serum 2,3,7,8-TCDD data clearly demonstrate that the workers were exposed to greater concentrations of 2,3,7,8-TCDD than the referents whose levels are consistent with those in unexposed populations of industrialized countries (Patterson et al, 1989). In addition, there is strong correlation between serum 2,3,7,8-TCDD levels and the length of exposure to contaminated processes (Sweeney et al, 1989). Thus, there is little opportunity for misclassification of exposure in either the worker or referent population. The serum 2,3,7,8-TCDD validated the selection of NaTCP production workers as a truly exposed group and the referents as unexposed.

Disease misclassification

In this study, bias introduced by differential misdiagnosis of peripheral neuropathy should be low, because extraordinary efforts were used to blind all examiners and medical history interviewers

to the exposure status of all participants. Additionally, as previously mentioned, attempts were made to minimize observation bias by examining all participants using standard procedures and protocols. Although some discrepancies were uncovered in the proportion of abnormal results for two measurements in the neurologic examination, the discrepancies were distributed evenly among workers and referents examined by the neurologist in question. While disease misclassification may have occurred, it was not differentially applied to either the worker or referent groups and, therefore, not a significant bias to the study.

Confounding

Confounding is a bias caused by factors which are independently related to the outcome (peripheral neuropathy) and to the exposure (2,3,7,8-TCDD contaminated chemicals). In this study potential biases introduced by confounding factors were controlled by several methods: matching, modeling and exclusions. Confounding may be assessed by comparing the unadjusted risk ratio with the stratum specific risk ratios or, in the logistic regressions models, comparing the -2 log likelihood ratio for the model containing only the intercept and the exposure variable to that for the models containing the variables of interest. If the risk ratios or the -2 log likelihood ratios differ substantially, the factor is a confounder. No substantial confounding was observed in this data set. Although age is a strong predictor for there was little or no

change in the coefficient of the exposure variable when age was added to the regression model.

Matching

Although in this analysis the matching was broken, the goal of the study was to collect examination data from workers and referents who matched each other by age, race, gender and socioeconomic status. As described, matching was successful for nearly 78% of the examined workers and for 84% of the examined referents. Theoretically, given the preponderance of matched pairs who were examined, the unadjusted analysis was influenced by the matching factors. A comparison of selected characteristics of the matched (N=432) and unmatched populations (N=109) was not different (Table 35). The proportion of cases of peripheral neuropathy for the upper or lower limbs did not differ significantly between workers and referents, whether a matched or unmatched analysis was conducted. Mean serum 2,3,7,8-TCDD was not different for matched or unmatched workers.

Exclusions

A total of 41 workers and 28 referents were excluded from the analysis of the upper limb and 41 workers and 29 referents were excluded from the analysis of the lower limb. The criteria for exclusion of study participants were established prior to the

analysis and were designed to remove from the analysis only those people who had conditions which were strongly associated with peripheral neuropathy in the absence of exposure to 2,3,7,8-TCDD. However, at least three of the exclusionary criteria were based on conditions which have been putatively associated with 2,3,7,8-TCDD, that is, abnormal glucose tolerance tests, multiple myeloma, and vascular disease (strokes). The number of individuals with strokes was too small to produce meaningful results. Therefore, logistic regression models were built with and without individuals with diabetes only. The results of the models which included workers and referents with diabetes were equivalent to the models which excluded participants in those categories. Exposure to 2,3,7,8-TCDD as measured by serum 2,3,7,8-TCDD level was not related to peripheral neuropathy controlling for age at examination and diabetic status. Therefore, the exclusion of individuals with diabetes did not influence the exposure disease relationship.

Power

As described, the predicted power of the study to detect a higher prevalence of peripheral neuropathy was based on an 18 percent increase in reduced pinprick sensation among former TCP workers with chloracne compared to TCP workers without chloracne (Moses et al, 1984). However, there were no other neurologic findings in

excess in the study group. Given the number of workers and referents in our study, the power was 100 percent to detect a two-fold elevation in loss of pinprick sensation.

Conclusion

The data presented in this report showed that exposure to 2,3,7,8-TCDD caused no excess chronic peripheral neuropathy in a group of exposed workers compared to unexposed referents. Although the workers were tested from 15 to 37 years after exposure terminated, serum 2,3,7,8-TCDD levels obtained concurrently with the neurologic examination revealed levels as high as 3390 ppt. The highest estimated level was approximately 34,000 ppt which was consistent with the levels observed in Seveso residents who lived in the region of highest contamination and whose serum 2,3,7,8-TCDD level was measured within a year after the accident. There was no dose-response relationship between serum 2,3,7,8-TCDD levels present at the time of the examination and the occurrence of peripheral neuropathy in this previously exposed population.

TABLES

TABLE 1: Potential Methods of Exposure to Dioxin and Dibenzofuran Contaminants

1. Manufacture of chlorinated phenols (dioxin contaminant)
2. Spraying of herbicide 2,4,5-T (dioxin contaminant)
3. Production of hexachlorophene from 2,4,5-trichlorophenol (dioxin contaminant)
4. Pentachlorophenol used as fungicide and wood preservative (hexa-, hepta- and octa-chlorinated dibenzodioxin contaminants)
5. Transformer and heat exchange fluids (PCBs)
6. Heating PCBs in transformer fluid (dioxins, dibenzofurans)
7. Investment casting (PCBs, terphenyls)
8. Burning of pentachlorophenol or 2,4,5-T-treated wood or brush (dioxins, dibenzofurans)
9. Municipal incinerators burning organochlorine refuse (dioxins, dibenzofurans)
10. Eating fish with high levels of dioxin or dibenzofurans (concentration in aquatic ecosystems)

From: Dunigan, WG: Cutaneous signs of toxicity due to dioxins. J Am Acad Dermatol 10:688-700, 1984 (with permission)

TABLE 2: Case Reports of Neurologic Effects Among Individuals Occupationally Exposed to 2,3,7,8-TCDD Contaminated Materials

EXPOSURE[a]	STUDY POPULATION	NEUROLOGIC FINDINGS	REFERENCE
Precursor & reaction products of TCP process, TCP, NaOH Tetrachlorobenzene 1949 (West Virginia)	Four employees involved in cleanup after explosion or worked with equipment used prior to explosion studied 6 mos. & 1 yr. after explosion	<u>Subject reports</u> Headaches Neck, back pain Lower limb pain Vertigo with vomiting Insommia, nervousness Fatigue Foot numbness <u>Examination Report</u> Normal physicals (N=3) reduced muscle strength (N=1) Hyperactive deep tendon reflexes. Reduced or absent sensory ability. Myelin sheath & fiber destruction of sural nerve	Ashe & Suskind, 1950
TCP 2,4,5-T 1953-1954 (Hamburg, Germany)	31 production workers with chloracne	<u>Symptoms Reported</u>: Tiredness (N=3) Headaches (N=5) Arm & Leg pain (N=6) <u>Signs Reported</u>: Polyneuritis (N=1) Encephalomyelitis (N=1) Reduced reflexes (N=1) Hearing disturbances (N=1)	Kimmig, & Schultz, 1957
TCP, 2,4,5-T 2,4-D HCB Explosion in 1960 Daily exposure 1951-1969 (New Jersey)	73 male volunteers in production, maintenance, office areas	Leg fatigue (2.7%) Headaches (N=8) Hearing loss (N=6) Decreased proprioception (N=2) Decreased Achilles tendon reflex (N=3) Reduced smell (N=1)	Poland et al, 1971

[a]TCP= 2,4,5-trichlorophenol; 2,4,5-T= 2,4,5-trichlorophenoxyacetic acid; PCP = pentachlorophenol; 2,4-D = 2,4-dichlorophenoxy acetic acid
HCB= hexachlorobenzene: NaOH= Sodium hydroxide

TABLE 2: (continued)

EXPOSURE[a]	STUDY POPULATION	NEUROLOGIC FINDINGS	REFERENCE
11 persons exposed after explosion of TCP reactor 3/8/49 25 persons exposed during production of TCP and 2,4,5T 1948-1953 (West Virginia)	36 workers with chloracne due to exposure during TCP reactor explosion or during normal production of TCP and 2,4,5-T Age range = 22-63 Mean age = 36	Subject reports Fatigue Nervousness (N=8) Lower back & limb pain (N=9) Vertigo (N=3) Parathesia (N=1) Intolerance to cold (N=3) Loss of libido (N=2)	Suskind et al,1953
PCP TCP 8/1948 - 2/1949 Nordheim Westfalen (West Germany)	10 men in PCP & experimental TCP TCP production	Subject reports Pain & weakness in lower limbs	Baader & Bauer, 1951

[a]TCP= 2,4,5-trichlorophenol; 2,4,5-T= 2,4,5-trichlorophenoxyacetic acid; PCP = pentachlorophenol

TABLE 2: (continued)

EXPOSURE[a]	STUDY POPULATION	NEUROLOGIC EVALUATION	NEUROLOGIC FINDINGS	REFERENCE
TCP 2,4,5-T Hamburg Before 1961 (West Germany)	31 employed in TCP & 2,4,5-T production Follow-up conducted due to residual chloracne, continual "Neuromuscular weakness", vasovagal disturbances, psychological disturbances" 5 yrs. after first exam	EMG EEG Rest of exam not described	<u>Subject reports</u> Tired & weakness in proximal leg muscles Headaches, dizziness Orthostatic collapse Decreased libido Increased irritability Depression <u>Examination results</u> Parathesia (N = 2) Reduced sensory ability & epicritic disturbances in lower limbs (N = 2) Abnormal EEG (N = 6). Overexcitability, hand trembling Increased sweating of hands, leg & underarm sweating; Indication of Chvostek's Sign No orthostatic collapse No paresis, muscle atrophy or absence of reflexes. No nerve damage (EMG). Psychological disturbances Change in sleep habits, mood Depression & anxiety	Bauer, Schultz, Spiegelberg, 1961

[a]TCP= 2,4,5-trichlorophenol; 2,4,5-T= 2,4,5-trichlorophenoxyacetic acid; PCP = pentachlorophenol

TABLE 2: (continued)

EXPOSURE[a]	STUDY POPULATION	NEUROLOGIC FINDINGS	REFERENCE
TCP 2,4,5-T 1953 (Ludwigshafen, Germany)	42 BASF production workers with chloracne	Symptoms in 7 workers with chloracne: Hyperflexia, hyperalgesia Fatigue of legs Paresis of N. olfactorius Disseminated encephalitis Reduced sensory & motor coordination of distal segments of arms and legs Altered sense of smell, taste & hearing loss Hypotonia of extremities	Goldman, 1973
TCP 2,4,5-T 1965-1968 (Czechoslovakia)	55 TCP & 2,4,5-T workers Followed from 1969-1973	Subject reports Pain under RT Costal Arch Headaches; sweating Unspecified CNS symptoms (N=17) CNS + PNS abnormalities (N=4) Lower limb PNS abnormality determined by EMG (N=13) Fatigue & weakness of lower limbs Psychologic exam results: 50% = normal 21% = borderline 27% = abnormal 2% = distinctly abnormal	Jirasek et al, 1974

[a]TCP= 2,4,5-trichlorophenol; 2,4,5-T= 2,4,5-trichlorophenoxyacetic acid; PCP = pentachlorophenol

TABLE 2: (continued)

EXPOSURE[a]	STUDY POPULATION	NEUROLOGIC FINDINGS	REFERENCE
Pure 2,3,7,8-TCDD 1970 (England)	3 laboratory workers	Subject A: No signs or symptoms reported Subject B: Headaches Loss of vigor Mood changes muscle coordination Blurry vision Fatigue Subject C: Loss of concentration, Reduced taste Changes in visual field Sleeping difficulties Transient superficial thigh pain	Oliver, 1975
TCP 2,4,5-T 1965-1968 (Czecho-slovakia)	4 year follow-up 55 of TCP production workers Follow-up in 1973-1979	Repeated neurologic exams indicated a decrease % of normal examinations; increase in polyneuropathy & encephalopathy -9% showed improvement over time	Pazderova-Vejlupkova et al,1981

[a] TCP= 2,4,5-trichlorophenol; 2,4,5-T= 2,4,5-trichlorophenoxyacetic acid; PCP = pentachlorophenol

TABLE 3: Cross-sectional Studies of Neurologic Effects Among Individuals Occupationally Exposed to 2,3,7,8-TCDD Contaminated Materials

EXPOSURE[a]	STUDY POPULATION	COMPARISON POPULATION	NEUROLOGIC EVALUATION	NEUROLOGIC FINDINGS	REFERENCE
TCP 2,4,5-T Explosion in 1949 Daily exposure-1948-1269 (West Virginia)	226 male volunteers invited to participate based on union record of employment in the production of TCP or 2,4,5-T Definition of exposure as current or history of chloracne"	Workers with no chloracne (N=109)	Not described	Significant difference in symptoms of muscle pain, Decreased libido, erection or ejaculation difficulties Pin prick sensation decreased in 18.3% with history of chloracne	Moses et al, 1984

[a]TCP= 2,4,5-trichlorophenol; 2,4,5-T= 2,4,5-trichlorophenoxyacetic acid; PCP = pentachlorophenol

TABLE 3: (continued)

EXPOSURE[a]	STUDY POPULATION	COMPARISON POPULATION	NEUROLOGIC EVALUATION	NEUROLOGIC FINDINGS	REFERENCE
2,4,5-T 2,4-D 1957-1979 (Arkansas)	55 of 190 active, retired or former workers of plant without positive history of diabetes, neurologic disease, excess alcohol consumption.	N = 25 8 subjects of another study 17 New York City residents with no diabetes, stroke, neurologic disease or have more than 4 drinks per day	Conduction velocities of median motor, median sensory, sural sensory on limbs without prior trauma or injury. Sural was not measured if report of disc disease or injury.	NCV of sural & median motor lower in exposed	Singer et al, 1984
TCP 2,4,5-T 1948-1969 (West Virginia)	204 production or or maintenance workers in TCP or 2,4,5-T	163 employees who never worked in TCP & 2,4,5-T areas	NCV of sural sensory & peroneal motor	No differences observed	Suskind & Hertzberg, 1984

[a]TCP= 2,4,5-trichlorophenol; 2,4,5-T= 2,4,5-trichlorophenoxyacetic acid; PCP = pentachlorophenol; 2,4-D = 2,4-dichlorophenoxyacetic acid; NCV=nerve conduction velocity

TABLE 4: Cross-sectional Studies of Neurologic Effects Among Individuals Environmentally Exposed to 2,3,7,8-TCDD Contaminated Materials

EXPOSURE[a]	STUDY POPULATION	COMPARISON POPULATION	NEUROLOGIC EVALUATION	NEUROLOGIC FINDINGS	REFERENCE
2,3,7,8-TCDD contaminated waste due to accident at TCP plant	446 residents of Seveso & Meda, Italy	255 residents of nearby towns without contamination	Not detailed but included clinical exam & NCV	1977: neurologic damage in 6.7% of Seveso residents & 1.2% in unexposed residents 1978: neurologic damage in 11.7% of Seveso residents	Pocchiari et al, 1979
July, 1976 (Seveso, Italy)	200 workers from ICMESA plant	None	Not detailed	workers: neuropathic included clinical signs (4%) exam, EMG, NCV	
see description above	308 residents of Seveso, Italy	305 residents of nearby towns without contamination	Symptoms: Pain, tingling, Numbness Sensory review Muscle tone & strength Deep tendon NCV of ulnar & peroneal nerves	Elevated PRR for peripheral neuropathy in Seveso residents with indicators of exposure, (high GGT, SGOT, SGPT or chloracne) (PRR=2.8, 95% CI = 1.2-6.5.) Seveso residents with predisposing factors (alcohol or inflammatory disease) (PRR=2.6, 95% CI = 1.2-5.6)	Filippini et al, 1981

[a]TCP= 2,4,5-trichlorophenol; 2,4,5-T= 2,4,5-trichlorophenoxyacetic acid; PCP = pentachlorophenol; 2,4-D = 2,4-dichlorophenoxyacetic acid; NCV= nerve conduction velocity; EMG=electromyography

TABLE 4: (continued)

EXPOSURE	STUDY POPULATION	COMPARISON POPULATION	NEUROLOGIC EVALUATION	NEUROLOGIC FINDINGS	REFERENCE
2,3,7,8-TCDD contaminated waste oil 1971 (Missouri)	68 volunteers in State Dioxin Registry; estimated exposure to 20-100 ppb TCDD for 2 yrs or 100 ppb for 6 months	36 volunteers in State Dioxin Registry with no history of exposure to 2,3,7,8-TCDD	See Missouri Health Dept. Report, 1983	No differences in contaminated neurologic exam or in feeling of pins-needles; loss of sensation in extremities, tingling in fingers & toes, diminished VIB 256, diminished VIB 64, diminished pin sensation, diminished thermal sensation (PRR=2%).	Webb et al, 1987

TABLE 5: Cross-sectional Studies of Neurologic Effects Among Vietnam Veterans

EXPOSURE	STUDY POPULATION	COMPARISON POPULATION	NEUROLOGIC EVALUATION	NEUROLOGIC FINDINGS	REFERENCE
Vietnam Service 1962-1971	1208 USAF Ranch Handers assigned to aerial spraying herbicides & insecticides over Republic of Vietnam	1238 individuals assigned to cargo mission organizations in Southeast Asia matched by month of birth, race occupational code	History of neurologic disease cranial nerve function muscle strength tendon reflexes vibration, pain & touch sensitivity	-Excluded positive syphilis test and edema of extremities Borderline association between status as enlisted, ground personnel and babinski reflex and abnormal vibration sense (tuning fork) and status as enlisted flying personnel. No distinct patterns between length of assignment and peripheral or cranial nerve function.	Lathrop et al, 1984
			NCV of ulnar and peroneal	Significantly decreased distal ulnar nerve conduction velocities were found among flying, enlisted personnel but not observed in any other group.	
			CNS function: tremor, gait, coordination, Romberg test	Peripheral nerve and CNS examination and nerve conduction velocities were strongly related to glucose level and alcohol consumption	

TABLE 5: (continued)

EXPOSURE	STUDY POPULATION	COMPARISON POPULATION	NEUROLOGIC EVALUATION	NEUROLOGIC FINDINGS	REFERENCE
Vietnam Service 1962-1971 (first follow-up)	1016 USAF Ranch Handers assigned to aerial spraying of herbicides & insecticides over Republic of Vietnam (see Lathrop et al, 1984)	1293 individuals assigned to cargo mission organization in Southeast Asia. (see Lathrop etal., 1984)	(see Lathrop et al, 1984) No NCV testing	No difference between exposure groups for cranial and peripheral nerve function Marginal association between exposure and abnormal CNS index	Lathrop et al, 1987
Vietnam Service 1965-1971	Male Vietnam veterans Serving 1 term of enlistment with a minimum of 16 weeks active duty earned military occupational specialty pay grade of E-5 or lower at discharge first entered duty 1/19/65 - 12/19/71	Male veterans not serving in Vietnam but had same study entry requirements as Vietnam Veterans	Symptom History Neurological examination NCV, vibration & thermal sensitivity hearing acuity visual acuity	No peripheral neuropathy as defined in case definition More reports of symptoms consistent with peripheral neuropathy in Vietnam Veterans Statistically significant increase in high-frequency hearing loss in Vietnam veterans consisstent with exposure to military noise Serum 2,3,7,8-TCDD levels similar to levels in U.S. general population	CDC VES, 1988 CDC, 1988

Table 6: Concentration of 2,3,7,8-TCDD in Human Adipose Tissue and Serum from Individuals with Potential Exposure to 2,3,7,8-TCDD.

Population	# of Years Since Exposure	N	Mean (ppt)	Range (ppt)	REFERENCE
Factory Workers					
Missouri, USA, 1985	14	9	245	67-978[a]	Patterson et al., 1989
FRG	1-34	45	--	6-2252[b]	Beck et al., 1989
Missouri & NJ	15-37	135	--	2-3389	Sweeney et al., 1989
Vietnam Veterans					
U.S. Air Force	15-20	147	49	3-313[a]	Wolfe et al., 1988
U.S. Army	15-20	646	4	ND-45[a]	CDC, 1988
Residential					
Seveso, Italy	<1	10	--	1772-27821[a]	Mocarelli et al., 1988
Missouri	15	16	27	5-59[c]	Andrews et al., 1989
Others					
Horse Arenas	15	16	145	5-557	Andrews et al., 1989
Waste Haulers	15	10	12	4-26	Andrews et al., 1989

[a] Serum on a lipid basis

[b] Adipose tissue on lipid basis

[c] Adipose tissue

ND=nondetectable

TABLE 7: Limits of Electrophysiologic and Quantitative Sensory Tests for Determination of Cases of Peripheral Neuropathy

Measure	Case Limit Value
Latency	
Median Motor-Distal	≥ 10.64[a]
Median Sensory-Distal	≥ 4.16
Median Sensory-Proximal	≥ 9.68
Ulnar Sensory	≥ 3.36
Peroneal Sensory-Distal	≥ 6.16
Sural Sensory	≥ 4.56
Fwave	≥ 58.40
Amplitude (mV)	
Median Motor	≤ 4589
Median Sensory	≤ 6.46
Ulnar Sensory	≤ 4.39
Peroneal Motor	≤ 879
Sural Sensory	≤ 3.59
Nerve Conduction Velocity (m/sec)	
Median Motor	≤ 47.32
Median Sensory-Distal	≤ 35.49
Median Sensory-Proximal	≤ 47.95
Ulnar Sensory	≤ 40.54
Peroneal Motor	≤ 37.25
Sural Sensory	≤ 35.71
Vibration thresold (V)	
Index Finger	≥ 2.075
Great Toe	≥ 9.175
Thermal Threshold (°C)	
Index Finger	≥ 2.012
Great Toe	≥ 2.5875

[a] Case limit values were based on the 5th percentile for the referents from New Jersey and Missouri cohorts combined for nerve conduction velocities and amplitude measurements and on the 95th percentiles for the referents from both plants for latency, vibration and thermal thresholds.

TABLE 8: Vital Status of Worker Population Targeted for Participation in the Cross-sectional Medical Study

	New Jersey No. (%)	Missouri No. (%)	Total No. (%)
Total	490 (100.0)	96 (100.0)	586 (100.0)
Alive	318 (64.9)	82 (85.4)	400 (68.3)
Deceased	132 (26.9)	10 (10.4)	142 (24.2)
Not Located	40 (8.2)	4 (4.2)	44 (7.5)

TABLE 9: Participation of Worker Population in the Cross-sectional Medical Study

	New Jersey		Missouri		Total	
	No.	(%)	No.	(%)	No.	(%)
Total Known Alive	318[a]	(100.0)	82	(85.4)	400	(68.3)
Interviewed and Examined	222	(69.8)	59	(72.0)	281	(70.3)
Interviewed Only[b]	63	(19.8)	16	(19.5)	79	(19.8)
Refused[c]	28	(8.8)	7	(8.5)	35	(8.8)

[a] Two workers were not contacted for participation in the study because they lived outside the United States; three workers did not participate because they were unable to travel due to disabilities.

[b] Participated in the in-home interview but refused to participate in the examination.

[c] Refused to participate in the in-home interview and the examination.

TABLE 10: Participation of Referent Population in the Cross-sectional Medical Study

	New Jersey		Missouri		Total	
	No.	(%)	No.	(%)	No.	(%)
Total Invited	808	(100.0)	130	(100.0)	938	(100.0)
Total Interviewed	252	(31.2)	73	(56.2)	325	(34.6)
Total Examined	204	(25.0)	56	(43.1)	260	(27.5)

TABLE 11: Selected Characteristics of Examined Workers and Referents

	Workers (N=281)	Referents (N=260)
Age[a] (yrs) (Range)	55.4 (33-84)	56.0 (31-78)
Race[b] (%)		
White	89.0	89.9
Black	10.7	9.6
Asian	0.3	1.5
Sex[b] (%)		
Male	95	93
Female	5	7
Education[b] (%)		
1-8 years	9.3	8.1
9-12 years	46.6	44.2
Vocational Training	8.5	9.2
Some College	35.6	38.5
Income[b] (%)		
less than 10,000	9.9	10.4
10,000 - 19,999	17.8	17.7
20,000 - 29,999	18.5	19.2
30,000 - 39,999	17.8	14.2
40,000 - 49,999	11.4	14.6
50,000 or greater	23.8	20.0
Refused	0.7	2.3
Current Alcohol Status[a](%)		
Never Drank	8.2	13.1
Former Drinker	27.4	23.5
Current Drinker	64.1	63.1
Unknown	0.4	0.4
Lifetime Alcohol Consumption[c]	45.5	72.1
Height (cm)[a]	173.4	173.2
(Range)	(150-199)	(146-193)

[a] No statistically significant differences based on Student's t-test. [b] No statistically significant difference for any variable based on chi-square test. [c] Lifetime Alcohol Consumption: Equivalent to one drink per day for number of years drank alcohol. Statistically significant based on student's t-test of log transformed variable (Workers N=255, Referents N=222).

TABLE 12: Percent and Number of Workers and Referents Excluded from Analysis of Peripheral Neuropathy

Cause for Exclusion	Workers (N=281) No. (%)	Referents (N=260) No. (%)
Diabetes	27 (9.6)	16 (6.2)
Neurotoxic[a] Medication	6 (2.1)	4 (1.5)
Stroke	8 (2.9)	9 (3.5)
Other Conditions	6[b] (2.1)	4[c] (1.2)
Missing Data	-	1 (0.4)
Total Exclusions[d,e]	43 (15.3)	30 (11.2)

[a] Dilantin, Hydralazine, Dapsone & Phenytoin

[b] Uncooperative during exam (N=3); Paralysizing spinal cord injury (N=1); elbow deformity (N=1) (excluded only from analyses of upper limbs); ankle deformity (N=1) (excluded only from analyses of lower limbs)

[c] Multiple myeloma (N=1); Charcot-Marie-Tooth Syndrome (N=2); Both legs & nerves damaged in accident (N=1) (excluded only from analyses of lower limbs)

[d] Total does not equal sum of columns. Some individuals are included in more than one exclusion category.

[e] No significant difference in proportion of workers and referents excluded from analysis.

TABLE 13: Workers and Referents Meeting the Case Definition[a] for Peripheral Neuropathy and Odds Ratios

	Workers	Referents	Unadjusted[b]	Adjusted[c,d]
	No. (%)	No. (%)	OR (90% CL)	OR (95% CL)
Upper Limbs	43 (17.9)	44 (18.9)	0.9 (0.6)	1.1 (0.6)
Lower Lower	44 (18.3)	44 (19.1)	1.0 (0.7)	1.0 (0.6)

[a] Case definition: At least one electrophysiologic measurement outside case limit value, plus one abnormality detected in the Neurological Exam, Quantitative Sensory Tests or 2 systems

[b] 78% of examined study group was matched

[c] One-sided 95% Confidence Limit (Lower limit)

[d] Adjusted for covariates included in the logistic regression model: age, race, sex, alcohol consumption, other neurotoxic exposures, other injuries and conditions

TABLE 14: Mean Severity Score for Workers and Referents with Peripheral Neuropathy

	Workers		Referents	
	Upper	Lower	Upper	Lower
Number of Cases	43	44	44	44
Mean Severity Score[a]	5.1	8.6	6.4	8.7
Range	2-13	2-30[a]	2-16	2-34

[a]Mean is not statistically significantly different based on Student's t-test

TABLE 15: Cases of Peripheral Neuropathy of the Upper Limb Stratified by Selected Variables

	Workers		Referents		Weighted	
	No.	(%)	No.	(%)	OR	95% CI
Plant						
New Jersey	33	(18.0)	--	--	--	--
Missouri	10	(17.5)	--	--	--	--
Age						
30-49	6	(6.5)	7	(8.9)		
50-55	12	(28.6)	10	(21.3)		
56-62	8	(16.3)	7	(16.3)		
63-69	10	(23.8)	9	(22.0)		
70 +	7	(50.0)	11	(50.0)	1.1[a]	0.7, 1.7[a]
Race						
White	41	(19.2)	37	(17.8)		
Black	2	(7.7)	7	(29.2)	0.9[a]	0.6, 1.5
Sex						
Male	43	(100.0)	42	(95.5)		
Female	0	--	2	(4.5)	0.9[a]	0.6, 1.5
Lifetime Alcohol Consumption						
<1-1.9	5	(17.2)	2	(11.1)		
2-16	9	(12.0)	10	(15.6)		
17-48	9	(16.7)	11	(26.2)		
49-202	9	(18.8)	11	(18.0)		
203+	7	(53.9)	4	(23.5)	1.0[a]	0.6, 1.6

[a]Summary odds ratio, Cochran-Mantel-Haenszel test

TABLE 16: Cases of Peripheral Neuropathy of the Lower Limb Stratified by Selected Variables

	Workers		Referents		Weighted	
	No.	(%)	No.	(%)	OR	95% CI
Plant						
New Jersey	35	(19.1)	--	--	--	--
Missouri	9	(15.8)	--	--	--	--
Age						
30-48	9	(11.1)	8	(11.1)		
49-52	10	(25.6)	3	(10.3)		
53-56	8	(23.5)	6	(17.4)		
57-62	7	(23.3)	6	(18.5)		
63 +	10	(17.9)	21	(33.3)	1.0[a]	0.6, 1.6
Race						
White	39	(18.2)	38	(18.2)		
Black	5	(19.2)	6	(26.1)	1.0[a]	0.6, 1.5
Sex						
Male	44	(100.0)	42	(95.5)		
Female	0		2	(4.5)	0.9[a]	0.6, 1.5
Lifetime Alcohol Consumption						
Never drank	2	(10.0)	8	(28.6)		
<1-2	6	(17.1)	3	(11.5)		
3-16	10	(14.3)	12	(21.4)		
17-43	9	(20.0)	9	(21.9)		
44-86	9	(23.6)	4	(11.4)		
87+	8	(25.8)	8	(18.6)	1.0[a]	0.6, 1.6

[a]Summary odds ratio, Cochran-Mantel-Haenszel test

TABLE 17: Disposition of Serum Samples for Measurement of 2,3,7,8-Tetrachlorodibenzo-p-dioxin

	Workers (N=281)	Referents (N=260)
Measurements Above LOD	262	75
Measurements Below LOD	10	24
Serum Not Obtained	9	161

Abbreviation: LOD=Limit of Detection

TABLE 18: Difference in Serum 2,3,7,8-Tetrachlorodibenzo-p-dioxin Calculations With and Without Workers and Referents With Levels Below the Limit of Detection (LOD)

	Workers		Referents	
	With LOD	Without LOD	With LOD	Without LOD
Number of Samples in Mean	272	262	86	75
Arithmetic Mean[a]	211	219	7	8
Median	68	74	6	6
Range	(2 - 3390)		(2 - 20)	
Geometric Mean	64	67	6	7

[a] $p<.0001$ comparison of worker and referent levels based on Student's t-test of log-transformed values

TABLE 19: Serum 2,3,7,8-Tetrachlorodibenzo-p-dioxin Levels (ppt) in Workers and Referents

	Workers (N=272)	Referents (N=86)
Arithmetic Mean[a]	211	7
Median	68	6
(Range)	(2 - 3390)	(2 - 20)
Geometric Mean	64	6

[a] $p<.0001$ based on Student's t-test of log transformed mean values

TABLE 20: Comparison of Serum 2,3,7,8-Tetrachlordibenzo-p-dioxin Levels (ppt) in Workers without Peripheral Neuropathy with Workers Meeting the Case Definition for Peripheral Neuropathy of the Upper and Lower Limbs

	Peripheral Neuropathy of Upper Body	Peripheral Neuropathy of Lower Body	Without Peripheral Neuropathy	
			Upper	Lower
Total	43	44	197	196
Valid Measurements	41	43	194	192
Arithmetic Mean[a]	219	102	164	190
Median	84	34	59	76
Range	(4 - 2100)	(3 - 722)	(2 - 2058)	(2 - 2100)
Geometric Mean	72	41	58	66

[a] p is not statistically significantly different based on Student's t-test of log transformed means

TABLE 21: Distribution of Serum 2,3,7,8-TCDD (ppt) in Workers by Case Status

	Cases		Noncases	
	No.	(%)	No.	(%)
Upper Limb				
0 - 19	10	(14.9)	57	(85.7)
20 - 57	8	(16.7)	40	(83.3)
58 -123	8	(20.0)	32	(80.0)
124-307	8	(17.0)	39	(83.0)
308+	7	(21.2)	26	(78.8)
Lower Limb				
0 - 19	15	(22.4)	53	(77.6)
20 - 34	7	(24.1)	22	(75.9)
35 - 72	7	(25.9)	20	(74.1)
73 -152	7	(16.8)	35	(83.3)
153+	7	(10.0)	63	(90.0)

TABLE 22: Coefficients in the Final Multiple Logistic Regression Model for Cases of Peripheral Neuropathy of the Upper limb

Variable	Beta	Standard Error	Chi-Square	p-value
Intercept[a]	-5.326	0.784	46.15	0.000
2,3,7,8-TCDD	-0.0001	0.0004	0.06	0.802
Age at exam	0.061	0.013	21.34	0.001
Lifetime Alcohol Consumption	0.002	0.001	3.13	0.077
Other Conditions[b]	0.457	0.253	3.26	0.071

[a] Sample size = 462 observations

[b] Composite variable includes a positive history of at least one of the following: head injury with loss of consciousness, carpal tunnel syndrome, sciatica, surgery on spine, slipped disc, arthritis and rheumatoid arthritis.

TABLE 23: Coefficients in the Final Multiple Logistic Regression Model for Cases of Peripheral Neuropathy of the Lower Limb

Variable	Beta	Standard Error	Chi-Square	p-value
Intercept[a]	-4.867	1.003	23.54	0.000
2,3,7,8-TCDD	-0.002	0.001	4.46	0.035
Age at exam	0.040	0.012	11.36	0.001
Sex (0=Male, 1=female)	1.333	0.747	3.19	0.052

[a] Sample size = 461

TABLE 24: Stratum Specific Odds Ratios of Serum 2,3,7,8-TCDD Levels for Cases of Peripheral Neuropathy of the Upper and Lower Limb based on Multiple Logistic Regression Models

	OR	95% CI
Upper Limb		
0 - 19	-	- -
20 - 57	1.1	0.5, 2.5
58 -123	1.5	0.4, 3.7
124-307	1.1	0.5, 2.6
308+	0.9	0.4, 2.8
Lower Limb		
0 - 19	-	- -
20 - 34	1.4	0.5. 3.4
35 - 72	1.4	0.6. 3.5
73 -152	0.8	0.3. 2.1
153+	0.4	0.1, 0.8

TABLE 25: Coefficients in the Final Multiple Logistic Regression Model for Cases of Peripheral Neuropathy of the Upper and Lower Limb Retaining Diabetes in the Model as an Independent Variable

Upper Limb[a]

Variable	Beta	Standard Error	Chi-Square	p-value
Intercept	-4.804	0.716	44.98	0.000
2,3,7,8-TCDD	-0.00003	0.0003	0.01	0.927
Age at exam	0.058	0.012	23.07	0.001
Diabetes	1.330	0.379	12.32	0.001

Lower Limb[b]

Intercept	-4.881	0.978	24.90	0.000
2,3,7,8-TCDD	-0.0008	0.0004	2.97	0.085
Age at exam	0.039	0.011	11.69	0.001
Sex (0=Male, 1=female)	1.333	0.744	3.21	0.073
Diabetes	0.979	0.385	6.45	0.011

[a] Sample Size = 497
[b] Sample Size = 496

TABLE 26: Workers and Referents With Abnormal[a] Neurologic Findings of the Cranial Nerves as Identified in the Neurologic Examination

	Workers			Referents					
	Sample Size	No.	(%)	Sample Size	No.	(%)	Unadjusted[c] OR	95% CI	
Smell, RT[b]	239	24	(10.0)	231	19	(8.6)	1.3	(0.7,	2.3)
Smell, LT[b]	239	23	(9.6)	231	26	(11.6)	0.8	(0.5,	1.5)
Visual Field, RT	237	2	(0.8)	230	5	(2.2)	0.4	(0.1,	1.9)
Visual Field, LT	237	2	(0.8)	230	2	(0.9)	1.0	(0.1,	7.0)
Optic Disc, RT	229	0	(4.6)	224	0	(3.5)	-		-
Optic Disc, LT	224	0	(6.3)	220	0	(4.3)	-		-
Light Reaction, RT	239	1	(0.4)	221	0	-	-		-
Light Reaction, LT	239	0	-	220	0	-	-		-
Ptosis, RT	239	2	(0.8)	231	5	(2.1)	0.4	(0.1,	1.9)
Ptosis, LT	239	2	(0.8)	231	3	(1.3)	0.6	(0.1,	3.8)
Occular Mobility, RT	238	2	(0.8)	229	0	-	-		-
Occular Mobility, LT	238	3	(1.3)	229	0	-	-		-
Nystagmus, RT	239	0	-	230	6	(2.6)	-		-
Nystagmus, LT	239	1	(0.4)	230	6	(2.6)	0.2	(0.1,	1.0)
Jaw Strength	236	1	(0.4)	226		-	-		-
Jaw Jerk	239	11	(4.6)	231	8	(3.5)	1.4	(0.5,	3.4)
Corneal Reflex, RT	239	5	(2.1)	230	5	(2.2)	1.0	(0.3,	3.4)
Corneal Reflex, LT	239	4	(1.7)	231	4	(1.7)	1.0	(0.2,	3.9)
Facial Muscles, RT	239	3	(1.3)	231	3	(1.3)	1.0	(0.2,	4.8)
Facial Muscles, LT	239	1	(0.4)	231	6	(2.6)	0.2	(0.1,	1.1)
Palate Motion, RT	239	0	-	230	2	(0.9)	-		-
Palate Motion, LT	239	0	-	231	1	(0.4)	-		-
Accessory Nerves, RT	238	0	-	231	1	(0.4)	-		-
Accessory Nerves, LT	238	0	-	231	1	(0.4)	-		-
Tongue Motion, RT	239	1	(0.4)	231	1	(0.4)	1.0	(0.1,	15.7)
Tongue Motion, LT	239	0	-	231	1	(0.4)	-		-
Head Flexors, RT	240	0	-	231	2	(0.9)	-		-
Head Flexors, LT	240	0	-	231	2	(0.9)	-		-
Head Extensors, RT	240	0	-	231	1	(0.4)	-		-
Head Extensor, LT	240	0	-	231	1	(0.4)	-		-
Other Cranial Nerve Conditions	239	2	(0.8)	231	4	(1.7)	0.5	(0.1,	2.6)

[a] As determined by examing neurologists

[b] Abbreviations: RT = right, LT = left

[c] 78% of the examined study group was matched

TABLE 27: Workers and Referents With Abnormal[a] Neurologic Findings of the Upper Limbs as Identified in the Neurologic Examination

	Workers		Referents		Unadjusted[c]	
	Sample Size	No. (%)	Sample Size	No. (%)	OR	95% CI
Muscle Strength						
Deltoids, RT[b]	240	1 (0.4)	231	2 (0.9)	0.5	(0.1, 5.1)
Deltoids, LT[b]	240	1 (0.4)	232	2 (0.9)	0.5	(0.1, 5.1)
Biceps, RT	240	1 (0.4)	231	2 (0.9)	0.5	(0.1, 5.1)
Biceps, LT	240	3 (1.2)	231	2 (0.9)	1.5	(0.2, 8.7)
Triceps, RT	240	1 (0.4)	231	2 (0.9)	0.5	(0.1, 5.1)
Triceps, RT	240	1 (0.4)	232	1 (0.4)	1.0	(0.2, 15.7)
Brachioradialis, RT	240	1 (0.4)	231	1 (0.4)	1.0	(0.1, 15.6)
Brachioradialis, LT	240	2 (0.8)	232	1 (0.4)	2.0	(0.2, 20.8)
Wrist Extensor, RT	240	1 (0.4)	231	0 -	-	-
Wrist Extensor, LT	240	1 (0.4)	232	2 (0.9)	0.5	(0.1, 5.1)
Wrist Flexors, RT	240	0 -	231	2 (0.9)	-	-
Wrist Flexors, LT	240	0 -	232	4 (1.7)	-	-
Opponens Pollicis, RT	240	1 (0.4)	231	6 (2.6)	0.2	(0.1, 1.0)
Opponens Pollicis, LT	240	2 (0.8)	230	7 (3.0)	0.3	(0.1, 1.2)
Interossei, RT	240	0 -	231	3 (1.3)	-	-
Interossei, LT	240	0 -	232	5 (2.2)	-	-
Finger Extensors, RT	240	0 -	231	3 (1.3)	-	-
Finger Extensors, LT	240	1 (0.4)	232	5 (2.2)	0.2	(0.3, 1.3)
Position						
Index Finger, RT	240	2 (0.8)	232	2 (0.9)	1.0	(0.1, 7.0)
Index Finger, LT	240	3 (1.3)	232	6 (2.6)	0.5	(0.1, 2.0)
Vibration						
Index Finger, RT	240	6 (2.5)	230	3 (1.3)	2.0	(0.5, 8.0)
Index Finger, LT	240	2 (0.8)	231	3 (1.3)	0.6	(0.1, 4.0)
Head of Radius, RT	240	3 (1.3)	232	4 (1.7)	0.7	(0.2, 4.0)
Reflex						
Biceps, RT	240	75 (31.3)	232	71 (30.5)	1.0	(0.7, 1.5)
Biceps, LT	240	73 (30.4)	232	71 (30.5)	1.0	(0.7, 1.5)
Light Touch						
Index Finger DD, RT	240	8 (3.3)	232	8 (3.1)	1.0	(0.4, 2.6)
Index Finger DD, LT	240	6 (2.5)	232	12 (5.2)	0.5	(0.2, 1.3)
Index Finger PD, RT	240	1 (0.4)	232	1 (0.4)	1.0	(0.1, 15.7)
Index Finger PD, LT	240	2 (0.8)	232	2 (0.9)	1.0	(0.1, 6.70

[a] As determined by examing neurologist

[b] Abbreviations: RT = right, LT = left

[c] 78% of the examined study group was matched

TABLE 27: (continued)

	Workers		Referents		
	Sample Size	No. (%)	Sample Size	No. (%)	Unadjusted[c] OR 95% CI
Light Touch (cont'd)					
Wrist Dorsal PD, RT[b]	240	1 (0.4)	232	1 (0.4)	1.0 (0.1, 15.7)
Wrist Dorsal PD, LT[b]	240	0 -	232	0 -	- -
Forearm-mid, RT	240	0 -	232	1 (0.4)	- -
Forearm-mid, LT	240	0 -	232	1 (0.4)	- -
Biceps Tendon, RT	240	0 -	232	1 (0.4)	- -
Pinprick					
Index Finger DD, RT	240	22 (9.2)	232	20 (8.6)	1.1 (0.6, 2.0)
Index Finger DD, LT	239	9 (3.8)	231	8 (3.5)	1.1 (0.4, 2.9)
Index Finger PD, RT	240	10 (4.2)	232	7 (3.0)	1.4 (0.5, 3.7)
Index Finger PD, LT	240	9 (3.8)	232	14 (6.0)	0.6 (0.3, 1.4)
Wrist, RT	240	15 (6.3)	232	18 (7.7)	0.8 (0.4, 1.6)
Wrist, LT	240	28 (11.7)	232	17 (7.3)	1.7 (0.9, 3.1)
Midforearm, RT	240	18 (7.5)	232	9 (3.9)	2.0 (0.9, 4.5)
Midforearm, LT	240	17 (7.1)	232	10 (4.3)	1.7 (0.8, 3.8)
Biceps Tendon, RT	240	6 (2.5)	232	4 (1.7)	1.5 (0.4, 5.2)
Tremors					
Hands at Rest, RT	240	2 (0.8)	231	1 (0.4)	1.9 (0.2, 20.7)
Hands at Rest, LT	240	4 (0.8)	232	1 (0.4)	2.0 (0.2, 20.8)
Hands Outstretched, RT	240	20 (8.3)	231	16 (6.9)	1.2 (0.6, 2.4)
Hands Outstretched, LT	240	18 (7.5)	232	16 (6.9)	1.1 (0.6, 2.2)
Finger to Nose, RT	240	25 (10.8)	231	24 (10.3)	1.0 (0.6, 1.9)
Finger to Nose, LT	240	31 (12.9)	232	27 (11.6)	1.1 (0.7, 2.0)
Head of Radius, LT	240	4 (1.7)	232	3 (1.3)	1.3 (0.3, 5.9)
Coordination					
Rapid Hand Rotation, RT	240	4 (1.7)	231	10 (4.3)	0.4 (0.1, 1.2)
Rapid Hand Rotation, LT	240	8 (3.3)	231	12 (5.2)	0.6 (0.3, 1.6)
Index Finger to Thumb, RT	240	3 (1.3)	231	5 (2.2)	0.6 (0.1, 2.4)
Index Finger to Thumb, LT	240	4 (1.7)	232	6 (2.6)	0.6 (0.8, 2.3)
Biceps Tendon, LT	240	7 (2.9)	232	0 (0)	- -

[a] As determined by examing neurologist

[b] Abbreviations: RT = right, LT = left, PD = proximal dorsal, DD = distal dorsal

[c] 78% of the examined study group was matched

TABLE 28: Workers and Referents With Abnormal[a] Neurologic Findings of the Lower Limbs as Identified in the Neurologic Examination

	Workers		Referents		Unadjusted[c]	
	Sample Size	No. (%)	Sample Size	No. (%)	OR	95% CI
Muscle Strength						
Hip Flexors, RT[b]	240	2 (0.8)	231	2 (0.9)	1.0	(0.1, 6.9)
Hip Flexors, LT[b]	240	2 (0.8)	231	3 (1.3)	0.6	(0.1, 3.8)
Knee Extensors, RT	240	2 (0.8)	231	4 (1.7)	0.5	(0.9, 2.5)
Knee Extensors, LT	240	1 (0.4)	231	6 (2.6)	0.2	(0.2, 1.0)
Knee Flexors, RT	240	5 (2.1)	231	4 (1.7)	1.2	(0.3, 4.6)
Knee Flexors, LT	240	2 (0.8)	231	6 (2.6)	0.3	(0.1, 1.5)
Feet Flexors, RT	240	2 (0.8)	231	2 (0.9)	1.0	(0.1, 6.9)
Feet Flexors, LT	240	3 (1.3)	231	5 (2.2)	0.6	(0.1, 2.4)
Toe Flexors, RT	240	10 (4.2)	231	7 (3.0)	1.4	(0.5, 3.7)
Toe Flexors, LT	240	14 (5.8)	231	10 (4.3)	1.4	(0.6, 3.1)
Position						
Great Toe, RT	240	12 (5.0)	231	10 (4.3)	1.2	(0.5, 2.8)
Great Toe, LT	239	9 (3.8)	231	8 (3.5)	1.1	(0.4, 2.9)
Vibration						
Great Toe, RT	240	92 (38.3)	231	89 (38.5)	1.0	(0.7, 1.4)
Great Toe, LT	240	86 (36.0)	231	90 (39.0)	0.9	(0.6, 1.3)
Lateral Malleolus, RT	240	46 (19.2)	231	40 (17.3)	1.1	(0.7, 1.8)
Lateral Malleolus, LT	240	45 (18.8)	231	45 (19.5)	1.0	(0.6, 1.5)
Reflex						
Quadriceps, RT	240	76 (31.7)	231	73 (31.6)	1.0	(0.7, 1.5)
Quadriceps, LT	240	71 (29.6)	231	73 (31.6)	0.9	(0.6, 1.4)
Achilles, RT	240	111 (46.3)	231	97 (42.0)	1.2	(0.8, 1.7)
Achilles, LT	240	104 (43.3)	231	103 (44.6)	1.0	(0.7, 1.4)
Tremors						
Heel to Shin, RT	240	27 (11.3)	231	18 (7.8)	1.5	(0.8, 2.9)
Heel to Shin, LT	240	31 (12.9)	231	23 (10.0)	1.3	(0.8, 2.4)
Pinprick						
Great Toe DD, RT	240	48 (20.0)	231	40 (17.3)	1.2	(0.8, 1.9)
Great Toe DD, LT	239	24 (10.0)	231	27 (11.7)	0.8	(0.5, 1.5)
Foot Dorsal, RT	240	16 (6.7)	231	21 (9.1)	0.7	(0.4, 1.4)
Foot Dorsal, LT	240	16 (6.7)	231	13 (5.6)	1.2	(0.6, 2.6)

[a] As determined by examing neurologist

[b] Abbreviations: RT = right, LT = left

[c] 78% of the examined study group was matched

TABLE 28: (continued)

	Workers			Referents			Unadjusted[c]	
	Sample Size	No.	(%)	Sample Size	No.	(%)	OR	95% CI
Pinprick (cont'd)								
Lateral Malleolus, RT	240	14	(5.8)	231	23	(10.0)	0.6	(0.3, 1.1)
Lateral Malleolus, LT	240	14	(5.8)	231	12	(5.2)	1.1	(0.5, 2.5)
Shin, RT	240	27	(11.3)	231	29	(12.6)	0.9	(0.5, 1.5)
Shin, LT	240	31	(12.9)	231	33	(14.3)	0.9	(0.5, 1.5)
Knee, RT	240	17	(7.1)	231	12	(5.2)	1.4	(0.7, 3.0)
Knee, LT	240	15	(6.3)	231	10	(4.3)	1.5	(0.7, 3.3)
Light Touch								
Great Toe DD, RT	240	9	(3.8)	231	11	(4.8)	0.8	(0.3, 1.9)
Great Toe DD, LT	240	9	(3.8)	231	8	(3.5)	1.1	(0.4, 2.9)
Foot Mid-dorsal, RT	240	2	(0.8)	231	5	(2.2)	0.4	(0.1, 1.9)
Foot Mid-dorsal, LT	240	5	(2.1)	231	3	(1.3)	1.6	(0.4, 6.8)
Lateral Malleolus, RT	240	0	(0.0)	231	4	(1.7)	-	-
Lateral Malleolus, LT	240	1	(0.4)	231	2	(0.9)	0.5	(0.1, 5.1)
Mid Shin, RT	240	3	(1.3)	231	8	(3.5)	0.4	(0.1, 1.3)
Mid Shin, LT	240	3	(1.3)	231	7	(3.1)	0.4	(0.1, 1.5)
Knee, RT	240	1	(0.4)	231	4	(1.7)	0.2	(0.1, 1.8)
Knee, LT	240	4	(1.7)	231	4	(1.7)	1.0	(0.2, 3.9)
Coordination								
Toe Tapping, RT	240	10	(4.2)	231	12	(5.2)	0.8	(0.3, 1.9)
Toe Tapping, LT	240	15	(6.3)	230	17	(7.4)	0.8	(0.4, 1.7)
Station								
Eyes Open	240	0	-	231	3	(1.3)	-	-
Eyes Closed	240	4	(1.7)	231	8	(3.5)	0.5	(0.1, 1.6)
Sudden Turn	240	2	(0.8)	230	8	(2.6)	0.3	(0.1, 1.5)
Toe Walk	240	1	(0.4)	230	11	(4.8)	0.1	(0.1, 0.4)
Heel Walk	240	13	(5.4)	229	20	(8.7)	0.6	(0.3, 1.2)
Tandem Walk	240	60	(25.0)	230	49	(21.3)	1.2	(0.8, 1.9)
Gait								
Stiff Leg	240	4	(1.7)	230	5	(2.2)	0.7	(0.2, 2.9)
Arm Swing	240	6	(2.5)	230	4	(1.7)	1.5	(0.4, 5.2)
Sway	240	0	-	230	5	(2.2)	-	-
Broad Based	240	5	(2.2)	230	4	(1.7)	1.2	(0.3, 4.5)
Foot Drop	240	1	(0.4)	230	4	(1.7)	0.2	(0.1, 1.8)

[a] As determined by examing neurologist

[b] Abbreviations: RT = right, LT = left

[c] 78% of the examined study group was matched

TABLE 29: Unadjusted Means for Electrophysiologic and Quantitative Sensory Tests of the Upper Limb

Measure	Workers[d] Sample Size[a]	Mean[b]	95% CI	Referents[d] Sample Size[a]	Mean[b]	95% CI
Nerve Conduction Velocity						
Median Motor	240	55.3	54.6, 56.0	232	55.0	54.5, 55.6
Median Sensory-D	239	48.9	48.0, 49.8	231	48.1	47.3, 49.0
Median Sensory-P	230	57.9	57.2, 58.6	230	57.5	56.8, 58.3
Ulnar Sensory	239	51.0	50.2, 51.8	232	51.5	50.7, 52.3
Amplitude						
Median Motor	240	9734	9276, 10,192	232	10234	9790, 10,678
Median Sensory	239	18.8	17.8, 19.9	232	19.6	18.2, 20.9
Ulnar Sensory[c]	239	15.9	14.9, 16.9	232	15.5	14.4, 16.8
Latency						
Median Motor-D[c]	240	3.6	3.6, 3.7	232	3.7	3.6, 3.8
Median Motor-P[c]	240	8.7	8.8, 9.0	232	8.9	8.7, 9.0
Median Sensory-D[c]	239	3.0	2.9, 3.1	232	3.1	3.0, 3.1
Median Sensory-P[c]	230	8.0	7.9, 8.1	231	8.0	7.9, 8.1
Ulnar Sensory	239	2.5	2.4, 2.5	232	2.5	2.4, 2.5
Vibration Threshold						
Index Finger[c]	240	1.1	1.1, 1.1	232	1.1	1.0, 1.2
Thermal Threshold						
Index Finger[c]	240	0.8	0.7, 0.8	232	0.9	0.7, 0.8

Abbreviations: P=proximal, D=distal

[a] Sample sizes differ due to missing measurements and number of exclusions

[b] No significant difference between means of workers & referents using two sample Student's t-test.

[c] Geometric mean for measurements with a log-normal distribution

[d] 78% of the examined study group was matched

TABLE 30: Unadjusted Means for Electrophysiologic and Quantitative Sensory Tests of the Lower Limb

Measure	Workers[d] Sample[a] Size	Mean[b]	95% CI	Referents[d] Sample[a] Size	Mean[b]	95% CI
Nerve Conduction Velocity						
Peroneal Motor	236	45.3	44.6, 46.1	230	45.3	44.7, 45.9
Sural Sensory[c]	224	42.8	42.1, 43.4	221	43.0	42.3, 43.8
Amplitude						
Peroneal Motor	221	5411.2	5082, 5740	210	5651.3	5300, 6002
Sural Sensory[c]	224	12.8	11.8, 13.8	221	11.9	10.9, 12.9
Latency						
Peroneal Motor-D[c]	236	4.5	4.3, 4.6	230	4.3	4.2, 4.4
Peroneal Motor-P[c]	236	11.7	11.5, 11.9	230	11.5	11.3, 11.7
Sural Sensory[c]	224	3.3	3.2, 3.4	221	3.3	3.2, 3.4
Vibration Threshold						
Great Toe[c]	240	3.9	3.6, 4.2	231	3.5	3.2, 3.8
Thermal Threshold						
Great Toe[c]	240	1.7	0.7, 0.9	232	1.2	0.6, 0.8

Abbreviations: P=proximal, D=distal

[a] Sample sizes differ due to missing measurements and number of exclusions

[b] No significant difference between means of workers & referents using two sample Student's t-test.

[c] Geometric mean for measurements with a log-normal distribution

[d] 78% of the examined study group was matched

TABLE 31: Number and Percent of Workers with Electrophysiologic and Quantitative Sensory Measurements Above or Below Case Limit Value for the Upper Limb

Measure	No.	(%)	Unadjusted[c] OR	95% CI
Nerve Conduction Velocity[a]				
Median Motor	9	(3.8)	0.8	0.3, 1.9
Median Sensory-D	8	(3.4)	0.7	0.3, 1.8
Median Sensory-P	10	(4.4)	0.9	0.4, 2.2
Ulnar Sensory	13	(5.4)	1.1	0.5, 2.6
Amplitude[a]				
Median Motor	11	(4.6)	1.0	0.4, 2.3
Median Sensory-D	16	(6.7)	1.4	0.6, 3.2
Ulnar Sensory	5	(2.1)	0.4	0.2, 1.2
Latency[b]				
Median Motor-D	12	(5.0)	1.0	0.4, 2.2
Median Motor-P	11	(4.6)	1.2	0.5, 2.9
Median Sensory-D	8	(3.4)	0.7	0.3, 1.8
Median Sensory-P	11	(4.8)	0.9	0.4, 2.1
Ulnar Sensory	8	(3.4)	0.8	0.3, 2.0
Vibration Threshold[b]				
Index Finger	17	(7.1)	1.5	0.7, 3.3
Thermal Threshold[b]				
Index Finger	13	(5.4)	1.2	0.5, 2.6

Abbreviations: P=Proximal, D=Distal

[a] Case limit value is the 5th percentile of referent measurement after exclusions

[b] Case limit value is the 95th percentile of referent measurement after exclusions

[c] 78% of the examined study group was matched

TABLE 32: Number and Percent of Workers with Electrophysiologic and Quantitative Sensory Measurements Above or Below Case Limit Value for the Lower Limb

Measure	No. (%)	Unadjusted[c] OR	95% CI
Nerve Conduction Velocity[a]			
Peroneal Motor	18 (7.6)	1.6	0.8, 3.5
Sural Sensory	14 (6.3)	1.3	0.6, 2.9
Amplitude[a]			
Peroneal Motor-D	6 (2.7)	0.6	0.2, 1.6
Peroneal Motor-P	16 (6.8)	1.6	0.7, 3.6
Sural Sensory-D	4 (1.8)	0.4	0.1, 1.1
Latency[b]			
Peroneal Motor-P	16 (6.8)	1.6	0.7, 3.6
Peroneal Motor-D			
Sural Sensory	8 (3.6)	0.7	0.3, 1.8
Vibration Threshold[b]			
Great Toe	20 (8.3)	1.8	0.9, 3.9
Thermal Threshold[b]			
Great Toe	25 (10.4)	2.3	1.1, 4.8

Abbreviations: P=Proximal, D=Distal

[a] Case limit value is the 5th percentile of referent measurement after exclusions

[b] Case limit value is the 95th percentile of referent measurement after exclusions

[c] 78% of the examined study group was matched

TABLE 33: Workers and Referents Reporting Symptoms Related to Peripheral Neuropathy [a]

Symptoms	Workers Sample Size	Workers No.	Workers (%)	Referents Sample Size	Referents No.	Referents (%)
Upper Limbs						
Numbing, RT	240	16	(6.7)	232	14	(6.0)
Numbing, LT	240	15	(6.3)	232	14	(6.0)
Tingling, RT	240	14	(5.8)	232	18	(7.8)
Tingling, LT	240	11	(4.6)	232	20	(8.7)
Burning, RT	240	3	(1.3)	232	5	(1.1)
Burning, LT	240	3	(1.3)	232	7	(3.0)
Weakness, RT	240	0	-	231	1	(0.4)
Weakness, LT	240	0	-	231	0	-
Muscle Twitching, RT	239	11	(4.6)	231	5	(2.2)
Muscle Twitching, LT	239	10	(4.2)	231	8	(3.5)
Difficulty Handling Small Objects	240	20	(8.3)	232	27	(11.6)
Lower Limbs						
Numbing, RT	240	12	(5.0)	231	14	(6.1)
Numbing, LT	240	20	(8.3)	231	10	(4.3)
Tingling, RT	240	15	(6.3)	231	15	(6.5)
Tingling, LT	240	19	(7.9)	231	17	(7.4)
Burning, RT	240	9	(3.8)	231	5	(2.2)
Burning, LT	240	7	(2.9)	231	5	(2.2)
Weakness, RT	240	3	(1.3)	230	4	(1.7)
Weakness, LT	240	5	(2.1)	230	5	(2.2)
Muscle Twitching, RT	240	6	(2.5)	231	6	(2.6)
Muscle Twitching, LT	239	8	(3.4)	231	7	(3.0)
Cramping[b]	240	70	(29.2)	231	42	(18.2)
Difficulty Balancing[b]	240	34	(14.2)	231	19	(8.2)

Abbreviations: RT=Right; LT= Left

[a] - Reported in the Medical History

[b] - $p<.05$ based on X^2, 1 df

TABLE 34: Percent and Number of Workers and Referents Reporting Selected Injuries and Conditions[a] Related to Peripheral Nerve Dysfunction

	Workers[b]		Referents	
Condition	Sample Size	No. (%)	Sample Size	No. (%)
Slipped Disc	238	22 (9.2)	230	28 (12.2)
Surgery on Back or Spine	241	18 (7.5)	232	11 (4.7)
Sciatica	239	18 (7.5)	232	20 (8.6)
Carpal Tunnel Syndrome	240	0	232	5 (2.2)
Head Injury with Loss of Consciousness	238	27 (11.3)	232	44 (18.9)
Rheumatoid Arthritis	240	4 (1.7)	231	2 (0.9)
Osteoarthritis	239	13 (5.4)	231	11 (5.6)
Gout	239	11 (4.6)	232	11 (4.7)

[a] Reported in the Medical History

[b] Proportions between workers and referents are not statistically significantly different based on X^2 test

TABLE 35: Comparison of Data for Examined Matched and Unmatched Workers and Referents

	Workers		Referents	
	Matched	Unmatched	Matched	Unmatched
Number	216	65	216	44
Age (yrs)	55.3	55.7	55.5	58.8
Race (%)				
White	90.2	84.6	88.9	88.6
Black	9.3	15.4	9.3	11.4
Asian	0	0.5	0	1.9
Sex (%)				
Male	94.0	98.5	94.0	90.9
Female	6.0	1.5	6.0	9.1
Education (%)				
1-8 yrs	8.3	12.3	7.4	11.4
9-12 yrs	47.7	43.1	44.9	40.9
Vocational Training	9.3	6.2	9.7	6.8
Some College	34.7	38.5	38.0	40.9
Income (%)				
Less than 10,000	8.8	13.9	10.7	9.1
10,000-19,999	18.5	15.4	17.1	20.5
20,000-29,999	20.4	12.3	18.5	22.7
30,000-39,999	19.9	10.8	14.8	11.4
40,000-49,999	9.7	16.9	14.4	15.9
50,000 or greater	22.2	29.2	19.9	20.5
Refused	0.5	1.5	4.6	0
Current Alcohol Status				
Never Drank	7.6	10.7	11.5	15.0
Former Drinker	22.2	32.1	22.9	17.5
Current Drinker	70.3	57.1	65.1	67.5
Unknown	-	-	0.5	-
Lifetime Alcohol Consumption	46.0	49.6	66.4	88.5

TABLE 35: Continued

	Workers		Referents	
	Matched	Unmatched	Matched	Unmatched
Days of Exposure	(N=216)	(N=65)	-	-
	888.1	1049.4	-	-
Serum 2,3,7,8-TCDD level (ppt)	(N=209)	(N=63)	(N=83)	(N=3)
	198.9	252.4	7.08	9.24
Cases of Peripheral Neuropathy				
Upper Limb	29	14	34	10
Lower Limb	34	10	34	10

TABLE 36: Summary of changes observed in mammals exposed to 2,3,7,8-TCDD

EFFECT	MONKEY	GUINEA PIG	MOUSE	RAT	HAMSTER
Body Weight Loss	+	+	+	+	+[b]
Chloracne[a]	+	No	+[c]	No	No
HEPATIC					
Liver Size	+	NO	+	+	NO
Cell/Lip Infiltration	+	+	+	+	NO
Cellular necrosis	+	NO	+	+	NO
Enzyme increases	+	NO	NO	+	NO
Bilirubin increases	NO	NO	NO	+	+
Bile duct epithelial hyperplasia	+	NO	+	+	NO
Hepatic Nodules	NO	NO	+	+	NO
Carcinoma NO	NO	NO	+	NO	
Porphyrin Changes	NO	NO	+	+	NO
Glucose Decreases	+	NO	NO	+	NO
Cholesterol Changes	+[c]	+	No	+	+
Serum Protein Decreased	+	+[d]	+	+	+[d]
Alveolar changes	NO	+	+	+	NO
Developmental effects	+	?	+	+	?
Immunologic effects	+	+	+	+	?

NO - Effect not observed
\+ - Effect demonstrated
[a] - Also observed in rabbbits
[b] - Failed to gain weight
[c] - HRS/J hairless mice
[d] - Decreased Cholesterol
[e] - Increased Serum Protein
? - Data not available

TABLE 37: Body weight loss following exposure to 2,3,7,8-TCDD

Species	Route	Dose*	Duration	Effect	Reference
monkey rhesus	oral	2-3	9 mo	13% loss	Allen et al, 1977
monkey	oral	2ppb	61 d	33% loss	McNulty, 1977
rhesus		20ppb	5 d	30% loss	
monkey rhesus	gavage	< 70	1 time	13-38% loss	McConnell et al[a], 1978
guinea pig Hartley	oral	1	1x/wk for 8wk	20% loss	Harris et al, 1973
guinea pig Hartley	oral	< 3	1 time	15-50% loss	McConnell et al[b], 1978
guinea pig	oral	0.44[a]	90 d	decreased weight gain	De Caprio et al, 1986
		1.3[a]	90d	38% loss	
mouse C57B1/6	oral	340	1 time	20-25% loss	McConnell et al[b], 1978
mouse C57B1/6	oral	25	1x/wk for 6 wk	10-50% loss	Vos et al, 1974

TPN = total parental nutrition; (NS) = not specified; SD = Sprague Dawley
*ug/kg unless otherwise specified
[a]total dose

TABLE 37: continued

Species	Route	Dose*	Duration	Effect	Reference
rat CD	oral	1.0	1x/d for 31d	1.0:23% decrease in gain	Harris et al, 1973
		10		10.0:12% loss in 7 days	
rat SD	oral	1.0	1x/d for 13 wk	22% reduced gain	Kociba et al, 1976
rat Wistar	oral	100	1 time	15-30% loss	Courtney et al, 1978
rat (NS)	i.p.	50 100	1 time	No loss in TPN fed rats. No loss in controls. 30% loss in chow fed exposed rats.	Gasiewicz et al, 1980
rat OM	gavage	0.005 0.025 0.25	2x/wk for 104 wk	dose related loss in males & females	NTP, 1982a
hamster Golden Syrian	oral ip	500 1000 2000	1 time	gain reduced up to 50% at 1000 & 2000 ug/kg bw.	Olson et al, 1980
rabbit New Zealand	oral ip	115	1 time	loss unspecified	Schwetz et al, 1973

SD = Sprague Dawely; NS=not specified
OM = Osborne-Mendel
*ug/kg unless otherwise specified

TABLE 38: Effects of exposure to 2,3,7,8-TCDD on the skin

Species	Route	Dose*	Duration	Effect	Reference
mouse Swiss/ A/Riop	gi a	7 700 7000	1x/wk for 1yr	dose-dependent occurrence amyloidosis with of skin lesions	Toth et al, 1979
rabbit (NS)	dermal (ear)	0.005% to 0.01%	1 time	inflammation hyperkeratosis (polyglocol solvent)	Kimmig and Schulz, 1957
rabbit (NS)	dermal	0.3 ug	1x/day for 3d	hyperkeratosis keratinaceous masses in follicular epithelium; reduced number of sebaceous cells; comedones (acetone solvent)	Jones and Kizek, 1962
rabbit New Zealand	dermal	0.04 400 (ug/ml)	5x/wk for 4 wk	comedomes, increased ear thickness, hyperkeratosis (benzene solvent)	Schwetz et al, 1973
monkey rhesus	gavage	2-3	7-9 mo	acne, enlarged hair follicles periorbital edema, swelling of eyelids, loss of facial hair and eyelashes; squamous metaplasia and keratinization of hair follicles, meibomian glands of eyelids and nails	Allen et al, 1977
monkey rhesus	gavage	< 70	1 time	facial alopecia, blepharitis, fingernail + eyelash loss; thickening of Meibomian glands; squamous metaplasia of sebaceousglands; hyperkeratosis of hair follicles & adjacent skin	McConnell et al a, 1978
monkey rhesus	oral	1 (total dose)	20 mo of arms	alopecia, hyperkeratosis	Schantz et al, 1979

NS=not specified
* = ug/kg unless otherwise specified
a = gastric intubation

TABLE 39: Effects of exposure to 2,3,7,8-TCDD on liver morphology

Species	Route	Dose*	Duration	Necrosis	Lipid[a] Changes	Enlarged Liver	Bile Duct[b] Changes	Cellular[c,d] Changes	Effect	Other References
mouse C57Bl/6	gavage	200	1 time	+	NO	NO	+	+	NO	Vos et al, 1974
mouse C57Bl/6	oral	0.2	1x/wk	NO	+	NO	NO	NO	NO	Vos et al, 1974
		5	for	+	NO	+	NO	+	NO	
		25	6 wk	+	+	+	NO	NO	NO	
mouse C57Bl/6	gavage	250	1 time	+	+	+	+	+	NO	Jones and Greig, 1975
mouse C57Bl/6	oral	≥ 100	1 time	+	+	+	+	+	NO	McConnell et alcb, 1978
mouse C57Bl/6J	i.p.	25	1x/wk	+	+	NO	+	+	NO	Jones et al 1981
		for								
			12 wk							
mouse HRS/J	dermal	15	3x	NO	+	NO	+	+	1	Jones et al 1981
			in							
			6d							
rat Porton	oral	200	1 time	+	NO	+	NO	+	NO	Greig et al, 1973
rat SD	oral	1.0	1x/d	NO	NO	NO	NO	NO	NO	Zinkl et al 1973
		10.0	for							
			30d							
rat	oral	0.1	28 wk	+	+	NO	NO	+	NO	King and Roesler, 1974
		1.0		NO	NO	NO	NO	NO	NO	
rat SD	oral	0.01**	5d/wk	NO	+	NO	NO	+	2, 3	Kociba et al, 1976
			for							
		1.0**	13 wk	+	+	NO	NO	+	NO	

SD=Sprague Dawley *ug/kg unless otherwise specified **ug/kg/d

TABLE 39: continued

Species	Route	Dose*	Duration	Necrosis	Lipid[a] Changes	Enlarged Liver	Bile Duct[b] Changes	Cellular[c,d] Changes	Effect	Other References
rat SD	oral	0.01**	1x/d for 2yr	+	+	+	+	+	4, 5	Kociba, et al 1978
rabbit	oral	0.05 to 0.1 mg/kg	1 time	+	+	NO	NO	NO	NO	Kimmig and Schulzb, 1957
guinea pig Hartley	oral	<3	1 time	NO	NO	NO	NO	NO	8	McConnell et al 1978b
quinea pig Hartley	ip	100 (TPN)	1 time	+	+	+	+	+	2,10	Gasiewicz et al, 1980
guinea pig Hartley	oral	0.44 (total dose)	90d	NO	+	NO	NO	+	2, 6	DeCaprio et al, 1986
monkey rhesus	oral	toxic fat	445 d	NO	+	+	+	+	7	Allen and Carstens, 1966

SD=Sprague Dawley *ug/kg unless otherwise specified **ug/kg/d

TABLE 39: continued

Species	Route	Dose*	Duration	Necrosis	Lipid Changes	Enlarged Liver	Biliary Changes	Cellular Changes	Other Effects	References
monkey rhesus	oral	0.9	20 mo							Schantz et al 1979
monkey rhesus	gavage	2-3 (total (dose)	9 mo	NO	NO	+	NO	NO	12	Allen et al, 1977
monkey rhesus	oral	>70	1 time	NO	NO	+	+	+	NO	McConnell et ala, 1978

SD=Sprague Dawley *ug/kg unless otherwise specified **ug/kg/d

TABLE 39: continued

Species	Route	Dose*	Duration	Necrosis	Lipid[a] Changes	Enlarged Liver	Bile Duct[b] Changes	Cellular[c,d] Changes	Other Effect	References
hamster Golden Syrian	ip	1000	1 time	NC	NC	NC	NC	NC	7	Olson et al, 1980
	po	1000	1 time	NC	NC	NC	NC	NC	7	

SD=Sprague Dawley *ug/kg unless otherwise specified **ug/kg/d

Footnote: Other effects

1. normal and iron supplemented rats only
2. altered hepatic architecture
3. brown pigmentation
4. hepatocellular carcinomas
5. hyperplastic nodules
6. no effects at lower doses
7. proliferation of smooth endoplasmic reticulum
8. no effects reported

a. lipid infiltration
b. bile epithelial cell changes
c. multinucleated cells
d. inflammatory infiltration
NC No Change
NO No effect reported

TABLE 40: Effects of exposure to 2,3,7,8 TCDD on liver enzyme levels

Species	Route	Dose (ug/kg)*	Dur-ation	GGT CTL,EXP	SGOT CTL,EXP	SGPT CTL,EXP	ALK CTL,EXP	LDH CTL,EXP	Total Bilirubin CTL,EXP (mg/100ml)	Reference
rat porton	oral	200	1x	NM	81, 99	27,24	NM	2,2	0.3,0.5	Greig et al, 1973
rat SD	oral	1.0	1x/d for 30d	NM	5,10	NC	NM	NM	0.4,0.4	Zinkl et al, 1973
		10.1		NM	5,30	15,25	NM	NM	0.4,5.6[a]	
rat SD	oral	0.1	5d/w for 13wks	NM	NM	37,25[c]	18,14[c]	NM	0.35,0.30[c]	Kociba et al, 1976
		1.0		NM	NM	36,37[d]	15,31[a,d]	NM	0.33,0.49[c,d]	
						37,36[c]	18,35[a,c]		0.35,3[a,c]	
						36,37[d]	15,27[a,d]		0.33.2[a,d]	
rat SD	oral	0.10	1x/d for 2 yr	0, 1 0,14	NM	49,42[c]	87,105[c]	NM	0.2,0.2[c]	Kociba et al, 1978
					NM	39,54[a,c]	60,205[a,d]	NM	0.2,0.2[d]	
rat (NS)	ip	100 (TPN)	1x	NM	69,182	21,31	154,427[a]	402,574	0.1,9[a]	Gasiewicz et al, 1980
		100 (chow fed)	1x	NM	57,341	20,34[a]	105,136	443,447	0.2,5[a]	

CTL =controls
EXP =exposed
SGPT=serum glutamic phruvic transaminase
SGOT=serum gluthmic
SD =sprague-Dawley
GGT =gamma-glutamyl transferase
LDH =lactate dehydrogenase
ALK =alkaline phosphatase
NM =not measured
NC =no change
*mg/kg unless otherwise specified
a=p<.05
b=data not shown in text
c=males
d=females

TABLE 40: continued

Species	Route	Dose (ug/kg)*	Dur-ation	GGT CTL,EXP	SGOT CTL,EXP	SGPT CTL,EXP	ALK CTL,EXP	LDH CTL,EXP	Total Bilirubin CTL,EXP (mg/100ml)	References
guinea pig Hartley	oral	0.44 (total dose)	90d	NC	NC[b,d] NC[b,c]	NC[b,d] NC[b,c]	NC	NC	NM	DeCaprio et al, 1986
monkeys rhesus	oral	toxic fat	445d	NM	NM	NM	NM	NM	NC	Allen & Carsten1967
monkeys rhesus	gavage	2-3 (total dose)	9m	NM	NM	( )[b]	NM	NM	NM	Allen et al, 1977
Monkey rhesus	oral	0.9	20m	NM	NM	( )[b]	NM	NM	NM	Schantz et al,1979
monkey rhesus	oral	>70	1x	NM	( )[b]	NM	NC[b]	NM	NC[b]	McConnell et al,1978
hamster golden Syrian	ip	1000	1x	NM	NC[b]	NC[b]	162,353[a]	NC[b]	0.6,0.3[a]	Olson et al 1980
	po	1000	1x				162,512[a]		0.6,0.8[a]	

CTL =controls
EXP =exposed
SGPT=serum glutamic phruvic transaminase
SGOT=serum gluthmic
SD =sprague-Dawley
GGT =gamma-glutamyl transferase
LDH =lactate dehydrogenase
ALK =alkaline phosphatase
NM =not measured
NC =no change
*mg/kg unless otherwise specified
a=p<.05
b=data not shown in text
c=males
d=females

TABLE 41: Effects of exposure to 2,3,7,8-TCDD on serum glucose levels

Species	Route	Dose*	Duration	% Change in Serum Glucose Level	References
rat CD	oral	0.1	1x/d	- 8	Zinkl et al, 1973
		1.0	for	-29	
		10.0	30d	-51[a]	
rat NS	ip (TPN)	100	1 time	-70[a]	Gasiewicz et al,1980
	ip (chowfed)			-49[a]	
rat Fischer	gavage	30	1 time	-12[a]	Schiller et al, 1986
		60		-36[a]	
		90		-67[a]	
		180		-52[a]	
		270		-58[a]	
		360		-57[a]	
monkey rhesus	gavage	70	1 time	(-)[b]	McConnell et al, 1978
		350			
guinea pig Hartley	oral	0.44	90d	NC[b,c,d]	DeCaprio et al, 1986

a = $p<.05$
b = data not shown
c = males
d = females
NC = no change
NS = not specified
* ug/kg unless otherwise specified

TABLE 42: Effects of exposure to 2,3,7,8-TCDD on cholesterol and triglyceride levels

Species	Route	Dose*	Duration	Effect (% change)		Reference
				CHOL	TRIG	
rat Porton	oral	200	1 time	+13	NM	Grieg, et al, 1973
rat CD	oral	1.0 10.0	1x/d for 30/d	+81[a] +88[a]	NM NM	Zinkl et al, 1973
rat SD	ip	unspecified	1 time	+70[a]	NC[b]	Poli et al, 1980
rat (NS)	ip (TPN) ip (chow-fed)	100	1 time	+150[a] +200[a]	-36[a] -181[a]	Gasiewicz et al, 1980
rat Fisher	gavage	60	1 time	+164[a]	+217[a]	Schiller et al, 1986
guinea pig hartley	ip	1	1 time	+400[a]	+350[a]	Gasiewicz and Neal, 1979
guinea pig hartley	oral	0.44	90 d	NM NM	+53[a,c] +52[d]	DeCaprio et al, 1986
monkey rhesus	oral	0.9	20 mo	(-)[b]	NR	Schantz et al, 1979
monkey rhesus	gavage	< 70	1 time	(-)[b]	(+)[b]	McConnell et ala, 1978
hamster Golden	oral	1000	1 time	+35[a]	-47[a]	Olson et al, 1980
Syrian	ip			+30[a]	-35[a]	

(NS) = not specified
NM = not measured
NC = No change
SD = Sprague Dawley
* = ug/kg unless otherwise specified

a = p<.05NR = not reported
b = data not shown
c = males
d = females

TABLE 43: Effects of exposure to 2,3,7,8-TCDD on serum protein levels

Species	Route	Dose*	Duration	% Change in Serum Protein Albumin or Globulins				Reference
					GLOB	PROT	ALB	
mouse C5781/6	oral	25	1x/wk for 6 wk			-18[a]	-0.4	Vos et al, 1974
				alpha	-35[a]			
				beta	-56[a]			
				gamma	-26[a]			
mice C5781/6	oral	100	1 time	alpha	-19[a]	-5	+0.8	McConnell et alb, 1978
				beta	-8			
				gamma	-16			
		200		alpha	-61[a]	-16[a]	-8[a]	
				beta	-30			
				gamma	+3			
		340		alpha	-75[a]	-32[a]	-28[a]	
				beta	-53[a]			
				gamma	-20[a]			
rat Porton	oral	200	1 time		NM	-9	NM	Greig et al, 1973
rat CD	oral	10	1 time		NM	-27[a]	NM	Zinkl et al, 1973
rat (NS)	ip (TPN)	100	1 time		NM	-24[a]	NM	Gasiewicz et al, 1980
	ip (chow-fed)				NM	-2	NM	
guinea pig Hartley	ip	1	1 time		NM	+130	+125	Gasiewicz and Neal, 1979

(NS) = not specified
* = ug/kg unless otherwise specified
a = p<.05
b = data not shown
c = males
d = females

TPN = total parenteral nutrition
PROT = serum protein
ALB = serum albumin
GLOB = globulins
NM = not measured
NC = no change

TABLE 43: continued

Species	Route	Dose*	Duration	% Change in Serum Protein Albumin or Globulins GLOB	PROT	ALB	Reference
guinea pig Hartley	oral	0.44	90d	NM	NC	NM	DeCaprio et al, 1986
monkey rhesus	gavage	75% TCDD	445 d	NM	-28	-43	Allen and Carstens, 1967
monkey rhesus	gavage	< 70	1 time	NM	(-)[b]	(-)[b]	McConnell et ala, 1978
hamster Golden Syrian	oral	1000	1 time	NM	+17[a]	-8[a]	Olson et al, 1980
	ip			NM	+15[a]	-14[a]	

(NS) = not specified
* = ug/kg unless otherwise specified
a = p<.05
b = data not shown
c = males
d = females

TPN = total parenteral nutrition
PROT = serum protein
ALB = serum albumin
GLOB = globulins
NM = not measured
NC = no change

TABLE 44: Effects of exposure to 2,3,7,8-TCDD on porphyrin metabolism

Species	Route	Dose*	Duration	Effect	Reference
mouse C57BL/6	oral	1 5 25	1x/wk for 4 wk	25 ug/kg:Elevated ALAS & 4000-fold increase 7- & 8 carboxyporphyrins ($p<0.05$)	Goldstein et al, 1973
mouse C57B1	gavage	C57B1 50 75	1 time	Decrease in hepatic decarboxylase	Smith et al, 1981
DBA		DBA 600		No change in porphyrin levels	
mouse C57B1/6	ip	25	1x/wk for 9wk	100-fold increased porphyrin content in liver & 5-fold in kidney ($p<0.05$)(7- & 8 carboxy porphyrins predominated); inhibition of uroporphyrinogen decarboxylase activity in liver and kidney	Cantoni et al,1984
rat CD-COBS	gavage	0.01 0.1 1.0	1x/wk for 45 wk	0.01 ug/kg: two-fold increase in excretion coproporphyrin after 6 m ($p<.05$) 0.1 ug/kg: three-fold increase in excretion of coproporphyrin after 3 m & uroporphyrins after 10 m ($p<.05$) 1.0 ug/kg: 200-fold increased excretion of coporporphyrin after 2 m & heptacarboxylic & uroporphyrin after 6 m	Cantoni et al, 1981

ALAS = aminolevulinic acid synthetase

SD=Sprague Dawley; AHH = aromatic hydrocarbon hydroxylase; ALAS = aminolevulinic acid synthetase

* ug/kg unless otherwise specified

TABLE 44: continued

Species	Route	Dose*	Duration	Effect	Reference
rat SD	gavage	0.01 0.1 1.0 10.0	1x/wk for 16 wk	0.1 & 1.0 ug/kg:1000-fold elevation in hepatic uroporphyrins (p<.05); elevated ALAS 0.01, 0.1, 1.0 ug/kg: elevated AHH and glucuronyl transferase	Goldstein et al, 1982
	oral	1 3 10 30	1 time	no changes in urinary porphyrins at 3 days or 16 weeks post exposure	
mouse C57B1/6J	im	25	1x/wk for 12 wk	No reduction in urinary porphyrins in low iron mouse	Jones et al, 1981
mouse C57BL/6J DBA/2J	ip	25	1x/wk for 12 wk	C5:7 fold increase in uroporphyrins excreted (p< 0.05) DBA: no change in porphyrin excretion; AHH activity increased for both species	Jones and Sweeney, 1980
mouse HRS/J	derm	15	3x in 6d	Elevated porphyrin in normal & iron supplemented diet; not in iron deficient diet	Jones et al, 1981
rat SD	oral	1.0**	1x/d for 13 wk	Two-fold increase in coproporphyrins, uroporphyrins and d-ALA (p<.05)	Kociba et al, 1976
rat SD	oral	0.1**	1x/d for 2 yr	Two-fold increase in coproporphyins, uroporphyrins and d-ALA (p<.05)	Kociba et al, 1978
chick embryo hepatocytes	--	0.1 uM 1.0 uM	1 time	Inhibition of uroporphyrin decarboxylase and increased porphyrin levels & d-ALAS activity	De Vernieul et al, 1983

SD = Sprague Dawley; ALAS=aminolevulinic acid synthetase; dALA=d-aminolevulinic acid; *ug 1 kg unless otherwise specified; ** = ug/kg/d

TABLE 45: Effects of exposure to 2,3,7,8-TCDD on the oral cavity and respiratory system

Species	Route	Dose*	Duration	Effect	Reference
rat Porton	oral	200	1 time	severe chronic and acute inflammatory lesions; petechial hemorrhage perivascular edema; massive infection	Greig et al, 1973
rat SD	gavage	0.1	1x/d for 2y	focal alveolar hyperplasia; hematogenous pigment aggregates, alveolar macrophage accumulation; cholesterol clefts, edema, interstitial inflammation & fibrosis, keratinizing squamous metaplasia squamous cell carcinoma of lung, hard palate/nasal turbinates and tongue	Kociba et al, 1978
guinea pig hartley	oral	0.44 1.3 (total dose)		lung edema at both doses	DeCaprio et al, 1986
monkeys rherus	oral	500 ppt (total dose)	9m	focal areas of hemorrhage Hypertrophy, hyperplasia & metaplasia of bronchial epithelium	Allen et al, 1977
monkeys rhesus	oral	?	445d	focal areas of atelectasis, congestion, edema & fibrosis (fibrosis due to mite infection	Allen and Carstens, 1967

SD = Sprague Dawley

* = ug/kg unless otherwise specified

TABLE 46: Vascular effects of exposure to 2,3,7,8-TCDD

Species	Route	Dose*	Duration	Effect	Reference
monkey rhesus	gavage	500 ppt	9 mo	gangrenous necrosis of distal phalanges; edema and ascites; bilateral ventricular dialation; cardiac enlargement & edema; hemorrhage in epicardium, myocardium, endocardium generalized hemorrhage	Allen et al, 1977
monkey rhesus	gavage	(?)	445 d	blood vessel degeneration, cardioedema	Allen & Carstens, 1967
rats SD	oral	0.1 ug/kg/d	1x/d for 2 yr	myocardial degenerative changes	Kociba et al, 1978
mouse C57B1/6	oral	100-200	1 time	hemorrhage in small intestine; submucosal edema in stomach and small and large intestine	Vos et al, 1973
guinea pig hartley	oral	3.0	1 time	subserosal hemorrhage in gastrointestinal tract	Gupta et al, 1973
guinea pig hartley	oral	< 3	1 time	gastrointestinal hemorrhage	McConnell et al, 1978b
rat Porton	gavage	25-50	1 time	hemorrhage of glandular stomach	Greig et al, 1973
rat CD	oral	1-10	1x/d for 31/d	stomach ulceration	Gupta et al, 1973

TABLE 46: continued

Species	Route	Dose*	Duration	Effect	Reference
rat SD	oral	0.05-1 ppm	4 weeks	gastrointestinal hemorrhage	Van Miller & Allen, 1977
monkey rhesus	gavage	20 ppb	58 d	hyperplasia & ulceration of gastric mucosa	Mc Nulty, 1977
monkey rhesus	gavage	70	1 time	gastrointestinal hemorrhage	McConnell et al, 1978a

SD = Sprague Dawley

* = ug/kg unless otherwise specified

TABLE 47: Effects of exposure to 2,3,7,8-TCDD on Hematologic Endpoints

Species	Route	Dose*	Duration	Effect	Reference
mouse C57B1/6	oral	25	1x/wk for 6wk	increased neutrophils; mean hemoglobin & corpuscular concentrations decreased ($p<.05$)	Vos et al, 1974
mouse CD-1	oral	1.0 10.0 50.0	1 time	decreased lymphocyte and leukocyte count at all doses ($p<.05$) after 1 week; returned to normal after 3 weeks	Zinkl et al, 1973
rat Porton	oral	200	1 time	increased erythrocytes and hemoglobin ($p<.05$); decreased leukocytes; ($p<.05$)	Greig et al, 1973
rat CD	oral	10	1x/d for 10-14 days	increased packed red cell volume & erthrocyte counts; neutrophilia; lymphocytosis; eosinopenia; thrombocytopenia without reduced platelet synthesis	Weissberg and Zinkl, 1973
rat CD	oral	0.1 1.0 10.0	1x/d for 30d	hemoconcentration due to dehydration	Zinkl et al, 1973
rat SD	oral	.001 -0.5 ppb	65 wk	aplastic anemia	Van Miller and Allen, 1977
rat	oral	1.0	1x/d for 13wk	Females: elevated packed cell volume, RBC, hemoglobin; Males: decreased packed cell volume, RBC counts, hemoglobin	Kociba et al, 1976

SD = Sprague Dawley

* = ug/kg unless otherwise specified

TABLE 47: continued

Species	Route	Dose*	Duration	Effect	Reference
guinea pig hartley	oral	0.08-0.2	1x/wk for 8wk	decreased lymphocytes ($p < .05$) at all doses	Zinkl et al, 1973
monkey rhesus	gavage	50 ppt 500 ppt	20 mo 9 mo	50: decreased hematocrit & WBC count; pancytopenia; leukocytopenia; thrombocytopenia; 50: decreased hematocrit & hemoglobin levels: hypocellularity of bone marrow	McNulty, 1977
monkey rhesus	gavage	<70	1 time	Hypocelluarity of bone marrow; increase in in myeloid elements, decrease in erythroid elements in sternal bone marrow; leukocytosis due to increased neutrophils	McConnell et al 1978a

* = ug/kg unless otherwise specified

TABLE 48: Carcinogenic effects of exposure to 2,3,7,8-TCDD

Species	Route	Dose*	Duration	Effect	Reference
rat SD	oral	0.1 0.01 0.001	1x/d for 2 yrs	0.001:no tumors 0.01:43% of all animals-hepatocellular nodules 0.1:22% of females-hepatocellular carcinoma ($p<.05$) :8% of all animals-carcinoma of hard palate/nasal turbinates :5% of all animals-carcinoma of tongue :14% of females-carcinoma of lung	Kociba et al., 1978

* = ug/kg unless otherwise specified

** = approximate weekly doses; animals fed diets containing 2,3,7,8-TCDD daily

a relative to unexposed animals

b dose per application

TABLE 48: continued

Species	Route	Dose*	Duration	Effect	Reference
mouse Swiss	g.i.	7.0 0.7 0.007	1x/wk for 1 y	Liver tumors: 7.0:12% increase[a] 0.7:30% increase 0.007:11% increase Lung tumors: 7.0:14% decrease 0.7:2% increase 0.007:22% increase Lymphona: 7.0:2% decrease 0.7:11% increase 0.007:7% increase	Toth et al., 1979
rat SD	oral	0.0003** 78 wks 0.001 0.01 0.4 2.0 24 240 500		>24 ug/kg: no tumors due to deaths 0.0003 ug/kg/wk:no tumors 0.001:1 lymphocytic leukemia 1 ear duct carcinoma 1 adenocarcinoma (kidney) 1 malignant histiocytoma (peroneal) 1 angiosarcoma(skin) 0.01: 1 fibrosarcoma(muscle) 1 carcinoma (skin) 0.1:adenocarcinoma(kidney) :carcinoma(skin) 0.4:2 malignant histiocytoma (peroneal) 1 angiosarcoma (skin) 1 cholangiosarcoma (liver) 1 glioblastoma (brain) 2.0:2 cholangiocarcinomas (liver)	Van Miller et al., 1977

* = ug/kg unless otherwise specified

** = approximate weekly doses; animals fed diets containing 2,3,7,8-TCDD daily

[a] relative to unexposed animals

TABLE 48: continued

Species	Route	Dose*	Duration	Effect	Reference
rat	gavage	Males+Females	2x/wk	Thyroid:males[a]	NTP, 1982a
OM		0.01	for	0.01:+9%[b]	
		0.05	104 wk	0.05:+11%[b]	
		0.5		0.5:+19%[b]	
				females: no change	
				Liver:males	
				0.01:no tumors	
				0.05:no tumors	
				0.5:+6%[b]	
				females	
				0.01:-5%	
				0.05: -1%	
				0.5:+22%[b]	
mouse	gavage	males	2x/wk	liver:males	NTP, 1982a
B6C3F1		0.01	for	0.01:+7%	
		0.05	104 wk	0.05:+5%	
		0.5		0.5:+23%	
		0.04		females	
		0.2		0.04:+3%	
		2.0		0.02:+3%	
				2.0:+12%	
				thyroid:males	
				0.01:+6%	
				0.05:no tumors	
				0.5:no tumors	
				females	
				0.04:+6%	
				0.2:+2%	
				2.0:+11%	
mouse	dermal	0.001[b]	3x/wk	30% treated & 5% of	NTP, 1982b
Swiss			for 104 wk	controls: fibrosarcoma of	
				integumentary system	
Webster					
hamster	ip	100	1x/mo	100 ug/kg for 6 mo:	
Golden			for	squamous cell carcinomas	
Syrian	sc		6 mo	of facial skin in 22% of	Rao et al.
			1x/mo	32 animals	1988
				100 ug/kg for	
	sc	50	1x/mo for	2 mo. or 50 ug/kg for 6	
			6 mo	mo:no tumors in 40 animals	

a = relative to unexposed controls; b = $p<0.05$; OM= Osborne Mendel; * = ug/kg unless otherwise specified

TABLE 48: continued

Species	Route	Substance	Dose	Duration	Effect	Reference
rat Charles River	s.c.	TCDD	0.14mg/kg or 1.4 mg/kg	2x/wk for 28 wk	No tumors with DEN or TCDD alone; hepatocellular carcinomas in 71% of treated DEN + TCDD rats *strong promoter	Pitot et al, 1980
		TCDD + DEN	0.14mg/kg or 1.4 mg/kg; 10mg/kg	2x/wk for 14 wk; 1 time		
mouse	dermal	DMBA then TCDD	0.2 um; 20 ng; 50 ng	1 time; 2x/wk for 8 wk; 2x/wk for 8 wks	hr/+: no papillomas hr/hr: 1.8 papillomas/ mouse *strong promotor	Poland et al, 1982

mouse CF-1	dermal	TCDD then DMBA then TPA	1ng-1ug; 10 or 25 ug; 10 ng	1 time; 1 time; 2x/wk for 20 wk	DMBA	TCDD dose	#[a] tumors	Lesca, 1983
					10	0	6	
						0.001	5	
						0.01	3	
						0.1	2	
						1	1	
					25	0	7	
						0.001	8	
						0.01	7	
						0.1	4	
						1	3	

TCDD=2,3,7,8-Tetrachlorodibenzo-p-dioxin
DEN=diethylnitrosamine
DMBA=7,12-dimethylbenz-(a)anthracene
TPA=12-O-tetradecanoyl-phorbol-13-acetate
#[a] - Approximate number of tumors
hr/hr=hairless mice
hr/+=haired mice

TABLE 48: continued

Species	Route	Substance	Dose*	Duration	Effect	Reference
mice DBA/2	ip	TCDD	100	1 time	no tumors	Kouri et al., 1978
	sc	MCA	150	1 time	3% mice had fibrosarcomas.	
		+				
	ip	TCDD	100	1 time	simultaneous exposure: 23% mice had fibrosarcomas.	
		+				
	sc	MCA	150	1 time		
	ip	TCDD	100	1 time	MCA 2 days after TCDD: no tumors	
	+					
	sc	MCA	150	1 time		
C57Bl/6N	ip	TCDD	100	1 time	no tumors	
	sc	MCA	150	1 time TCDD+3MC	81% mice had fibrosarcomas	
	ip	TCDD	100	1 time	simultaneous exposure: 71% mice had fibrosarcomas	
		+				
	sc	MCA	150	1 time		
	ip	TCDD	100	1 time	MCA 2 days after TCDD: 84% mice had fibrosarsarcomas	
		+				
		MCA	150	1 time		

3 MC=3 methylcholanthrene
DMBA=7,12-dimethylbenz(a)anthracene
*ug/kg unless otherwise specified

TABLE 48: continued

Species	Route	Substance	Dose	Duration	Effect	Reference
mouse CD-1	dermal	TCDD + DMBA + TPA	2 ug 2.56 ug 5 ug	1 time 1 time 2x/wk for 32 wk 1 wk after TCDD	TCDD + TPA: 0.1 papilloma/mouse TCDD + DMBA + TPA: 2.2 papillomas/mouse *very slight initiator	DiGiovanni et al, 1977
mouse CD-1	dermal dermal	DMBA + TCDD	200 nmol 0.1 ug	1 time 2x/wk for 30 wk	No papillomas on TCDD promoted mouse Reduction in tumors with 2,3,7,8-TCDD pretreatment	Berry et al, 1979
mouse Sencar	dermal	B(a)P or DMBA DMBA TCDD	100nmol 10nmol 1 ug	1 time 1 time 1 time 72 hr prior to B(a)P or DMBA	DMBA+TPA: 9.1 papillomas/mouse *DMBA+TCDD: 0.1 papillomas/mouse B(a)P+TPA: 3.8 papillomas/mouse *B(a)P+TCDD+TPA: 0.3 papillomas/mouse *inhibition of tumors	Cohen et al, 1979

sc = subcutaneous
TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin
TPA = 12-o-tetradecanoyl-phorbol-13-acetate
B(a)P = benzo(a)pyrene
DMBA = 7,13-dimethylbenzanthoracene

TABLE 49: Developmental Effects Due to Exposure to 2,3,7,8-TCDD

Species	Sex	Route	Dose*+	Dose period (days of gestation)	Effect	Reference
rat SD	male female	oral	0.001 0.01 0.1	daily 90d prior mating + throughout pregnacy	0.1 ug/kg/d: decreased infertility and neonatal survival ($p<.05$) in F_0 generation 0.01 ug/kg/d: reduced fertility in F_1, F_2 & F_3 generations ($p<.05$); decreased litter size & gestation survival, neonatal survival & growth 0.001 ug/kg: no effect	Murray et al, 1979
rat CRCD	female	gavage	0.125 0.5 2.0	daily 14 days prior to mating	0.5 ug/kg: increased post-implantation loss 2 ug/kg: reduced ovulation rate, increased pre and post-implantation loss ($p<0.05$), fetal growth retardation ($p<0.05$); malformation of pups including cystic kidney, edema, gastrointestinal hemorrhage	Giavini et al, 1983
mouse C57BL/6N	female	gavage	12 17 22	10	% of fetus with cleft palate: 12 ug/kg: 9% 17 ug/kg: 44% 22 ug/kg: 78% % kidneys/litter with $\geq$2 lesions: 12 ug/kg: 85% 17 ug/kg: 95% 22 ug/kg: 93% no maternal toxicity at any dose	Weber et al,1985
mouse C57BL/6N	female	gavage	12 14 31	11 11 10-13	36% fetuses per litter with cleft palate; mild hydronephrosis 70% fetuses per litter with cleft palate 4-8% fetuses per litter with cleft palate; moderate to severe hydronephrosis & dilated renal pelvis	Birnbaum et al, 1985

SD Sprague Dawley; SC Subcutaneous; * ug/kg unless otherwise specified; + exposure is to 2,3,7,8-TCDD unless otherwise specified

TABLE 49: continued

Species	Sex	Route	Dose period (days of gestation)	Effect	Reference
mouse CD-1 DBA/2J C57B1/6J		sc	6-15 (daily)	Cleft palate in all species and both doses; unspecified kidney anomalities; gastrointestinal hemorrhage	Courtney and Moore, 1971
mouse C57B1/6	female	oral	10-13 (daily) 10-13 (daily) 1 time on day 10	3.0 ug/kg/d: 50% incidence of cleft palate & 95% incidence of; hydronephrosis; 1.0 ug/kg/d: 2% incidence of cleft palate & 60% incidence of hydronephrosis 1 ug/kg: no cleft palate & 35% hydronephrosis	Moore et al, 1973
mouse CD-1	female	sc	7-16 (daily)	All doses: Cleft palate, hydronephrosis, hydrocephalus, open eye, petechiae; 100 ug/kg: fetotoxic; 200 ug/kg & 400 ug/kg: elevated abortion rates	Courtney, 1976
mouse CF-1	female	gavage	6-15 (daily)	3.0 ug/kg/d: Cleft palate & dilated renal pelvis ($p<.05$) 1.0ug/kg/d: Cleft palate ($p<.05$) $\leq$ 0.1ug/kg/d: no malformations	Smith et al, 1976
monkeys rhesus	female	oral	20 mo[1] (daily)	4 abortions 1 stillbirth 2 no conceptions 2 normal births	Schantz et al., 1979

*ug/kg bw unless otherwise specified

[1] monkeys mated to control males 7 months after exposure began

TABLE 50: Immunologic effects related to exposure to 2,3,7,8-TCDD

Species	Route	Substance	Dose*	Duration	Effect	Reference
mouse CD or C57B1/6	oral	TCDD	10 50	1 time	thymic atrophy	Harris et al, 1973
mouse C57B1/6	oral	TCDD	25	6wk	thymic atrophy	Vos et al, 1974
mouse B6C3F1	gavage	TCDD	1 5 15	day 14 gestation & day 1, 7 & 14 after birth	1.0 ug/kg:no effect; 5.0 ug/kg: thymic atrophy and depletion of lymphocytes; reduced total nucleated cells and CFU-S cells in bone marrow; suppressed lymphoproliferative response to CMA and PHA; reduced resistance to Listeria; 15 ug/kg: toxic to dams & litters	Dean et al, 1981
mouse C57B1/6	ip	TCDD	0.4 4 40 100 400	1x/wk for 4 wk	Lymphatic organ changes; 0.4-40 ug/kg: minor decreased cellularity of spleen, thymus, peripheral lymph nodes and lymphocytes 40 ug/kg: severe decrease in spleen, thymus, peripheral lymph nodes immune response changes 40 ug/kg: marked suppression of antibody to sheep RBC and B abotus; 0.4-40 ug/kg: suppression of cytotoxic lymphocyte response due to enhanced suppression cell response	Clark et al, 1981
rat CD	oral	TCDD	5 25	1 time	thymic atrophy	Harris et al, 1973

*ug/kg unless otherwise specified

TABLE 50: continued

Species	Route	Substance	Dose*	Duration	Effect	Reference
rat CD	gavage	TCDD	100	1 time	severe thymic atrophy	Gupta et al, 1973
			50	1 time	severe thymic atrophy	
			25	1 time	slight thymic atrophy	
			10	1x/d for 16-30	severe thymic atrophy	
			1	1x/d for 15-31	severe thymic atrophy	
guinea pig hartley			3.0	1 time	severe thymic atrophy	
			1.0	1x/wk for 8 wk	severe thymic atrophy	
			0.2	1x/wk for 8 wk	slight thymic atrophy	
mice			50.0	1 time	slight thymic atrophy	
rat (NS)	ip	TCDD	50	1 time	thymic atrophy	Gasiewicz et al, 1980
			100			
guinea pig hartley	oral	TCDD	0.44	90 d	decreased thymic weight;	DeCaprio et al, 1986
			1.3		thymic atrophy	
hamster Golden Syrian	ip	TCDD	500	1 time	thymic atrophy	Olson et al, 1980
			1000			
			2000			
			3000			
monkey rhesus	oral	TCDD	<70	1 time	thymic atrophy	McConnell et ala, 1978

(NS) = not specified

* = ug/kg unless otherwise specified

TABLE 50: continued

Species Route	Substance	Dose*	Duration	Effect	Reference
cultured thymus & spleen cells (mouse)	TCDD			inhibition of cytotoxic lymphocyte (CTL) precursors	Clark et al, 1983
mouse ip C57B1/6(B6) C3H/Hen(C3) B6C3F1/B6(C3) DBA/2(D2) AKR	TCDD	1.2	1 time	thymus weight loss in B6, C3 & B6/D2; minor loss in D2 & AKR ($p<.05$) 1.2,6.0,30.0 ug/kg: immunosuppression of humoral antibody production in B6, C3, B6/D2 ($p<.05$); 6.0, 30.0ug/kg; immunosuppression of humoral antibody production D2 ($p<.05$) no difference in cell-mediated immune reaction (popliteal lymph node assay)	Vecchi et al, 1983
ip	TCDD	6.0	1 time	no reaction to sheep RBC by B6 and C3 strains; reaction to sheep RBC 50% of normal by D2 & AKR	
oral	TCDD	2 ug/kg/wk or 0.5	1x/wk for 5wk 1x/wk for 8 wk		

TCDF = 2,3,7,8-tetrachlorodibenzofuran

* = ug/kg unless otherwise specified

TABLE 50: continued

Species	Rte	Substance	Dose*		Duration	Effect	Reference
mouse BCF DBA/2	oral	TCDD	BCF 0.2 1.0 2.0 5.0 10.0	DBA/2 5.0 10.0 50.0	1 time	reduced number of granulocyte-macrophage progenitor cells & erythrocyte precursor cells in bone marrow & decrease in bone marrow hematopoesis at 1.0 ug/kg in BCF & at 10 ug/kg in DBA/2	Luster et al, 1985
mouse C57B1/6	ip	TCDD or TCDF	1 or 100		1 time 1 time	TCDD or TCDF: no reduction in thymic weight; TCDD, 1ug/kg: reduced antibody production by 70%	Vecchi, 1985
	ip	TCDD or TCDF	1 10		1 time	Reduced plaque antibody production ($p<.05$)	
	ip	TCDD or TCDF	1 10		1 time	7-fold increase in AHH activity	
mouse C57B1/6	ip	TCDD	30 60 120		1 time	Immature B cells more sensitive than mature B cells *	Chastain & Pasternik, 1985

* = ug/kg unless otherwise specified

TABLE 50: continued

Species	Route	Substance	Dose*	Duration	Effect	Reference
mouse BCF C 7BL/6J (B6)	gavage	TCDD	0.2 1.0 5.0	1 time	BCF: Dose related suppression of T cell dependent & independent antibody responses ($p<.05$); <5.0 ug/kg: no thymic atrophy BCF, 5ug/kg: resistance to parasitic infection reduced ($p<.05$);	Tucker et al, 1986
mouse C57B1/6Cr1 BR DBA/2Cr1 BR	ip	TCDD	1 (C57B1/6) 6 (DBA)	1 time	TCDD: depressed antibody production in both species ($p<.05$); TCDD + 3MC or BNF or PB: reduced antibody formation & mitogen stimulation & enhanced AHH activity in C57B1/6 only	Vecchi et al, 1986

3MC = 3-methylcholanthrene
BNF = beta-naphthalamine
PB = phenobarbitol
AHH = arylhydrocarbon hydroxylase
* = ug/kg unless otherwise specified

TABLE 50: continued

Species	Route	Substance	Dose*	Duration	Effect	Reference
mouse B6C3F1	gavage	TCDD	>0.01	1x/d for 14d	Suppressed serum total hemolytic complement activity component (C3); increased susceptibility to S pneumonia	White et al, 1986
mouse C57BL/6	gavage	TCDD	1.0	1x/d for 14d	decrease in antibody response to both T-dependent and T-independent antigens ($p<.05$)	Holsapple et al, 1986
rat Fisher 344	gavage	TCDD	5	day 14 gestation & weeks 1, 7, 14 postnatal	Decrease in thymic weight of offspring until wk 9 ($p<.05$); Response to PHA and ConA depressed until wk 9 and 14 ($p<.05$)	Luster et al, 1982

3MC = 3-methylcholanthrene
BNF = beta-naphthalamine
PB = phenobarbitol
AHH = arylhydrocarbon hydroxylase
* = ug/kg unless otherwise specified

Table 51: Summary of Health Effects other than Neurologic Noted in Reports of Chemical Workers Exposed to 2,3,7,8-TCDD Contaminated Materials

	ASH 1950	BADDER 1951	KIMMIG 1957	BAUER 1961	BLEIBERG 1964
Exposure	TCP	TCP, PCP	TCP, 2,4,5-P	TCP, 2,4,5-T	TCP, 2,4,5-T
Dermatologic					
Chloracne	+	+	+	+	+
Other	+[1,2,3]	-	+[2]	+[1]	+[1]
Hepatic					
Size increase	+	NR	NR	NR	NR
PCT	-	NR	NR	NR	+[4]
Enzyme rise	-	NR	NR	NR	+[5]
Other	+[5,6]	NR	NR	+[6]	NR
Gastrointestinal					
Ulcers	+	NR	NR	NR	NR
Lipid rise	NR	NR	NR	NR	NR
Other	+[7]	+[7]	NR	+[7]	NR
Pulmonary	+	+	NR	NR	NR
Cardiac	NR	+	NR	NR	NR
Other effects	+[8]	+[8]	+[8]	+[8]	NR

[1] Hyperpigmentation or hirsatism
[2] Cysts on eyelids, blepharitis or conjuctivitis
[3] Skin fragilily
[4] Uroporphyrins
[5] SGPTand/or SGOT
[6] Hepatitis (not specified)
[7] Right upper quadrant pain
[8] Reduced libido

+=Positive finding reported in exposed group
-=Negative finding reported in exposed
NR=Not Reported
TCP=trichlorophenol
2,4,5-T=2,4,5-trichlorophenoxy acetic acid

Table 51: continued

	POLAND 1971	GOLDMAN 1973	MAY 1973	OLIVER 1975	JIRASEK 1974
Exposure	TCP 2,4,5-T	TCP	TCP 2,4,5-T	Pure 2,3,7,8-TCDD	TCP 2,4,5-T, PCP
Dermatologic					
Chloracne	+	+	+	+	+
Other	+[1,2]	NR	NR	+[1]	+[1]
Hepatic					
Size increase	N	NR	NR	NR	NR
PCT	+[4]	+	NR	NR	+[4,9]
Enzyme rise	+[11]	NR	NR	NR	+[5,12,13]
Other	NR	+[6]	NR	NR	NR
Gastrointestinal					
Ulcers	NR	NR	NR	NR	NR
Lipid rise	NR	NR	NR	+	+
Other	NR	NR	NR	+	+[7]
Pulmonary	NR	NR	NR	NR	NR
Cardiac	NR	+	NR	NR	NR
Other effects	NR	NR	NR	NR	+[14]

[1]Hyperpigmentation or hirsutism
[2]Cysts on eyelids, blepharitis or conjuctivitis
[4]Uroporphyrins
[5]SGPTand/or SGOT
[6]Hepatitis (not specified)
[7]Right upper quadrant pain
[9]UV flourescence of liver
[11]LDH
[12]ALK
[13]Delta-ALA
[14]Diabetes or abnormal glucose tolerance test

+=Positive finding reported in exposed group
-=Negative finding reported in exposed
NR=Not Reported
TCP=trichlorophenol
2,4,5-T=2,4,5-trichlorophenoxy acetic acid

Table 51: continued

	Pazderova 1981	Martin 1982
Exposure	TCP 2,4,5-T	TCP 2,4,5-T
Dermatologic		
Chloracne	+	+
Other	NR	NR
Hepatic		
Size increase	NR	NR
PCT	NR	NR
Enzyme rise	NR	+[15]
Other	NR	NR
Gastrointestinal		
Ulcers	NR	NR
Lipid rise	+	+
Other	NR	NR
Pulmonary	NR	NR
Cardiac	NR	NR
Other effects	+[14]	NR

[14]Diabetes or abnormal glucose tolerance test

[15]GGT

+=Positive finding reported in exposed group

-=Negative finding reported in exposed

NR=Not Reported

TCP=trichlorophenol

2,4,5-T=2,4,5-trichlorophenoxy acetic acid

Table 51: continued

	May 1983	Van Houdt 1983	Bond 1983	Martin 1984	Suskind 1984
Exposure	TCP 2,4,5-T	2,4,5-T	TCP 2,4,5-T	TCP 2,4,5-T	TCP 2,4,5-T
Dermatologic					
Chloracne	+	NR	NR	+	+
Other	NR	NR	NR	NR	+[16]
Hepatic					
Size increase	-	NR	NR	NR	-
PCT	-[15,17]	-	NR	NR	-
Enzyme rise	+[5]	-[5,15]	NR	+[15,17]	-
Other	-	-	NR	NR	-
Gastrointestinal					
Ulcers	-	NR	+	NR	+
Lipid rise	-	NR	+[8]	+	+
Other	-	NR	-	NR	NR
Pulmonary	-	NR	NR	NR	+
Cardiac	-	+	NR	NR	+
Other effects	-	NR	NR	NR	+[8]

[5] SGPT and/or SGOT
[8] Reduced libido
[15] GGT
[16] Actinic changes
[17] D-glucaric acid

+=Positive finding reported in exposed group
-=Negative finding reported in exposed
NR=Not Reported
TCP=trichlorophenol

Table 51: continued

	Moses 1984	Lathrop 1984	Lathrop 1987	Jennings 1988	
Exposure	TCP 2,4,5-T	2,4,5-T	2,4,5-T	TCP 2,4,5-T	
Dermatologic					
Chloracne	+	-	-	NR	
Other	+[16]	+[18]	+[18]	+	
Hepatic					
Size increase	NR	+	+	NR	
PCT	NR	-	-	NR	
Enzyme rise	+[15]	-[15,11]	-	NR	-
Other	NR	+	-	NR	-
Gastrointestinal					
Ulcers	NR	-	-	NR	
Lipid rise	+	-	-	NR	
Other	NR	-	-	NR	
Pulmonary	NR	-	-	NR	
Cardiac	NR	+	+[19]	NR	
Other effects	+[8]	+[20]	-	+[21]	

[3]Skin fragility
[8]Redcued libido
[11]LDH
[15]GGT
[16]Actinic changes
[18]Basal Cell Carcinoma
[19]Heart Diseases
[20]Hemoglobin Volume
[21]Increased immune complex

+=Positive finding reported in exposed group
-=Negative finding reported in exposed
NR=Not Reported
TCP=trichlorophenol

Table 52: Summary of Health Effects Other than Neurologic Among Residents of Seveso, Italy

	Reggiani 1980	Filippini 1981	Assennato 1989	Ideo 1985	Mocarelli 1986
Study Type	Case Report	Cross Sectional	Cross Sectional	Cross Sectional	Cross Sectional
Dermatologic					
Chloracne	+	+	+	NR	NR
Other	+[22]	NR	+	NR	NR
Hepatic					
Size increase	+	NR	NR	NR	NR
PCT	NR	NR	NR	NR	NR
Enzyme rise	+[15]	NR	-	+[17]	+[5,15]
Other	NR	NR	NR	NR	NR
Gastrointestinal					
Ulcers	NR	NR	NR	NR	NR
Lipid rise	+	NR	+	NR	NR
Other	NR	NR	NR	NR	NR
Pulmonary	NR	NR	NR	NR	NR
Cardiac	NR	+	+[19]	NR	NR
Other effects	NR	NR	NR	NR	NR

[5]SGPT and/or SGOT
[15]GGT
[17]D-glucaric acid
[19]Heart Disease
[22]Blisters and burn-like lesions

+=Positive finding reported in exposed group
-=Negative finding reported in exposed
NR=Not Reported
TCP=trichlorophenol

Table 52: continued

	Kimbrough 1977	Steinberg 1985	Hoffman 1986	Webb 1987	Webb 1989
Study Type	Case Report	Cross Sectional	Cross Sectional	Cross Sectional	Cross Sectional
Dermatologic					
Chloracne	+	NR	-	-	-
Other	NR	NR	-	-	-
Hepatic					
Size increase	NR	NR	-	-	-
PCT	NR	NR	+[4]	-	-
Enzyme rise	NR	.5,17	+	-	-
Other	NR	NR	-	-	-
Gastrointestinal					
Ulcers	NR	NR	-	-	-
Lipid rise	NR	NR	-	-	-
Other	NR	NR	-	-	-
Pulmonary	NR	NR	-	-	-
Cardiac	NR	NR	-	-	-
Other effects	+[4]	NR	+[25]	-	-

[4]Uroporphyrins
[5]SGPT and/or SGOT
[17]D-glucaric acid
[23]ALT
[25]Anergic responses

+=Positive finding reported in exposed group
-=Negative finding reported in exposed
NR=Not Reported
TCP=trichlorophenol

Table 53: Reproductive Effects of Exposure to Chemicals Contaminated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin

STUDY POPULATION	COMPARISON	OUTCOME	OBS/EXP or CASES/CONTROLS	RISK RATIO	95% CI	AUTHOR
Offspring of male workers assigned at least 1 month to production of 2,4,5 TCP or PCP 1939-1975 (Michigan) #CONCEPTUSES=1503	Offspring of male workers never exposed to 2,4,5 TCP or PCP #CONCEPTUSES=332	Miscarriage Stillbirth Congenital Malformations	116.8/119.3 19.0/ 18.5 57.1/ 48.7	0.97 1.02 1.17	NA NA NA	Townsend et al., 1982
Offspring of chemical applicators, sprayed 2,4,5,-T (New Zealand)	Agricultural contractors	Miscarriage Congenital Defects	43/40 13/9	0.89 1.19	0.61,1.30 0.58,2.45	Smith et al., 1982
Births 1/1/72-12/31/82 whose mother's address was area of TCDD contamination (Missouri) #BIRTHS=402	Unexposed births matched for maternal age, race, year of birth, hospital, plurality #BIRTHS=804	Total Birth defects Fetal Deaths Low Birth weights	17/42 4/5 4/5 1/4	0.78 1.60 0.50	0.40,1.47 0.32,7.43 0.01,5.05	Stockbauer et al., 1988
Births 1/1/77-12/31/82 whose mother resided in areas contaminated with 2,3,7,8-TCDD (Areas A,B,R) (Seveso, Italy) #BIRTHS=2900	Births of mothers residing in unexposed regions (Area nonABR) #BIRTHS=12391	Total Defects	137 / 605 2900 / 12391 (ABR/nonABR)	0.97	0.83,1.13	*Mastroiacovo et al., 1988

*90%CI; 2,4,5-TCP=2,4,5-trichlorophenol; PCP=pentachlorophenol

TABLE 54: Investigations of the relationship between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Exposure and Soft Tissue Sarcoma (STS)

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP or CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Males ages 26-80 admitted to Oncology Dept. Umea, Sweden 1970-77 (Sweden)	Phenoxy herbicides chlorophenols	Case control (52/206)	STS	46/201 phenoxy herbicides 40/193 chlorophenol	OR = 5.3 OR = 6.6	2.4, 11.5 2.4, 18.5	Exposure	Hardell et al, 1979
Chemical workers (West Virginia)	TCP	Cohort Mortality	STS	1/not calculated	SMR = N/A	N/A	Power	Zack and Suskind, 1980
Cases reported to National Social Welfare Board 1974-78 (Sweden)	Phenoxy herbicides chlorophenol	Case control 330/110	STS	11/8 chlorophenols 14/5 phenoxy herbicides	OR = 3.3 OR = 6.8	1.8, 8.1 2.6, 17.3	Exposure	Eriksson et al, 1981
White males age 20+ deceased 1950-79 in Washington State in occupations with exposure to phenoxy herbicides and chlorophenols (Washington State)	Phenoxy herbicides chlorophenols	Proportionate mortality	STS	25/16 (farmers) 3/2 (orchards) 4/3 (railroad laborers)	PMR = 152 PMR = 145 PMR = 120	101,231 30,438 36,341	Exposure Power	Milham, 1982
Chemical workers (West Virginia)	TCP	Cohort Mortality	STS	1/not calculated	SMR = N/A	N/A	Power	Zack and Gaffey, 1983

OBS = # Observed Cases; TCP = Trichlorophenol; SIR = Standardized Incidence Ratio; EXP = Expected cases; PMR = Proportionate Mortality Ratio; OR = Odds Ratio; SMR = Standardized Mortality Ratio

TABLE 54: continued

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Males registered with New Zealand Cancer Registry between 1976-1980 (New Zealand)	Phenoxy herbicides	Case control (82/83)	STS	7/9 forestry	OR = 0.9	0.3, 2.3*	Exposure	Smith et al, 1984
				17/7 railway	OR = 3.2	1.3, 7.9	Power	
	Chlorophenols			19/9 meatworks	OR = 2.8	1.6, 5.5		
				6/1 tannery or pelt department	OR = 7.2	1.1, 46.		
Males registered with New Zealand Cancer Registry between 1976-1982	Phenoxy herbicides	Case Control	STS	23/59	OR=1.1	0.7, 1.8*		Smith et al, 1986
Males diagnosed in 1968-76 in England & Wales registered in the National Cancer Registry (England & Wales)	Phenoxy herbicides chlorophenols	Cancer incidence (1961/1961)	STS	42/24.7 farm managers, market gardeners farmers	RR = 1.7	1.0, 2.9	Exposure	Balajaran and Acheson, 1984

OBS = # Observed Cases; EXP = Expected cases; OR = Odds Ratio; SMR = Standardized Mortality Ratio; RR = Relative Risk

TABLE 54: continued

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Male Chemical workers (Denmark)	Phenoxy herbicides & other chemicals	Cumulative cancer incidence	STS	1/03 PH 3/0.6 manual service 1/0.8 other	SIR = 3.3 SIR = 5.0 SIR = 1.3	0.1, 18.6 1.0, 14.6 0.1, 7.0	Power Exposure	Lynge, 1985
354,620 men born between 1891-1941 who were agricultural or foresting workers (Sweden)	Phenoxy herbicides chlorophenols	Cancer incidence	STS	331/NA	RR = 0.9	0.8, 1.0	Exposure	Wiklund et al 1986
Histologically confirmed cases diagnosed in 1981-83; 20 yrs or older (Italy)	Phenoxy herbicides (rice weeders)	Case control (68/158)	STS	4/5 (living women) 4/13 (deceased women)	OR = 2.7 OR = 1.1	0.4, 13.9 0.2, 6.9	Exposure Power	Vineis et al 1986
37,000 chemical Chemical workers employed 1 year between 1940-1979 (Michigan)	PCDD	Case control (14/126)	STS	0/7	OR = N/A (PCDDs)	N/A	Power	Sobel et al, 1986

OBS = # Observed Cases; TCP = Trichlorophenol; SIR = Standardized Incidence Ratio; EXP = Expected cases; PMR = Proportionate Mortality Ratio; 245T = 2,4,5-Trichlorophenoxyacetic Acid; OR = Odds Ratio; SMR = Standardized Mortality Ratio;
PCP = Pentachlorophenol; RR = Relative Risk; PCDD = polychlorinated dibenzodioxins; 90% confidence limit

TABLE 54: continued

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Cases diagnosed 1975-1981 registered with the Seveso Cancer Registry (Italy)	Effluent from TCP Reactor Explosion contaminated with 2,3,7,8-TCDD	Cancer incidence	STS	5.73/3.23	RR = 1.77	NA	Exposure	Puntoni et al, 1986
Males 20-79 diagnosed 1981-84; in cancer registry (Western Washington State)	Phenoxy herbicides chlorophenols	Case control (128/695)	STS	128/695	Phenoxy herbicide OR=0.80 Chlorophenols OR = 0.99	0.5, 1.2 0.7, 1.5	Multiple tests	Woods et al, 1987
Males 20 + years registered with New Zealand Cancer Registry (New Zealand)	Abattoir workers	Case control (pooled)	STS		OR=1.9	1.2, 3.1*	Exposure	Pearce et al, 1988

OBS = # Observed Cases; EXP = Expected cases; 245T = 2,4,5-Trichlorophenoxyacetic Acid; OR = Odds Ratio; RR = Relative Risk

TABLE 55: Investigations of the relationship between 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Lymphatic and Hematopoietic Cancers

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
122 chemical workers with chloracne (West Virginia)	TCP 2,4,5-T	Cohort mortality	Lymphatic- & hematopoietic	3/0.88	SMR=341	69, 996	Power	Zack and Suskind, 1980
Washington State white male deaths age 20+, 1950-79 in occupations with exposure to phenoxy herbicides and chlorophenols (Washington State)	Phenoxy herbicides chlorophenols	Proportionate mortality	Hodgkins disease	38/36 (farmers)	PMR=106	75, 145	Exposure	Milham, 1982
				9/5 (orchardist)	PMR=180	82, 342	PMR	
				17/9 (paper & pulp mill)	PMR=189	110, 302		
			Lympho-sarcoma	12/9 (orchardist)	PMR=133	69, 233		
			reticulo-sarcoma	13/11 (wheat farmers)	PMR=118	63, 202		
				17/13 (paper & pulp mill)	PMR=131	76, 209		
			Other lymphomas	9/6 (wheat farmers)	PMR=148	68, 285		
				12/7 (railroad laborers)	PMR=171	88, 299		

OBS = # Observed Cases; TCP = Trichlorophenol; EXP = Expected cases; PMR = Proportionate Mortality Ratio; 245T = 2,4,5-Trichlorophenoxyacetic Acid; SMR = Standardized Mortality Ratio;

TABLE 55: continued

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Males age 25-85 diagnosed between 1974-78 admitted to Dept of Oncology (Sweden)	Phenoxy herbicides chlorophenols	Case control	Non-Hodgkins lymphoma & Hodgkins disease	169/338	OR = 4.8 (Phenoxy herbicide)	2.9, 8.1	Exposure	Hardell et al, 1981
					OR = 4.3 (Chloro-phenols)	2.7, 6.9		
Males under age 70 registered with New Zealand Cancer Registry 1977-81 (New Zealand)	Phenoxy herbicides chlorophenols	Case control	Non-Hodgkins Lymphoma	37/0.49	OR = 2.0 (fencing)	1.1, 2.8	Power Exposure	Pearce et al, 1986
				19/23	OR = 1.8 (meat works)			
Chemical workers (Michigan)	TCP; 2,4,5-T phenoxy herbicides	Cohort mortality	NHL	5/2.6	SMR = 192	62, 449	Power	Ott et al, 1987
Pesticide applicators licensed between 1965-1976 (Sweden)	Phenoxy herbicides	Cumulative cancer incidence	Non-Hodgkins Lymphoma	21 Cases	SIR = 1.01	.6, 1.5	Exposure	Wiklund et al, 1987
			Hodgkins Disease	11 Cases	SIR = 1.2	.6, 2.2		

OBS = # Observed Cases; TCP = Trichlorophenol; SIR = Standardized Incidence Ratio; EXP = Expected cases; 245T = 2,4,5-Trichlorophenoxyacetic Acid; OR = Odds Ratio; SMR = Standardized Mortality Ratio; NHL = non-Hodgkins Lymphoma

TABLE 55: continued

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Males 20-79; diagnosed 1981-84; in cancer registry of Western Washington State (Washington)	Phenoxy herbicides chlorophenols	Case control	Non-Hodgkins lymphoma	576/694	OR = 0.92 chlorophenols	0.8, 1.8	Multiple tests	Woods et al, 1987
					OR = 1.33 (Farmers, Phenoxy herbicide	1.0, 1.7		
					OR = 4.8 Forest sprayers	1.2, 19.4		
354,620 men born 1891-40 employed in agriculture or forestry in 1960 census	Phenoxy herbicides	Cumulative cancer incidence	Non-Hodgkins Lymphoma	61	No elevated RR in 6 occupational groups		Exposure	Wiklund, et al, 1987
			Hodgkins Disease	15 silviculture	RR = 2.26	1.3, 3.9		
(Sweden)				5 furfarming	RR = 4.45	1.41, 10.15		

OBS = # Observed Cases; TCP = Trichlorophenol; EXP = Expected cases; OR = Odds Ratio; RR = Relative Risk; dibenzodioxins

TABLE 56: Investigations of the relationship Between (TCDD) 2,3,7,8-tetrachlorodibenzo-p-dioxin Exposure and Respiratory Cancers

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Chemical workers with chloracne (West Virginia)	TCP	Cohort mortality	Lung cancer	5/2.85	SMR = 175	57, 409	Power	Zack and Suskind, 1980
1658 who worked as pesticide applicators between 1948-1972 (West Germany)		Cohort mortality	Bron-chial carcinoma	59/27.5	SMR = 215	163, 277	Exposure No smoking status	Barthel, 1981
Chemical workers (West Virginia)	2,4,5-T	PMR	Lung	6/3.57	PMR = 168	61, 366	Power	Zack and Gaffey, 1982
Males aged 25-85 yrs reported to Swedish Cancer Registry 1970-79 (Sweden)	Phenoxy-herbicides	Case control	Nasal naso-pharyn-geal	38/541 13/541	OR = 2.1 OR = 6.7	0.9, 4.7 2.8, 16.2	Exposure Power	Hardell et al, 1982

OBS = # Observed Cases; TCP = Trichlorophenol; SIR = Standardized Incidence Ratio; EXP = Expected cases; PMR = Proportionate Mortality Ratio; 245T = 2,4,5-Trichlorophenoxyacetic Acid; OR = Odds Ratio; SMR = Standardized Mortality Ratio; PCP = Pentachlorophenol; RR = Relative Risk; PCDD = polychlorinated dibenzodioxins

TABLE 56: continued

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
74 chemical workers exposed to TCP reactor explosion (West Germany)	TCP	Cohort Mortality	bron-chial carcinoma	3/1.26	SMR = 238	48, 696	Power	Theiss et al, 1982
Cases from the 1970-82 Danish Cancer Registry	Chlorophenols	Case Control (839/2465)	Nasal cancer	839/2465	RR = 0.6 (adjusted for wood dust)	0.3, 1.2	Exposure	Olsen and Jensen, 1984
Chemical workers (Denmark)	Phenoxy herbicides	Cumulative cancer incidence	Lung cancer	11/5.3 (men)	SIR = 207	103, 371	Exposure	Lynge, 1985

OBS = # Observed Cases; TCP = Trichlorophenol; SIR = Standardized Incidence Ratio; EXP = Expected cases; SMR = Standardized Mortality Ratio; RR = Relative Risk

TABLE 57: Investigations of the Relationship Between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Exposure and Gastrointestinal Cancers

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Railroad workers pesticide applicators (Sweden)	Phenoxy herbicides	Cohort mortality	Stomach	3/1.34	RR = 2.2	0.45, 6.45	Exposure Power	Axelson et al, 1980
Males age 25-85 residents in region of the Dept. of Oncology and reported to Swedish Cancer Register 1978-79 (Sweden)	Phenoxy herbicides chlorophenols	Case control	Colon	11/43 phenoxys	OR = 1.3	0.6, 2.8	Exposure Power	Hardell, 1981
				6/13 chlorophenols	OR = 1.8	0.6, 5.3		
74 chemical workers involved in TCP reactor explosion (West Germany)	TCP	Cohort mortality	Stomach	3/0.7	SMR = 428	86, 1252	Power	Theiss et al, 1982
			Colon	1/0.42	SMR = 238	3, 1325		
Chemical workers (Denmark)	Phenoxy herbicides	Cumulative cancer incidence	Stomach	males 2/1.47	SIR = 1.36	0.15, 4.91	Exposure Power	Lynge, 1985
			Rectal	males 4/1.49	SIR = 2.68	0.72, 6.87		
Chemical workers (Michigan)	TCP 2,4,5-T	Cohort mortality	Stomach	6/3.8	SMR = 158	62, 449	Power	Ott et al, 1987
			Intestine	10/7.1	SMR = 141	67,259		

OBS = # Observed Cases; TCP = Trichlorophenol; SIR = Standardized Incidence Ratio; EXP = Expected cases; 245T = 2,4,5-Trichlorophenoxyacetic Acid; OR = Odds Ratio; SMR = Standardized Mortality Ratio; RR = Relative Risk

TABLE 58: Investigations of the Relationship Between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Exposure and Other Cancers

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Chemical workers (Denmark)	Phenoxy herbicides	Cumulative cancer incidence	Cervix	5/1.8	SIR=278	90, 648	Exposure	Lynge, 1985
Air Force Ranch Handers (baseline study)	Vietnam Service	Cross-sectional	Nonmel-anotic skin cancer (basal cell)	31/21	RR=2.4	1.2, 5.1	Exposure	Lathrop et al, 1984
Air Force Ranch Handers (follow up study)	Vietnam Service	Cross-sectional	Nonmel-anotic skin cancer (basal cell)	29/30 verified 36/48 verified & suspected	RR=1.2 RR=1.0	0.7, 2.1 0.6, 1.5	Exposure	Lathrop et al, 1987
Chemical workers Midland, MI (Michigan)	TCP 2,4,5-T	Cohort mortality	Prostate cancer	8/4.2	SMR=190	82, 375	Power	Ott et al, 1987

OBS = # Observed Cases; TCP = Trichlorophenol; SIR = Standardized Incidence Ratio; EXP = Expected cases; PMR = Proportionate Mortality Ratio; 245T = 2,4,5-Trichlorophenoxyacetic Acid; OR = Odds Ratio; SMR = Standardized Mortality Ratio; PCP = Pentachlorophenol; RR = Relative Risk; PCDD = polychlorinated dibenzodioxins

TABLE 59: Studies Investigations of the Relationship Between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Exposure and Nonmalignant Causes of Death

POPULATION	EXPOSURE EVALUATED	STUDY TYPE	SITE OF DISEASE	OBS/EXP OR CASES/CONTROLS	RATE RATIO	95% C.I.	STUDY LIMITS	REFERENCE
Forestry Workers employed 1950-1982	2,4-D 2,4,5-T	Cohort Mortality	Suicide	4/1.50(<5 yrs)	SMR = 267	107,426	Power	Green, 1988
				5/1.95(5-14yrs)	SMR = 256	116,396	Multiple tests	
N = 1222 (Canada)				2/1.74 (≥15yrs)	SMR = 115	0,263	Exposure	

OBS = # Observed Cases; EXP = Expected cases; 245T = 2,4,5-Trichlorophenoxyacetic Acid; SMR = Standardized Mortality Ratio; 2,4-D=2,4-dichlorophoxy acetic acid

APPENDICES

APPENDIX A

REVIEW OF THE EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN IN MAMMALIAN SYSTEMS

Non-Malignant Effects

Lethality and Sensitivity

The lethal effects of 2,3,7,8-TCDD vary significantly with animal species, dose and duration of exposure. Acute single dose effects illustrate the dramatic species difference in tolerance to exposure. Male guinea pigs are the most sensitive of the species evaluated having an LD_{50} of 0.6 ug/kg body weight (bw) (Schwetz et al., 1973), while the male Golden Syrian hamster is the hardiest of the species and can tolerate up to approximately 3000 ug/kg bw before 50% of the exposed animals die (Olson et al., 1980). This represents an approximately 5000-fold difference in species sensitivity. Other species have sensitivities intermediate to the guinea pig and hamster in the following order of decreasing LD50 dose: rat, monkey, mouse, rabbit (Neal et al., 1982). Intraspecies variations in lethality may be due to strain, age and sex of the

animal. In general, younger (weanling) animals, females and Ah responsive strains are more sensitive to the effects of 2,3,7,8-TCDD (Neal et al., 1982; Neal, 1985; NTP, 1982b). Low dose, chronic exposures appear to be cumulative, causing more severe effects than single doses of the same strength (McNulty, 1977).

When compared to the toxicity of other chlorinated dibenzodioxins, the isomer chlorinated at the 2,3,7 and 8 carbons is the most toxic configuration (Neal et al., 1982; Poland et al., 1976; Neal, 1985). The dibenzofurans share a similar toxicologic profile with the dibenzodioxins. However, the 2,3,7,8-tetrachlorodibenzofuran is approximately two to four times less toxic than 2,3,7,8-TCDD (Moore et al., 1979).

Weight Loss

One of the most consistently reported outcomes of exposure to 2,3,7,8-TCDD is body weight loss of the treated animals, commonly termed the "wasting syndrome" (Table 37). Single dose administration of 2,3,7,8-TCDD and long-term exposure cause body mass reduction in almost every species evaluated. Reduction of pre-exposure body mass in animals administered 2,3,7,8-TCDD has been recorded in Rhesus monkeys, (McConnell et al., 1978a; McNulty, 1977; Allen et al., 1977), in Hartley guinea pigs (McConnell et

al., 1978b; Harris et al., 1973; DeCaprio et al., 1986), in C57B1/6 mice (McConnell et al., 1978b; Vos et al., 1974, and in Wistar rats (Courtney et al., 1978), CD (Harris et al., 1973) and Sprague-Dawley rats (NTP, 1982; Kociba et al., 1979).

In a few studies, treated animals (CD and Sprague Dawley rats and Golden Syrian hamsters) did not lose weight, rather they failed to gain the same amount of weight recorded in the untreated age-matched controls (Harris et al., 1973; Kociba et al., 1976; Olson et al., 1980). The reason for the observed loss of weight has not been explained; however, researchers agree that, although many animals are reported to reduce food consumption (McConnell et al., 1978b; DeCaprio et al., 1986) or to stop eating all together (McNulty, 1977), the loss is due to unexplained mechanisms.

Dermal Effects

One of the earliest recognized feature of human exposure to 2,3,7,8-TCDD contaminated chemical is chloracne, an acne-like condition caused by exposure to a variety of halogenated aromatic hydrocarbons (Ashe and Suskind, 1949, 1950; Suskind et al., 1953; Baader and Bauer, 1951; Bauer et al., 1961; Goldman, 1972; Poland et al., 1971). In a series of three independent rabbit ear skin painting studies, Kimmig and Schulz (1957) identified the chemical source of the chloracne as 2,3,7,8-TCDD (Table 38). Jones and

Kizek (1962) and Schwetz et al., (1973) described the pathology of the condition as hyperkeratosis of the follicular epithelium, hyperplasia of surface epidermis, comedones, and thickening of the epidermal keratin. Similar changes were noted in HRS/J (hairless mice) (Jones et al., 1981). Systemic administration in rhesus monkeys caused what may be presumed as more severe effects including: acne, squamous cell metaplasia of the sebaceous gland, disturbances of keratin-producing follicles causing loss of hair, eyelashes, and nails. Petechial hemorrhages were observed around the nares, and on the buccal cavity and gums possibly due to increased fragility of the capillaries (McConnell et al., 1978a; Allen et al., 1977; Schantz et al., 1979).

Hepatic and Biliary Effects

Hepatic response to a single or repeated doses of 2,3,7,8-TCDD presents a diverse range of effects which appear to be common to most species. The responses include increased liver size and weight, cellular and lipid infiltration, liver cell necrosis, enzymatic elevations, bilirubin changes and bile duct epithelial hyperplasia (Table 39). With the exception of the golden Syrian hamster (Olson et al., 1980), at least one of these effects were observed in mice (Vos et al., 1974; Jones and Greig, 1975), rats (McConnell et al., 1978a, 1978b; Greig et al., 1973; Kociba et al., 1976; Kociba et al., 1978, Zinkl et al., 1973), monkeys (McConnell et al, 1978; Schantz et al., 1979; Allen et al., 1977) and guinea pigs (DeCaprio et al, 1986).

Hepatocellular and bile duct changes subsequent to exposure to 2,3,7,8-TCDD present a consistent picture among the species tested, whether the animals are given a single dose or are given repeated doses over a prescribed period. Morphologically, livers of exposed monkeys (Allen and Carstens, 1967; McConnell et al., 1978), mice (Jones and Greig, 1975; McConnell et al. 1978b; Vos et al., 1974; NTP, 1982b; Jones et al., 1981), rats (Greig et al., 1973; Gasiewicz et al., 1980; Kociba et al., 1976, 1978) and guinea pigs (DeCaprio et al., 1986) increased in relative weight, characterized by hepatocellular necrosis, cellular infiltration and vacuolarization of hepatocytes with lipid. In rats (Greig et al., 1973; Gasiewicz et al., 1980; Kociba et al., 1978) and monkeys (Allen and Carstens, 1967), hepatocytes were described as multinucleated and often of bizarre sizes and shapes. Mice hepatocytes were not observed to be multinucleated. No histopathological changes of the liver were observed in Golden Syrian hamsters administered one dose of 3000 ug 2,3,7,8-TCDD/kg (Olson et al., 1980).

In addition to nonneoplastic morphological changes, increases in hepatic nodules were observed in 2,3,7,8-TCDD treated rats (Kociba et al., 1978) and mice (Toth et al., 1979; NTP, 1982a). Futhermore, statistically significant increases in hepatocellular carcinoma was demonstrated in Sprague-Dawley rats (Kociba et al., 1978), in Osborne-Mendel rats (NTP, 1982a) and B6C3F1 mice (NTP, 1982a).

Cellular proliferation and hyperplasia of bile duct epithelium was common in exposed mice, (Jones and Greig, 1975; Vos et al. 1974; McConnell et al., 1978), rats (Gasiewicz et al., 1980; Kociba et al., 1976) and in rhesus monkeys (Allen and Carstens, 1967; Allen et al., 1977).

Enzyme levels commonly associated with liver damage (SGOT, SGPT, GGT, ALK) when measured after exposure to 2,3,7,8-TCDD, were not consistently changed (Table 40). In general, SGOT was increased in rats (Greig et al., 1973; Zinkl et al., 1973; Gasiewicz et al., 1980) and in monkeys (McConnell et al., 1978) but not in hamsters or guinea pigs (Olson et al. 1980; DeCaprio et al., 1986). SGPT was either slightly increased or unchanged in approximately equal number of studies of rats (Greig et al., 1973; Zinkl et al., 1973; Kociba et al., 1976; Gasiewicz et al., 1980), guinea pigs (DeCaprio et al., 1986) and hamsters (Olson et al., 1980). Bilirubin was measured in eight studies of rats, monkeys and hamsters. Two to 20-fold increases in mean bilirubin levels were noted in rats (Gasiewicz et al., 1980; Zinkl et al., 1973; Kociba et al., 1976) and in Golden Syrian hamsters (Olson et al., 1980). No changes in mean bilirubin level were reported in two studies of Rhesus monkeys (Allen and Carstens, 1967; McConnell et al., 1978).

Hepatic damage due to exposure to 2,3,7,8-TCDD has also been associated with decrease in serum glucose levels in rats (Zinkl et al., 1973; Gasiewicz et al., 1980; Schiller et al., 1986) and in

monkeys (McConnell et al., 1978). Increases in serum cholesterol have been demonstrated in rats (Greig et al., 1973; Zinkl et al., 1973; Gasiewicz et al., 1980) and in hamsters (Olson et al., 1980). Changes in serum protein levels have also been attributed to 2,3,7,8-TCDD exposure in monkeys (Allen and Carstens, 1967; McConnell et al., 1978), mice (Vos et al., 1974) and rats (Greig et al., 1973; Gasiewicz et al., 1980). Alteration of porphyrin metabolism has also been observed in exposed rats (Kociba et al., 1976; Kociba et al., 1978; Cantoni et al., 1981) and in mice (Goldstein et al., 1973; Sweeney et al., 1979) but not in monkeys (McConnell et al., 1978a).

Three studies showed statistically significant decreases in serum glucose levels in 2,3,7,8-TCDD treated rats (Schiller et al., 1986; Zinkl et al., 1973; Gasiewicz et al., 1980), one of which demonstrated significant decreases in serum glucose within two days after exposure (Schiller et al., 1986) (Table 41). Nonspecific reductions in serum glucose levels were observed in one study of rhesus monkeys (McConnell et al., 1978). The consistent reduction in serum glucose concentrations is thought to be due to severe hepatic damage or perhaps an alteration in the regulation of lipid synthesis from carbohydrates (Gasiewicz et al., 1980; Zinkl et al., 1973), however, the precise mechanism for this effect has not been determined (Lutz et al., 1987).

Consistent and apparently dose-dependent elevations in serum cholesterol levels have also been reported after acute and chronic exposure to 2,3,7,8-TCDD in a total of eight studies of rats (Poli et al., 1980; Schiller et al., 1986; Albro et al., 1978; Zinkl et al., 1973; Greig et al., 1973; Gasiewicz et al., 1980), guinea pigs (Gasiewicz and Neal, 1979) and hamsters (Olson et al., 1980) (Table 42). Unlike the elevations of serum cholesterol in rats, hamsters and guinea pigs, rhesus monkeys experienced decreased cholesterol levels after exposure to 2,3,7,8-TCDD (McConnell et al., 1978; Schantz et al., 1979). Serum triglyceride levels were also measured in eight studies of rats (Poli et al., 1980; Schiller et al., 1986; Albro et al., 1978; Gasiewicz et al., 1980), guinea pigs (Gasiewicz and Neal, 1979; DeCaprio et al, 1986), monkeys (McConnell et al., 1978) and hamsters (Olson et al., 1980). The results, however, are not consistent among the studies and did not reflect similar changes in serum cholesterol levels.

Alterations in serum protein and albumin have been observed as a consistent effect in mice (Vos et al., 1970; McConnell et al., 1978), rats (Greig et al., 1973; Gasiewicz et al., 1980; Zinkl et al., 1973) and monkeys (Allen and Carstens, 1967; McConnell et al., 1978a) (Table 43). In contrast, statistically significant increases in serum protein were reported in hamsters (Olson et al., 1980), and guinea pigs (Gasiewicz and Neal, 1979). Changes in serum albumin generally followed the same pattern as serum protein levels, although the observed fluctuations were not consistent.

Gasiewicz and Neal (1979) speculate that increased serum proteins in 2,3,7,8-TCDD dosed animals may reflect a state of dehydration and hemoconcentration.

Increased excretion of porphyrins and alterations in porphyrin excretion patterns after repeated exposure to 2,3,7,8-TCDD was demonstrated in mice, and rats (Table 44). Exposure to 2,3,7,8-TCDD caused increased excretion of uroporphyrins and heptacarboxlic porphyrins in mice (Goldstein et al., 1973; Sweeney et al., 1979; Jones and Sweeney, 1980; Cantoni et al., 1984), and in rats (Kociba et al., 1976; Kociba et al., 1978; Cantoni et al., 1981). Monkeys administered single oral doses of at least 70 2,3,7,8-TCDD ug/kg bw did not develop signs of porphyria nor had evidence of UV flourescence of liver tissue (McConnell et al., 1978a).

Porphyria induced by 2,3,7,8-TCDD appears to have a latency period from the time of exposure to the time porphyric changes become evident. The latency period may be species and strain specific, and it may be also dose related. Although not confirmed, the latent period has been attributed to the time necessary for sufficient liver damage to occur to cause changes in the porphyrin pathway (Goldstein et al, 1982). In mice the induction period has been shown to be as short as one week and as long as six weeks. In rats induction of porphyria has been shown to occur within 2 months of treatment, although no study has examined the possibility of induction within sixty days of exposure.

Exposure related effects have also been reported in a variety of other organ systems including respiratory, vascular and hemoatopoeitic systems. These effects are described below.

Respiratory and Vascular Effects

Respiratory Effects

Studies of chronic exposure to 2,3,7,8-TCDD in Sprague-Dawley rats (Greig et al., 1973; Kociba et al., 1978), B6C3F1 mice (NTP, 1982a), rhesus monkeys (Allen and Carstens, 1976; Allen et al., 1977) and hartley guinea pigs (DeCaprio et al., 1986) reported profound changes in bronchiolar or alveolar tissue including alveolar edema and hyperplastic, keratinizing squamous metaplasia and squamous cell carcinomas (Table 45).

In the oral cavity, stratified squamous cell carcinoma of the hard palate and nasal turbinates were observed in 8 of 99 Sprague-Dawley rats administered daily doses of 0.1 ug 2,3,7,8-TCDD/kg bw (Kociba et al., 1978). Other long-term dosing studies of rats were negative for this site (NTP, 1982a; NTP, 1982b).

Vascular Effects

Profound degenerative changes in vessels and the heart (cardioedema) were reported in rhesus monkeys administered fat

contaminated with an unknown amount of 2,3,7,8-TCDD (Allen and Carstens, 1967) (Table 46). In a separate study, nine months of exposure to 500 ppt 2,3,7,8-TCDD by gavage caused gangrenous necrosis of the fingers and toes in rhesus monkeys as well as generalized edema and ascites. Cardiac involvement included bilateral ventricular dilation, edema and enlargement of hemorrhage were found in the epicardium, myocardium and endocardium (Allen et al., 1977). Myocardial degenerative changes were also reported in Sprague-Dawley rats after two years of daily exposure to 0.1 ug/kg 1d bw 2,3,7,8-TCDD (Kociba et al., 1978). Vascular changes may also account for reports of hemorrhage in the stomach or gastrointestinal tract of dosed C57B1/6 mice (Vos et al., 1973), hartley guinea pigs (Gupta et al., 1973; McConnell et al., 1978b) porton, CD or Sprague-Dawley rats (Greig et al., 1973; Gupta et al., 1973; Van Miller and Allen, 1977) and rhesus monkeys (McNulty, 1977; McConnell et al., 1978a). It is also possible that the changes observed in the stomach and intestinal tract are due to localized irritation caused by direct contact of the organs with 2,3,7,8-TCDD contaminated food. In these studies, the 2,3,7,8-TCDD was administered with chow or by gavage.

Hematologic Effects

Exposure to 2,3,7,8-TCDD elicited a variety of alterations in the cellular components of blood (Table 47) (Vos et al. 1974; Zinkl it al., 1973; Greig et al., 1973; Weissberg and Zinkl, 1973; Allen et

al., 1977; Kociba et al., 1976) No consistent pattern of white or red blood cell change is readily discernible. McConnell (1989) suggests that this confusing picture of effects may be due to the interspecies variation in hematologic responses to polyhalogenated aromatic hydrocarbons; to the possibility that the effects of acute and chronic dosing studies are not comparable due to the variation in the life span of the various cellular components; and, to the fact that near lethal doses may cause widely varied hematological responses.

Developmental Effects

In 1987, Van den Berg et al. (1987), found 2,3,7,8-TCDD in the liver of fetuses whose mothers had been fed 2,3,7,8-TCDD contaminated fly ash on days 10 to 17 of pregnancy. This study clearly demonstrates the ability of 2,3,7,8-TCDD to cross the placenta and deposit in fetal tissue. The study strengthens the findings of earlier research which found that 2,3,7,8-TCDD caused reduced fertility, increased fetal death and malformations in all tests of mice and rats tested. (Table 49) (Murray et al., 1979; Giavini et al., 1983; Weber et al., 1985; Birnbaum et al., 1985; Courtney and Moore, 1971; Moore et al., 1973; Courtney, 1976; Smith et al., 1976).

The most common malformations due to <u>in utero</u> exposure to 2,3,7,8-TCDD are cleft palate and kidney anomalies (hydronephrosis

and dilated renal pelvis) (Birnbaum et al., 1985; Moore et al., 1973; Smith et al., 1976; Weber et al., 1985). Other effects observed hydrocephalus, open eye, petechiae, fetal resorption and spontaneous abortions (Courtney, 1976). Common malformations in rat offspring were edema, hemorrhage, and kidney anomalies (Khera and Ruddick, 1973; Giavini et al., 1973; Giavini et al., 1983).

Subsequent studies have demonstrated that increases in the incidence of cleft palate in mice was related to the genetic ability of the strain to respond at the Ah locus (Poland and Glover, 1980; Hassosen and Dencker, 1982). Poland and Glover (1980) observed that in responsive mice the incidence of cleft palate was 50% higher than in nonresponsive mice.

While fetal malformations have not been observed in offspring of rhesus monkeys exposed to 2,3,7,8-TCDD prior to and during pregnancy, fetal loss and infertility (failure to conceive) were increased when compared to unexposed controls (Allen et al., 1979; McNulty, 1978; McNulty, 1984).

Immunologic Effects

The effects of 2,3,7,8-TCDD on the immune function in experimental animals include thymic involution and atrophy and suppression of both cell-mediated and humoral immunity. The types of immunologic responses observed are dependent upon the species and age of the animal as well as the test protocol employed (Table 50).

Thymic degeneration has been observed in all species tested including mice (Harris et al., 1973; Vos et al., 1974; Clark et al., 1981), rats (Harris et al., 1973; Gupta et al., 1973; Gasiewicz et al., 1980.) Hartley guinea pigs (DeCaprio et al., 1986; Gupta et al., 1973), golden Syrian hamsters (Olson et al., 1980), and rhesus monkeys (McConnell et al., 1978.)

Thymic atrophy has been correlated with other effects of cell-mediated immunity (reviewed in Vos and Luster, 1989) such as delayed type hypersensitivity responses (Clark et al., 1981; Faith and Moore, 1977; Thomas and Hinsdill, 1979), depressed graft versus hast response (Vos and Moore, 1974), ability to reject skin allografts (Vos and Moore, 1974), decreased response to mitogens (PHA and Con A) (Dean et al., 1981; Dean and Lauer, 1984; Vos and Moore, 1974; Faith and Moore, 1977), and suppression of cytotoxic lymphocyte response (Clark et al., 1981; 1983).

2,3,7,8-TCDD affects humoral immunity by suppression of bone marrow precursor cells (hemoatopoietic stem cells) (Luster et al., 1985; Tucker et al., 1986; Chastain and Pazdernik, 1985) and supression of antibody producing cells (Vecchi et al., 1983; Vecchi et al., 1986; Tricker et al., 1986; Holsapple et al., 1986).

In experimental animals, the developing immune system, whether exposed <u>in utero</u> or <u>postnatally</u>, has been shown to be the most susceptible to the effects of 2,3,7,8-TCDD (Vos and Moore, 1974;

Faith and Moore, 1977; Dean and Lauer, 1984). Although antibody responses are not suppressed in animals perinatally exposed (Faith and Moore, 1977), thymic atrophy, depression of T-cell mediated responses and bone marrow toxicity are greater in the perinatally exposed animal than in the adult animal (reviewed by Sonawane et al., EPA Risk Assessment, 1988).

One possible mechanism of 2,3,7,8-TCDD induced immune effects appears to be related to genetically controlled responsiveness to AHH induction. Studies indicate that suppression of antibody response (Tucker et al., 1986; Vecchi et al., 1983; Chastain and Pazdernik, 1985; Vecchi et al., 1986; Holsapple et al., 1986) serum total hemolytic complement (C3) (White et al., 1986), thymic atrophy (Poland and Glover, 1980) and bone marrow precursor cell proliferation (Luster et al., 1985) occur at lower doses in Ah responsive species in comparison with non-responsive species.

Carcinogenic Effects

In 1987, the International Agency for Research on Cancer (IARC) determined that there is sufficient evidence to classify 2,3,7,8-TCDD as a definite carcinogen (IARC, 1987). This decision was based on data from at least 9 different studies which demonstrated increased incidence of a variety of tumors after exposure to 2,3,7,8-TCDD in rats (Kociba et al, 1978; Van Miller et al., 1977; NTP, 1982a; Pitot et al., 1980; Kouri et al. 1978), mice

(Toth et al., 1979; NTP, 1982a; NTP, 1982b), and Golden Syrian hamsters (Rao et al., 1988) (Table 48). The rat liver appears to be the target organ for carcinogenesis after 2,3,7,8-TCDD exposure (NTP 1982a; Kociba et al., 1978).

Rats

Three studies of rats, two of Sprague-Dawleys and one of Osborne-Mendel rats, found elevated incidence of a variety of tumors after treatment with 2,3,7,8-TCDD. Male and female Sprague-Dawley rats were fed diets supplying 0.1, 0.01 or 0.001 ug 2,3,7,8-TCDD/kg daily for two years (Kociba et al., 1978). Incidence of malignant tumors was not elevated at doses of 0.01 or 0.001 ug 2,3,7,8-TCDD/kg although hepatocellular hyperplastic nodules were increased (18 or 50 animals, $p<0.05$) in females only at levels of 0.01 ug 2,3,7,8-TCDD/kg/day. Increased incidence of malignancies was observed in four sites in the 50 male or the 49 female rats treated with 0.1 ug 2,3,7,8-TCDD/kg/day: hepatocellular carcinoma (2 male [4%], 11 females [22%]); stratified squamous cell carcinoma of the hard palate or nasal turbinates (4 male [8%], 4 female [8%]; stratified squamous cell carcinoma of the tongue (3 male [6%], 2 female [4%]); and, keratinizing squamous cell carcinoma of the lung (1 male [2%], 7 female [14%]).

In support of the findings of previous studies, statistically significant ($p<0.05$) increases in the incidence of neoplastic nodules of the liver or hepatocellular carcinoma were observed in Osborne-Mendel rats treated by gavage twice weekly, with 0.5 ug 2,3,7,8-TCDD/kg for 104 weeks (2 years) (NTP, 1982a). As in the study by Kociba et al., (1978) female rats developed appreciably more liver tumors than males at the same dose (22% in females vs. 6% in males).

Unlike the study by Kociba et al. (1978) which found minimal increases in follicular cell adenomas in Sprague-Dawley rats, statistically significant increases in follicular cell adenomas of the thyroid ($p<.001$) were observed in male Osborne-Mendel rats at all dose levels (0.01 ug/kg=9% increase; 0.05 ug/kg=1% increase; 0.5 ug/kg=19% increase). No measurable increases were noted in female Osborne-Mendel rats at any dose. In addition, no increases in lung or hard palate/nasal turbinate malignancies were found in the Osborne-Mendel Rats. This difference may reflect the differences in treatment modalities between the two studies. Contact with 2,3,7,8-TCDD supplemented chow by the Sprague-Dawleys may have provided the opportunity for inhalation of contaminated dust from the chow. Treatment of the Osborne-Mendels was by gavage only, thus preventing extraneous respiratory contact with 2,3,7,8-TCDD laden dust. This finding by Kociba et al. (1978) may be an artifact of exposure, however, it provides some evidence that

continuous low-level respiratory exposure to 2,3,7,8-TCDD-contaminated dusts may increase the risk of humans to the development of respiratory cancers.

Mice

The evidence for carcinogenicity of 2,3,7,8-TCDD in mice is illustrated in three separately conducted studies (NTP, 1982a; NTP, 1982b; Toth et al., 1979). In one of the earlier studies, Swiss/H/Riop mice developed liver tumors (malignant and nonmalignant tumors combined) in 30%, 21% and 29% of the animals after treatment for 1 year with weekly doses of 7.0, 0.7 or 0.007 ug 2,3,7,8-TCDD/kg, respectively (Toth et al., 1979). Lung tumors were increased to 61% in animals treated with 0.007 ug 2,3,7,8-TCDD/kg, while 41% and 25% of mice treated with 0.7 and 7 ug 2,3,7,8-TCDD/kg developed lung tumors. In the same study, eighteen percent (18%) and 39% of the unexposed control mice developed liver and lung tumors, respectively. When compared to unexposed controls, the rate of lymphomas was also higher in mice treated with 0.7 ug (27%) or 0.007 ug 2,3,7,8-TCDD/kg (23%) than with 7.0 ug 2,3,7,8-TCDD/kg (14%). Hypothetically, this decrease in lung tumors and lymphomas may be due to the reduction in average life span of mice administered 7.0 ug 2,3,7,8-TCDD/kg, because these tumors may appear later than liver tumors after exposure. The authors, however, did not detail the number of days each treatment group survived post-exposure.

Further research by the National Toxicology Program (NTP), also demonstrated a statistically significant increase in the incidence of hepatocellular carcinoma in male and female B6C3F1 mice administered 0.5 ug 2,3,7,8-TCDD/kg (males) or 2.0 ug 2,3,7,8-TCDD/kg (females) twice weekly for 104 weeks (NTP, 1982a). At these doses, 23% and 12% increases in hepatocellular carcinoma were observed in male and female mice, respectively. Female B6C3F1 mice also developed significantly more follicular-cell adenomas of the thyroid compared to unexposed controls (11% increases in lung tumors or lymphomas were found in B6C3F1 mice. Both studies dosed the animals by gavage.

A single study evaluated the effect of dermal exposure of 2,3,7,8-TCDD (NTP, 1982b). Male and female Swiss Webster mice were administered 0.001 ug or 0.005 ug 2,3,7,8-TCDD per application three times per week on alternate days for 99 or 104 weeks, respectively. The total weekly dose approximated 0.15 ug/kg for males and 0.75 ug/kg for females. Thirty percent ($p<.05$) of the treated females developed fibrosarcoma of the integumentary system whereas 5% of the controls and 21% of the treated males developed these types of tumors.

Hamsters

A single study examined the carcinogenic potential of 2,3,7,8-TCDD in Golden Syrian hamsters which are considered the species most

resistant to the effects 2,3,7,8-TCDD (Rao et al., 1988). Twenty-one percent of all animals treated monthly by either s.c. or i.p. injection with 100 ug 2,3,7,8-TCDD/kg for 6 months (total of 600 mg 2,3,7,8-TCDD/kg) developed squamous cell carcinomas of the facial skin within 12-13 months of the beginning of the study. No tumors of the tongue, hard palate/nasal turbines or lungs were found. None of the control animals nor any of the hamsters receiving 2 monthly injections of 100 ug 2,3,7,8-TCDD/kg or 6 monthly injections of 50 ug 2,3,7,8-TCDD/kg developed tumors of any kind.

Proposed Mechanisms of the Carcinogenicity of 2,3,7,8-TCDD

The mechanism by which 2,3,7,8-TCDD induces tumor growth has been a point of considerable debate. Chemical carcinogenesis is thought to occur through two basic mechanisms, initiation and promotion (Pitot et al., 1980). Initiation is considered an irreversible process caused by the administration of a carcinogen which covalently binds to DNA. Promotion is a reversible cellular process of unscheduled or mis-controlled cellular growth resulting from the administration of non-tumor producing substances, which convert initiated cells into neoplastic cells. The body of evidence from animal toxicologic studies suggest that 2,3,7,8-TCDD is a strong tumor promotor (Pitot et al., 1980; Poland et al., 1982; Kouri et al., 1978; Abernethy et al., 1985; Abernethy and Barieko, 1987) and may also be a tumor initiator (DiGiovanni et al, 1977; Kociba et al, 1978; Holder and Menzel, 1989) .

Pitot et al (1980) demonstrated that 2,3,7,8-TCDD is an extremely potent promotor in previously damaged livers undergoing cellular regeneration. In this study, partially hepatectomized Charles River rats received a single intragastric intubation of a 10-mg/kg dose of the initiator diethylnitrosamine (DEN) and, one week later, injected with 0.14 or 1.4 ug 2,3,7,8-TCDD/kg, twice weekly for 14 weeks (Pitot et al., 1980). Hepatocellular carcinomas were observed in 71% of the rats treated with 1.4 ug 2,3,7,8-TCDD and DEN; no carcinomas were noted in animals receiving 0.14 ug 2,3,7,8-TCDD/kg and DEN or 2,3,7,8-TCDD alone or DEN alone.

In another study, 2,3,7,8-TCDD was capable of promoting a dose related increase of keratinizing squamous cell papillomas in HRS/(hr/hr) hairless mice but not in HRS/J(hr/+) mice (Poland et al, 1982) following initiation by two initiators, DMBA or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Hairless mice, painted with one application of 2 umol of DMBA followed by application of 20 ug 2,3,7,8-TCDD twice weekly for 8 weeks, then 50 ug 2,3,7,8-TCDD for 17 weeks, developed approximately 1.4 papillomas per mouse in over 80% of the treated animals. One tumor developed after administration of DMBA alone; TCDD alone produced no tumors. No tumors were produced in HRS/J (hr/+)mice. In the same study 2,3,7,8-TCDD was also found to be a significant promotor in HRS/J (hr/hr) mice after initiation with MNNG. Twice weekly administration of 3.75, 7.5 or 15 ug 2,3,7,8-TCDD per mouse resulted in a dose-related increase in the incidence of papillomas

(control=5%; 3.75 ng=55%, 7.5 ng=77%, 15 ng=100%). In a third study, a 4% increase in fibrosarcomas were observed in a third strain of mice, DBA/2, which received 100 ug 2,3,7,8-TCDD/kg by ip 2 days prior to s.c. administration of 150 ug 3-methylcholanthrene (3-MC) (Kouri et al., 1978). When 2,3,7,8-TCDD and 3-MC were administered simultaneously, the percent of mice with sarcomas was increased by 13%.

Lastly, a single treatment of C3H/10T1/2cells with 0.5 ug/ml MNNG prior to continuous treatment in the medium with 4pM or greater concentrations of 2,3,7,8-TCDD increased cell transformation (Abernethy et al., 1985). However, Berry et al. (1978) found no tumor promotion after application of 2,3,7,8-TCDD.

Supporters of the promotion theory postulate that because there is little evidence that 2,3,7,8-TCDD is a mutagen and, unlike most chemical carcinogens, does not covalently bind to RNA and DNA (Poland and Glover, 1979), 2,3,7,8-TCDD is most likely not an initiator. Shu (1987) points out that when 2,3,7,8-TCDD was used as an initiator in the studies in which it showed strong promoting ability (Poland et al., 1982; Pitot et al., 1980; Abernethy et al., 1985), tumor formation in exposed and control animals was similar, thus, strongly implying that little if any initiation occurred.

The finding of a single well-conducted study support the argument that 2,3,7,8-TCDD functions as a complete carcinogen. In a two

year feeding study of Sprague Dawley rats, Kociba et al., (1978) found rare tumors of the hard palate, nasal turbinates, and tongue in males and adenocarcinoma of the lung, a rare cell type, in females. Di Giovanni et al. (1977) also found weak initiation due to 2,3,7,8-TCDD; however, this attribute is disputed because the incidence of tumor formation was low, occurring at the end of the animals' life and there was no unexposed control group for comparison (Shu et al., 1987).

The complexity of the mechanism of 2,3,7,8-TCDD carcinogenicity is further illustrated by evidence that 2,3,7,8-TCDD may inhibit tumor initiation by known initiators benzo-[a]-pyrene or 7,13-dimethylbenzanthracene and promoted with 12-0-tetradecanoyl-phorbol-13-acetate (Cohen et al., 1979). Additionally, 2,3,7,8-TCDD has been shown to decrease both benign and malignant tumors of some endocrine organs (Kociba et al., 1978; Holder and Menzel, 1987). Whether or not 2,3,7,8-TCDD exposure confers a protective effect on these systems has not yet been fully evaluated.

The data accumulated to date strongly suggest that 2,3,7,8-TCDD is carcinogenic in rodents. There is no available evidence to confirm this assertion in higher order mammals. Chronic, low-dose administration of 2,3,7,8-TCDD did not result in tumor formation in rhesus monkeys. However, other morbid effects were observed as previously described (Allen et al., 1977).

Liver tumors, both adenomas and carcinomas, were seen in excess in each of the species administered 2,3,7,8-TCDD orally or by injection. These data suggest, as do the studies of acute toxicity, that the liver may be one of the primary target organs in rats and mice but not in hamsters. The plethora of other tumor sites generated by exposure to 2,3,7,8-TCDD may suggest that some cells are more sensitive to the tumor inducing effect of 2,3,7,8-TCDD, such as liver cells, and develop tumors first, but that constant insult by 2,3,7,8-TCDD of other less sensitive cells, triggers the same tumorigenic response as liver cells.

In summary, well-conducted studies have demonstrated that 2,3,7,8-TCDD is a strong promoter; however, there is also sufficient evidence to argue that 2,3,7,8-TCDD is also an initiator.

Mechanisms of the Toxicity of 2,3,7,8-TCDD

The mechanism by which 2,3,7,8-TCDD evokes a toxic response has been extensively studied and continues to be researched. A number of comprehensive reviews, compiling the knowledge to date, have been published recently (Goldstein and Safe, 1989; Skene et al., 1989; Silbergeld and Gasiewicz, 1989). The toxicity of 2,3,7,8-TCDD appears to be associated with two related factors: structure-activity relationship and the resulting ability to bind with an intracellular receptor. Of the dibenzo-p-dioxins and related compounds [dibenzofurans (PCDF) and polychlorinated

biphenyls (PCB)], the most toxic are planar or nearly planar structures, with a minimum of three halogens occupying the lateral ring positions, and one position is unsubstituted (Poland and Knutsen, 1982). This configuration permits the molecule to bind with a high affinity stereospecific receptor. Based upon studies by Poland and Glover (1973; 1974) and Poland et al. (1979), there is strong evidence that the receptor is associated with genes (Ah loci) regulating the activity of cytochrome P-450-dependent enzymes, including aryl hydrocarbon hydroxylaze. (Cytochrome P-450 is a family of monooxygenases which metabolize carcinogens, drug, pesticides and other xenobiotics.) A widely studied 2,3,7,8-TCDD receptor, called the Ah receptor, binds to certain halogenated aromatic hydrocarbons, such as 2,3,7,8-TCDD, and to structurally related polycylic aromatic hydrocarbons, such as 3-methylcholanthrene(3-MC). The 2,3,7,8-TCDD/Ah receptor has been found in a number of species including guinea pigs, monkey, mice, rat and hamster (Gasiewicz and Rucci, 1984).

The organ distribution of 2,3,7,8-TCDD/Ah receptors is species dependent (Gasiewicz and Rucci, 1984; Mason and Okey, 1982; Carlstedt-Duke, 1979). In the cytoplasm the Ah receptor binds to the 2,3,7,8-TCDD to form a 2,3,7,8-TCDD receptor complex. It is this complex that moves through the nuclear membrane and binds to the DNA. (2,3,7,8-TCDD does not easily penetrate the nuclear membrane nor readily covalently bind with DNA (Poland and Glover, 1979). It is the binding of the 2,3,7,8-TCDD receptor complex to

the DNA that initiates derepression of genes which regulate synthesis of cellular proteins (reviewed by Goldstein and Safe, 1989).

Although the body of evidence supports a receptor theory, the mechanisms by which 2,3,7,8-TCDD interacts with the Ah receptor and those that permit complex binding to DNA are yet to be fully determined. It has also been suggested that 2,3,7,8-TCDD can alter the binding of cellular receptors such as the epidermal growth factor receptor, the estrogen receptor and the glucocorticoid receptor (reviewed by Goldstein and Safe, 1989). The effects caused by the binding of 2,3,7,8-TCDD to these receptors and the mechanisms of toxicity are currently being examined.

Other proposed mechanisms which may explain other effects of 2,3,7,8-TCDD include depletion of vitamin A stores (Thunberg et al., 1979), alterations in the metabolism of testosterone and estrogens, particularly causing androgen deficiency (Moore et al., 1985) and alteration of the metabolism of adrenal steroids.

Throughout the past two decades, the scientific community has put forth considerable effort to understand the toxicology of 2,3,7,8-TCDD. The primary reason for this effort is because 2, 3,7,8-TCDD represents one of the most toxic of a class of similar compounds which have become common contaminants of the modern environment. While much work has already been conducted to examine

every aspect of 2,3,7,8-TCDD toxicity, it has become evident that its effects are many and the mechanisms of action are complex. Collectively this research has documented that, in animals, 2,3,7,8-TCDD causes a host of clinical and subclinical health effects, both benign and malignant. Studies at the molecular level suggest that these effects are moderated by the action of a 2,3,7,8-TCDD-receptor molecule which binds with DNA and alters normal expression of certain genes. Other data also indicate that 2,3,7,8-TCDD may bind with other receptors, particularly steroid receptors, and compete for the natural binding sites of these molecules. These recent findings clearly emphasize that there is much more to know about the activity of 2,3,7,8-TCDD.

APPENDIX B

HUMAN HEALTH EFFECTS OF EXPOSURE TO 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN

Non-malignant Effects

Dermal Effects

The most widely recognized dermal effect of exposure to 2,3,7,8-TCDD contaminated substances is chloracne (Table 51). Chloracne is a persistent acneiform condition characterized by comedones, keratin cysts, inflamed papules with hyperpigmentation and a unique anatomic distribution, occurring subsequent to acute and chronic exposure to a variety of chlorinated aromatic compounds (Crow, 1978; Moses and Prioleau, 1985). This acne-like condition is reported to have occurred with and without other health effects in at least a few people after all reported accidents at TCP production facilities (Ashe and Suskind, 1950; Suskind et al, 1953;

Goldman, 1972; May, 1973; Reggiani, 1978; Filippini et al, 1981), among individuals involved in daily production of 2,3,7,8-TCDD contaminated products (Bleiberg et al, 1964; Poland et al, 1971; Pazderova-Vejlupkova et al, 1981; Moses et al, 1984; Moses and Prioleau, 1985; Suskind and Hertzberg, 1984; Bond et al, 1989) and among three laboratory workers exposed to pure 2,3,7,8-TCDD (Oliver, 1975).

Other dermal effects included a variety of symptoms and conditions which occurred less frequently than chloracne but appeared in several groups subsequent to acute and continuous exposure to TCDD contaminated TCP and 2,4,5-T. Two reports indicated that after acute episodes of exposure, e.g. accidents, individuals complained of red and irritated eyes, conjuntivitis and blepharitis (inflammation of the eyelids) (Ashe and Suskind 1950; Baader and Bauer, 1951). Other investigators also found cases of eyelid cysts several months after acute exposure (Suskind et al, 1953; Kimmig and Schulz, 1957; Poland et al, 1971; Reggiani, 1981) and up to 25 years after exposure (Suskind and Hertzberg, 1984).

Hyperpigmentation, hirsutism (also known as hypertrichosis or abnormal distribution of hair) was diagnosed among chemical workers in the United States (West Virginia and New Jersey) (Ashe and Suskind, 1950; Suskind et al, 1953; Bleiberg et al, 1964; Poland et al, 1971), in Germany (Bauer et al, 1961; Goldman, 1972) and in Czechoslovakia (Jirasek et al, 1974) who were exposed to

contaminated TCP and its derivatives during manufacturing processes or industrial accidents, and among laboratory workers in England exposed while synthesizing pure 2,3,7,8-TCDD (Oliver, 1975). These effects were not seen upon reexamination twenty-five years later among workers from the West Virginia plant (Suskind and Hertzberg, 1984; Moses et al, 1984).

Actinic or solar elastosis was found to be more prevalent among West Virginia workers diagnosed with active chloracne at the time of their examinations in 1979 (Suskind and Hertzberg, 1984)(Exposed = 59.1%; Unexposed = 30.1%, $p<.01$). Actinic elastosis is directly related to sun exposure, however, the amount of sun exposure, skin type or other factors contributing to the sensitivity of the skin to sunlight was not assessed in the report. No other studies of TCP production workers have found an increase in the prevalence of actinic elastosis. Among this same group, Suskind noted three cases of Peyronie's disease, a rare condition characterized by progressive scarring of the penile membrane. No explanation for this finding was expressed nor has the condition been noted (or perhaps looked for) in other studies.

In 1984, a statistically significant excess of non-melanotic skin cancer was reported among Air Force personnel involved in the aerial spraying of herbicides over Vietnam compared to a matched comparison group (Lathrop et al, 1984). The comparison group was composed of Air Force personnel assigned to cargo missions outside

the sprayed areas of Vietnam. A follow-up study of the same cohorts in 1987, confirmed the excess of basal cell carcinoma, and attributed the increase to sunlight exposure (Lathrop et al, 1987).

Gastrointestinal Effects

Liver size

Changes in liver function and structure after exposure to 2,3,7,8-TCDD are commonly observed in treated animals. The changes are not always consistent from one species to another but they prompted examination of hepatic effects among exposed human populations. As with animals, there is wide variation in the type and degree of hepatic effects reported in humans after exposure to 2,3,7,8-TCDD contaminated materials (Table 51).

One symptom which has been consistently reported in the animal literature after exposure to 2,3,7,8-TCDD is increased liver size. Five studies of humans reported enlarged liver size. A two fold statistically nonsignificant increase in hepatomegaly was found among Air Force Ranch Handers in the baseline study (Lathrop et al, 1984). In the followup study, 0.8% of Ranch Handers compared to 0.2% of the comparison group were found to have enlarged livers (Lathrop et al, 1987). Liver size was increased among TCP production workers in West Virginia (Suskind and Ashe, 1950; Suskind et al, 1953) and in Czechoslovakia (Jirasek et al, 1973).

Liver enlargement was found among 5 of 22 Seveso residents with severe chloracne. The hepatomegaly lasted "several" months without concomitant elevation in hepatic enzymes (Reggiani. 1980).

Enzyme levels

Animal studies have also demonstrated changes in hepatic enzyme levels, although there is considerable interspecies variation in the observed effect. Seven studies and case reports reported elevated liver enzymes among exposed workers and among Seveso residents. Increased levels of gamma glutamyl transferase (GGT) may suggest activity such as cholestases, liver regeneration or drug or xenobiotic metabolism. Elevation in GGT levels were found among Seveso adults (Filippini et al, 1981) (data not shown) and among boys in Seveso living in a more highly contaminated region at the time of the accident who showed a 12-40% increase in GGT levels up to three years after the accident (Mocarelli et al, 1986) (Table 52). A 20% increase in GGT level was noted among British TCP workers with chloracne tested 10 years after exposure to 2,3,7,8-TCDD contaminated chemical as a result of a TCP reactor explosion (May, 1982; Martin, 1984) (Table 51). Only slight increases in mean GGT level (Ranch Handers = 40.1 vs controls = 39.3) were observed in Air Force Ranch Handers. A statistically significant excess in the proportion of individuals with abnormally high GGT levels was found among West Virginia workers with

chloracne who were examined as many as 30 years after exposure (Moses et al, 1984) (chloracne = 23% abnormal vs. no chloracne = 9% abnormal, $p<.03$).

Abnormal levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) may indicate liver cell damage from a number of etiologies including hepatic necrosis, metastatic carcinoma or obstructive jaundice (SGOT and SGPT), or infectious or toxic hepatitis and cirrhosis (SGOT) (Henry, 1979). Elevated levels of these enzymes may also be due to nonhepatic origins, such as, myocardial infarction, acute pancreatitis (SGOT and SGPT) or skeletal, cerebral or renal necrosis (SGOT). Both enzymes were elevated among TCP production workers in New Jersey (Bleiberg et al, 1964) and in Czechoslovakia (Jirasek et al, 1974). SGOT was increased in West Virginia TCP workers with chloracne (3% abnormals with chloracne vs 0 abnormals without chloracne) (Moses et al, 1984), and SGPT was increased in 5 of 14 TCP workers from Great Britain who were in the manufacturing building at the time of a reactor explosion (May, 1973). Filippini et al (1981) found increased SGOT and SGPT among adult Seveso residents and Mocarelli et al (1986) observed a 24% elevation in SGPT levels among male children in Seveso tested one year after the accident compared to unexposed comparisons. None of the studies reported clinical evidence of liver disease in these populations. Therefore, in the absence of reports among exposed individuals of

hepatic or nonhepatic diseases related to changes in SGOT or SGPT levels, it is possible that the fluctuations in enzyme levels may be due to activities related to metabolism of xenobiotics.

Other enzymes, delta amino levulinic acid (d-ALA) (Jirasek et al, 1974), lactate dehydrogenase (LDH) (Poland et al, 1971; Lathrop et al, 1984) and alkaline phosphatase (ALK) (Jirasek et al, 1974) were found elevated in one or two groups. No abnormal levels of ALK, SGOT, SGPT or GGT were found among West Virginia workers examined by Suskind and Hertzberg (1984) or among Michigan TCP or 2,4,5-T workers who participated in yearly medical surveillance examinations between 1976-1978 (Bond et al, 1983).

In some instances, follow-up studies found that, over time, liver enzyme levels returned to normal. Ten years after their initial study of the Czechoslovakian TCP workers (Jirasek et al, 1974), Pazderova-Vejlupkova et al (1981) found enzyme levels (SGPT, SGOT, d-ALA, ALK) in the surviving subjects were not increased. GGT levels in children of Seveso were normal three years after the accident (Mocarelli et al, 1986) and were not elevated in Air Force Ranch Handers when retested in the first follow-up study conducted in 1985 (Lathrop et al, 1987). SGPT levels among the Seveso children also returned to normal within six years after the accident (Mocarelli et al, 1986). Finally, LDH levels found increased in Ranch Handers in the baseline study were not raised upon reexamination (Lathrop et al, 1984; Lathrop et al, 1987).

In ten studies, d-glucaric acid excretion was measured as a possible indicator of enzyme induction by 2,3,7,8-TCDD but with little consistency in the results. Elevated levels (chloracne = 2.09 vs unexposed controls = 1.59) were found in chemical workers in England tested 10 years after exposure to TCDD contaminated effluent from a TCP reactor explosion (May, 1982; Martin, 1984). Statistically significant d-glucaric acid excretion was elevated in urines collected in 1978 from adults residing in Seveso, Italy at the time of the ICMESA accident compared to residents of unexposed communities (Seveso = 27.1 umole/g vs unexposed = 19.8 umole/g $p<.05$) and among Seveso children with chloracne (39 umole/g) compared to those without chloracne (20.5 umole/g) (Ideo et al, 1985). None of the studies described other exposures or conditions which could have increased d-glucaric acid. Elevated levels of d-glucaric acid were not observed among individuals exposed to TCDD contaminated waste oils in Times Beach or Quail Run, Missouri (Webb et al, 1987; Hoffman et al, 1986) or measured among Air Force Ranch Handers (Lathrop et al, 1984; Lathrop et al, 1987) or chemical workers from West Virginia (Suskind and Hertzberg, 1984; Moses et al, 1984) or among Dutch forestry workers presumed to be heavily exposed to 2,4,5-T for many years (van Houdt et al, 1983).

Porphyrin metabolism

Porphyria cutanea tarda (PCT) has been reported in two studies of TCP production workers (Bleiberg et al, 1964; Jirasek et al, 1974)

and among members of a family with inherited uroporphyrindecarboxylase deficiency (UROD) who were living in Seveso at the time of the reactor accident (Strik et al, 1980). Doss et al (1984) suggests that, in this family, exposure to 2,3,7,8-TCDD contaminated effluent caused an exacerbation of the pre-existing enzyme deficiency.

PCT is a form of acquired or inherited porphyria caused by a deficiency of the enzyme uroporphyrinogen decarboxylase and the resulting over-production and excretion of uroporphyrin (Sweeney, 1986). The predominant characteristics of PCT include skin fragility, blistering upon sun exposure, dark pigmentation and excess hair growth, hepatomegaly, reddish-colored urine and urinary excretion of uro- and heptacarboxylicoporphyrins (Strik, 1979). PCT has been associated with excessive alcohol intake, oral estrogens, iron overload, hepatomas, and exposure to polyhalogenated hydrocarbons (Strik, 1979). A particularly large outbreak of PCT occurred after consumption of grain treated with hexachlorobenzene (HCB) (Cam and Nigogosyan, 1963). While 2,3,7,8-TCDD has been related to alterations in porphyrin metabolism in mice and rats (Goldstein et al, 1973; Smith et al, 1981; Jones et al, 1981; DeVerneiul et al, 1983; Cantoni et al, 1981; Goldstein et al, 1982). No PCT was reported among three laboratory workers exposed to pure 2,3,7,8-TCDD (Oliver, 1975). These individuals are the only humans to have documented exposure to uncontaminated 2,3,7,8-TCDD.

In 1977, 60 Seveso residents were tested for elevated porphyrins, exclusive of the family with inherited deficiency UROD. None of the 60 residents developed PCT, however, 22% (N=13) exhibited secondary coproporphyrinuria, 5 of whom showed a slight increase of uro- and heptacarboxyporphyrins and coproporphyrins (Doss et al, 1984). Porphyrin levels were retested in 1980 and in 12 of the cases porphyrin levels returned to normal. In three others, porphyrin levels were more severe and were attributed to liver damage and alcohol consumption.

In 1964, Bleiberg et al reported that based on the Watson-Schwartz test, 11 of 29 New Jersey workers with chloracne who were employed in the manufacture of TCP, 2,4,5-T and 2,4-D had porphyria cutanea tarda due to increased urinary uroporphyrins, coproporphyrins and urobilinogen. In a later study of 73 workers from the same plant (including four of the individuals Bleiberg et al (1964) found to have elevated urinary porphyrins), Poland et al (1971) identified one individual with uroporphyrinuria. The report did not explain if this individual was one of the four described by Bleiberg et al (1964). Jirasek et al (1974) found 11 individuals of 55 Czeckoslovakian TCP workers to have elevated urinary uroporphyrins which decreased over the observation period; the authors did not describe the test used to measure urinary uroporphyrins or coproporphyrins. Ten years later, Pazderova-Vejlupkova et al (1981) found no evidence of increased excretion of uroporphyrins or dermatological indications of PCT in the same group of workers.

There is some doubt that the porphyria noted in the New Jersey and Czechoslovakian workers was due to 2,3,7,8-TCDD exposure. Jones and Chelsky suggest that the observed cases of PCT among the TCP workers from New Jersey and Czechoslovakia may be due to exposure to HCB or a combination of both 2,3,7,8-TCDD and HCB (Jones and Chelsky, 1986). HCB was manufactured at the New Jersey plant from 1951 until 1960 and was produced at the facility in Czechoslovakia during the production of pentachlorophenol (Jirasek et al, 1973).

There is also some question as to the appropriateness of the clinical test Bleiberg et al (1964) used to measure porphyrin levels (Watson, 1964). In a letter to the editor, Watson pointed out that the Watson-Schwartz test was capable of measuring only the presence of porphobilinogen, that the test was rarely positive in cases of exposure to hepatotoxins, and suggested that either Bleiberg et al (1964) used other, but unspecified tests, to measure uro- and coproporphyrin levels, or that they misinterpreted the function of the Watson-Schwartz test. No response was made to this observation by Bleiberg or the other authors.

Evidence of porphyria in other studies of individuals exposed to 2,3,7,8-TCDD contaminated substance is minimal. Although Suskind and Hertzberg (1984) sampled urine for porphyrins in the examination of West Virginia TCP workers, the specimens were incorrectly collected and the data not presented. Moses et al (1984) found no difference in porphyrin levels when comparing TCP

workers with and without chloracne. These data are not useful for assessing exposure-disease relationships because both groups may have contained exposed workers. In the baseline study of U.S. Air Force Ranch Handers, there was no difference in the levels of uroporphyrins or coproporphyrins (Lathrop et al, 1984). However, in the follow-up study, the mean uroporphyrin level in the comparison group (17.9 mg/24 hrs) was significantly higher than in the Ranch Handers (16.9 mg/24 hrs, $p<.05$) (Lathrop et al, 1987). In contrast, the mean coproporphyrin level in Ranch Handers (119.1 mg/24 hrs) was higher than in the comparison group (115.6 mg/24 hrs), however, the increase appeared to be strongly associated with age and alcohol use at the time of the study.

It is possible that the PCT and elevated urinary porphyrins observed in the New Jersey and Czechoslovakian workers was a direct result of exposure to HCB. 2,3,7,8-TCDD, however, is a potent porphyrigen in rats and mice and, therefore, may have contributed to the change in porphyrin levels in these two populations.

A variety of gastrointestinal disorders other than liver conditions are reported among TCDD exposed groups (Table 51). After heavy, acute or chronic exposure, chemical workers in West Virginia (Ashe and Suskind, 1950), in West Germany (Baader and Bauer, 1951; Bauer et al, 1961) and in Czechoslovakia (Jirasek et al, 1974) consistently reported transient episodes of right upper quadrant pain, loss of appetite and nausea. None of the reports suggest an

etiology for these symptoms nor were the symptoms reported in later follow-up studies of either cohorts (Suskind and Hertzberg, 1984; Moses et al, 1984; Pazderova-Vejlupkova et al, 1981).

Three investigations of TCP production workers reported increased prevalence of upper gastric ulcers across all age strata of West Virginian workers (exposed = 20.7% vs unexposed = 5.5%) (Suskind and Hertzberg) and all digestive system diseases (type not specified) among workers employed in a plant in Midland Michigan (Prevalence: exposed = 1.5% vs unexposed = 0.5%) (Bond et al, 1983). The factors contributing to these conditions have not been examined fully.

Lipid Metabolism

Elevations in various serum lipid fractions have been reported in studies of TCP production workers and laboratory workers, however the data are inconsistent between studies (Table 51). Total cholesterol and lipid levels were elevated in 50% of the 55 Czechoslovakian TCP production workers examined between 1968 and 1969 (Jirasek et al, 1974). In a follow-up study 10 years later, lipid levels among workers removed from exposure were not significantly different from control levels (selection of controls was not specified) but total cholesterol levels remained significantly increased (Pazderova-Vejlupkova et al, 1981). Two independent studies of British TCP workers from the same plant

found elevated triglycerides in exposed workers with (1.97 mmol/l) and without chloracne (1.90 mmol/l) compared to unexposed controls (1.41 mmol/l) (Martin, 1984). Martin (1984) also found significantly elevated cholesterol levels in exposed workers with (6.02 mmol/l) and without (6.14 mmol/l) chloracne compared to unexposed controls (5.6 mmol/l), whereas May (1982) found unexposed workers (6.6 mmol/l) to have cholesterol higher levels than exposed workers with chloracne (5.97mmol/l). Martin (1984) also found reduced HDL cholesterol among exposed workers with chloracne (1.19 mmol/l) compared to unexposed controls (1.25mmol/l). The differences in the results may be due to differences in the control groups and inclusion of different workers in the exposed groups.

Cholesterol and triglyceride levels in West Virginia TCP production workers were compared with unexposed workers from the same plant. No difference was identified in mean cholesterol levels and lower mean triglyceride levels between workers and controls (Suskind and Hertzberg, 1984). When lipid fractions were examined, however, there was a larger percent age of exposed workers with elevated LDL cholesterol (7.7%) compared to unexposed controls (6.3%). In a second study which compared West Virginia workers with and without chloracne no difference was found in mean cholesterol levels although individuals with chloracne had statistically nonsignificantly increase in mean triglyceride levels (chloracne = 153.6 mg/dl vs without chloracne = 132.3) (Moses et al, 1984). Three laboratory workers who were synthesizing pure 2,3,7,8-TCDD

developed serum cholesterol levels in excess of 300 ug/dl (Oliver, 1975). When compared to children living in uncontaminated areas of Italy, mean cholesterol and triglyceride levels measured yearly from July 26, 1976 through June 30, 1982 were not elevated in children age 6-10 years who resided in the areas of Seveso, Italy, which were most highly contaminated with 2,3,7,8-TCDD (Mocarelli et al, 1986). (Table 52)

The effect of exposure to 2,3,7,8-TCDD contaminated chemicals on lipid or cholesterol levels is not clearly demonstrated in the available studies. Although the studies by May (1982), Martin (1984), and Suskind and Hertzberg (1984) used unexposed control groups, the control groups may not have been appropriate due to age differences (Suskind and Hertzberg, 1984) and potential for exposure to 2,3,7,8-TCDD contaminated chemicals (May, 1982; Moses et al, 1984). In addition, none of the studies were able to evaluate pre-exposure lipid levels which would help to confirm an exposure-outcome relationship more convincingly. Other factors, such as dietary cholesterol intake, familial hypercholesterolemia and exercise, which also effect cholesterol and other lipid levels were not considered in any of these studies. The one study of Air Force Vietnam Veterans which had an appropriate comparison groups reported no difference in the various lipid fractions between exposed and unexposed populations (Lathrop et al, 1984, 1987).

Respiratory and Cardiovascular Effects

Respiratory effects

Adverse outcomes of the respiratory system associated with 2,3,7,8-TCDD exposure are varied and inconsistent among exposed populations. Effects include acute bronchitis-like symptoms and hemorrhagic pleurisy in German TCP workers (Goldman, 1973) and reduced overall pulmonary function in West Virginian TCP workers (Suskind et al, 1953; Suskind and Hertzberg, 1984) (Table 51). A cross-sectional medical assessment of West Virginia TCP production workers found a statistically significant increase in the percent of abnormal findings among workers who smoked at the time of the examination compared to unexposed smokers for forced expiratory volume (FEV) (exposed = 27% abnormals vs unexposed = 4.4% abnormals), forced vital capacity (FVC), (exposed 25.7% abnormals vs unexposed 2.2% abnormals), forced expiratory volume in one second (FEV1)/FVC ratio (exposed = 25.7% abnormals vs unexposed = 7.7% abnormals) and forced midexpiratory flow rate (FEF25-75) (exposed = 36.5% abnormals vs unexposed = 11.1% abnormals) (Suskind and Hertzberg, 1984). This trend remained when pack-years of smoking was taken into account. In contrast, differences between exposed and unexposed were not observed in workers who never smoked or in former smokers. In a study of New Jersey TCP workers Poland et al (1971) identified 18 workers with impaired "diaphramatic excursion", 14 or 77% of whom were smokers at the time of the

examination and three were former smokers. Other morbidity studies or case series have not found or reported these or other types of respiratory system impairment in exposed populations (Moses et al, 1984; Jirasek et al, 1974; Pazderova-Vejlupkova et al, 1981; Lathrop et al, 1984; Lathrop et al, 1987). Futhermore, deficits in the proportionate mortality from non-malignant respiratory diseases were found among West Virginian 2,4,5-T workers (observed = 2 vs expected = 2.67) (Zack and Gaffey, 1983) and the standardized mortality of Michigan TCP and chlorophenol production workers (Ott et al, 1987) from diseases of the respiratory system (observed = 16 vs expected = 21.2).

Cardiovascular effects

Two studies found evidence of cardiovascular disease related to exposure to 2,3,7,8-TCDD contaminated chemicals. In the first of the Air Force Ranch Hand Health Studies, Ranch Handers had significantly reduced peripheral pulses when measured using a manual procedure (Lathrop et al, 1984) and greater mean corpuscular volume and corpuscular hemoglobin volume. In the first follow-up study conducted in 1985, these effects disappeared. The reversal in the results of the peripheral pulse was attributed to a change to a more objective measuring method, a Doppler procedure, and to the prohibition of smoking for four hours prior to the test (Lathrop et al, 1987). In the baseline study, no difference was observed in the rate of heart disease among Ranch Handers or their

comparisons. In the first follow-up study, however, Ranch Handers reported significantly more confirmed heart disease than in the comparison group (RR = 1.22, 95% CI = 1.00, 1.50), although the finding did not consistently correlate with 26 other clinical measures of cardiovascular function. Studies of workers from the West Virginia plant found no relationship between history of coronary artery disease (Suskind and Hertzberg, 1984), angina (Suskind and Hertzberg, 1984; Moses et al, 1984) and myocardial infarction (Moses et al, 1984) and employment in TCP production or presence of chloracne (Moses et al, 1984). Pazderova-Vejlupkova (1981) described a fatal case of unusually severe atherosclerosis in a 57 year old worker identified as having a "severe type of TCDD intoxication". History of hyperlipidemia or the presence of other risk factors was not described.

Statistically nonsignificant increases in proportional mortality from atherosclerotic heart disease were found among 2,4,5-T workers employed at the West Virginia plant (observed = 27 vs expected= 19.72; PMR=117) (Zack and Gaffey, 1983). The proportional mortality for other diseases of the circulatory system was decreased (observed = 4 vs expected 6.76; PMR=59). Mortality studies of other cohorts of TCP workers found no elevation in mortality from cardiovascular disease among employees at the BASF plant in Ludwigshafen (Theiss et al, 1982) or among workers employed in the production of chlorophenols at the Dow Chemical Company in Midland, Michigan (Ott et al, 1987; Bond et al, 1989).

The discrepancies observed among these studies may be due to the differences in the study designs and demographics of the study populations, and the selection of the comparison group.

Endocrine and Metabolic Effects

A frequently reported symptom of men who were exposed to 2,3,7,8-TCDD contaminated materials as a result of daily exposure and industrial accidents is reduced libido (Baader and Bauer, 1951; Suskind, 1953; Kimmig and Schulz, 1957; Bauer et al, 1961) (Table 51). In two independently conducted studies of West Virginia TCP workers, exposed study subjects also reported this condition approximately 50% more often than either the unexposed controls or individuals without chloracne (Moses et al, 1984; Suskind and Hertzberg, 1984). Endocrine studies or reviews of conditions or situations which may lead to a reduction in libido were not conducted.

One case report of 55 TCP workers followed over 10 years, noted that approximately 50% of the subjects had either confirmed cases of diabetes or abnormal glucose tolerance tests (Pazderova-Vejlupkova, 1981). Other studies of TCP workers did not examine abnormalities of glucose metabolism.

Immunologic effects

Although animal toxicologic evidence demonstrates adverse immunologic effects after exposure to 2,3,7,8-TCDD, in humans, there is little information with which to assess the immunologic consequences of exposure (Table 51).

An immunologic assessment was conducted on 18 British workers 17 years after accidental industrial exposure to chemicals contaminated with 2,3,7,8-TCDD (Jennings et al, 1988). There were no significant difference in the levels of immunoglobulins G, A, M, D and E, in the number of T and B lymphocytes, in the responsiveness to phytohemagglutinin A, and in the number of helper and suppressor T cell counts in peripheral blood between exposed workers and unexposed controls matched for age, race, sex, smoking habit, alcohol consumption and percent of ideal body weight. Three measures were found to be statistically significantly ($p<.05$) higher in workers than in controls: antinuclear antibodies (ANA) (8 workers vs 0 controls $p<.01$) (when Hep2 cells were used as substrate but not when rat liver cells were used), immune complexes (workers = 11 vs 3 controls $p<.05$) and natural killer cells (NK) (workers = $0.21 \times 10^6/l$ vs controls = $0.59 \times 10^6/l$ $p<.002$) identified by the monoclonal antibody Leu-7. No other well conducted studies of exposed individuals have measured these parameters. In the discussion, the authors could not justify their findings physiologically and suggested that futher research was needed.

Immunologic function among Ranch Handers in the baseline study measured by analysis of lymphocyte surface markers, total lymphocytes and functional studies using antigenic (tetanus toxiod) or mitogen (phytohemagglutinin, concavalin A, and pokeweed) did not differ from that of the unexposed comparison group (Lathrop et al, 1984). Immunologic evaluation in the first follow-up study was the same as that in the baseline study with the addition of skin testing with Candida, mumps, trichophyton, Staph-phage-lysate (Lathrop et al, 1987). Again, no differences were observed between Ranch Handers and the matched comparison group. The study found profound effects for the comprehensive cell surface marker and functional stimulation studies due to smoking, increasing age and alcohol use but not exposure.

A statistically significant increase in anergy (inability to respond to a challenge by common antigens) was reported among residents of a trailer park in Missouri which was sprayed with contaminated 2,3,7,8-TCDD waste oil (Hoffman et al, 1986). However, corroborating results from in vitro assays of immunologic function did not support the conclusion that the subjects were anergic. Upon reexamination of only those individuals who were anergic in the first study, the results of the first study were determined to be invalid. All of the retested subjects reacted normally to the antigen challenge (Evans et al, 1987).

Immunoglobulin levels measured in Seveso residents exposed to 2,3,7,8-TCDD were similar to unexposed controls (Reggiani, 1978). In the same study, exposed children from Seveso also had normal percentages of T and B lymphocytes and normal responses to mitogens (Table 52).

Renal Effects

There is little evidence in the animal or human data to suggest that exposure to 2,3,7,8-TCDD is related to renal or bladder dysfunction. In a single case report, a child exposed to 2,3,7,8-TCDD after contact with soil sprayed with contaminated waste oil was diagnosed with focal pyelonephritis (Kimbrough et al, 1977) (Table 51). After diagnosis and treatment, the condition resolved with no reported recurrence. No major renal or bladder dysfunctions were noted among Air Force Ranch Handers (Lathrop et al, 1984; Lathrop et al, 1987) or among TCP workers from West Virginia (Suskind and Hertzberg, 1984) or from New Jersey (Poland et al, 1971).

Reproductive Effects

The results of human studies designed to examine the reproductive effects of 2,3,7,8-TCDD contaminated chemicals have not produced convincing evidence to support the animal data. In animals, exposure to 2,3,7,8-TCDD has been associated with excesses of birth

defects (Moore et al, 1973), fetal loss (Courtney, 1976) and reduced fertility (Giavini et al, 1983). In general, the human studies suffer from several limitations: insufficient power to detect relatively rare events, inadequate information on maternal and paternal exposure to 2,3,7,8-TCDD contaminated chemicals, possible incomplete ascertainment of reproductive events and incomplete ascertainment of confounders.

Two studies of occupational groups, U.S. chemical workers exposed to TCP, 2,4,5-T or pentachlorophenol (Townsend et al, 1982) and New Zealand 2,4,5-T sprayers (Smith et al, 1982) found no overall statistically significant association between exposure and adverse reproductive events such as congenital defects or miscarriages (Table 53).

A study of the frequency of birth defects occurring in the Seveso population between 1977 and 1982 and reported to the Seveso Congenital Malformations Registry found no difference in the rate of birth defects or stillbirths in the exposed population when compared to residents from unexposed regions (Mastroiacovo et al, 1988). As described by the authors, the major limitations of this study included a small sample size (N=15,291 births), possible misclassification of exposure and the exclusion of spontaneous abortions which may have been due to fetal malformations.

Similar results were found in a study of 402 births occurring between 1972 through 1982 in the state of Missouri to women whose address on the birth or fetal death certificate corresponded to an area in which 2,3,7,8-TCDD contamination was at least 1 ppb (Stockbauer et al, 1988). When compared to births of unexposed mothers matched for maternal age, race, hospital of birth, year of birth, plurality (multiple births), no statistically significant risk ratios were observed for fetal, perinatal or infant deaths, intrauterine growth retardation and low or very low birth weight. As in the study by Mastroiacovo et al (1988) the study suffers from a small sample size, limited information on maternal exposure as well as information on confounding information on maternal alcohol consumption and smoking as well as other medical conditions which may have place the baby at high risk.

Malignant Effects

Among the long-term health effects more extensively examined in relation to exposure to chlorophenols and phenoxy herbicides are a variety of malignancies, particularly soft tissue sarcomas and cáncers of the lymphatic and hematopoietic system.

Soft tissue sarcomas

In 1977, Hardell, reported several cases of soft-tissue sarcomas (STS) among individuals with previous exposure to phenoxy

herbicides and suggested that further investigation was warrented (Hardell, 1977) (Table 54). In a case-control study of 52 cases of soft-tissue sarcomas conducted in 1979, Hardell and Sandstrom showed a statistically significant five-fold excess (OR=5.3, 95% CI=2.4, 11.5) of STS among individuals reporting occupational exposure to phenoxy herbicides and a statistically significant six-fold increase among cases (OR=6.6, 95% CI=2.4, 18.5) reporting occupational exposure to chlorophenols (Hardell and Sandstrom, 1979). The 1979 study was strongly supported by one other case-control study based on cases reported to the National Social Welfare Board in Sweden which found statistically significant odds ratios among cases who worked with chlorophenols (OR=3.3, 95% CI=1.3, 8.1) or phenoxy herbicides (OR=6.8, 95% CI=2.6, 17.3) (Ericksson et al, 1981).

Chlorophenols, particularly 2,4,6-trichlorophenol, which is used in New Zealand for treatment of pelts, were also implicated in the elevated risk (OR=7.2, 90% CI=1.0, (lower bound not calculated due to small numbers)) among New Zealand residents ever employed in tannery or meat works departments (Smith et al, 1984). Further studies of abbatoir workers suggest that exposure to 2,4,6-trichlorophenol does not explain the observed increase in soft-tissue sarcoma, however, authors suggest that the the New Zealand data suggest that native abbatoir workers are at increased risk for STS (Pearce et al, 1988). However, it is important to

note that 2,4,6-TCP does not contain 2,3,7,8-TCDD. It is produced by direct chlorination, a process which does not generate the contaminant 2,3,7,8-TCDD.

STS has been reported among U.S. chemical production workers exposed to 2,3,7,8-TCDD contaminated TCP and 2,4,5-T operation, however, in studies of West Virginia 2,4,5-T workers the number of cases (one) was too few to calculate statistically valid rate ratios and the power was too low to detect excess mortality (Zack and Suskind, 1980; Zack and Gaffey, 1983). Another study of TCP production workers from a Michigan plant determined, using a comprehensive exposure assessment of the work history of each case, that none of the cases worked in processes with the potential for contamination with 2,3,7,8-TCDD (Sobel et al, 1986). Among employees of a chemical manufacturing plant in Denmark, one case of STS was found among production workers with potential exposure to phenoxy herbicides; three cases were found among manual service employees with no documented exposure to contaminated products (SIR=3.33, 95% CI= 1.03, 14.62) and one case occurred in an individual who was never assigned to a department where contaminated materials were handled (Lynge, 1985). Ten other studies evaluating the etiology of soft-tissue sarcomas found little or no evidence of excess risk among residents of Western Washington state (Woods et al, 1987), among male residents from Sweden (Wiklund et al, 1986), New Zealand (Smith et al, 1984) or England and Wales (Balajaran and Acheson, 1984), employed as

farmers or as agricultural workers, among Italian female rice weeders (Vineis et al, 1986), among Finnish 2,4,5-T herbicide applicators (Riihimaki et al, 1982), or among U.S. Air Force Ranch Handers (Lathrop et al, 1984; Lathrop et al, 1987). In a follow-up of their 1984 publication, Smith and Pearce (1986) concluded that, overall, there was little evidence that STS in New Zealand was related to 2,3,7,8-TCDD exposure.

The inconsistent nature of these results may be due to a variety of factors including the inability to accurately quantify type, duration or frequency of exposure among study subjects, the lack of sufficient power, and the difficulty in correctly histologically classifying STS (Fingerhut et al, 1984). On-going surveillance of cancer incidence among residents of Seveso at the time of the accident has revealed an increase in the rate of soft-tissue sarcoma during the years 1976-1981 in exposed Seveso residents when compared to unexposed residents (Puntoni et al, 1986). Interpretation of this finding is limited by the lack of comparable STS rates prior to the accident, the lack of good information on exposure to 2,3,7,8-TCDD, and short latency to onset of disease.

Lymphatic and Hematopoietic System

Interest in the relationship between exposure to phenoxy herbicides and chlorophenols and risk of cancer of the lymphatic system, particularly non-Hodgkin's lymphoma (NHL) and Hodgkin's disease

(HD) was generated after Hardell first suggested such an association in a case series of lymphomas presented in 1977 (Hardell, 1977) (Table 55). In a case-control study of Swedish males published in 1981, Hardell and colleagues found a statistically significant four-fold increase in the incidence of NHL and HD combined for individuals reporting exposure to either phenoxy herbicides or chlorophenols (Hardell et al, 1981). Hardell confirmed the study results in a follow-up paper which examined the possible biases of case-control studies and concluded that the increased rate of NHL and HD associated with phenoxy herbicide or chlorophenol was real (Hardell, 1981).

Researchers in Sweden and other countries attempted to repeat Hardell's findings in different populations and by examining NHL and HD separately, but have not demonstrated the striking excesses found by Hardell. Statistically significant elevations in the risk of developing NHL were shown among individuals with exposure to phenoxy herbicides through farming (OR=1.33, 95%CI=1.03, 1.70) in western Washington state (Woods et al, 1987) and in forestry sprayers reporting mixed phenoxy and chlorophenolic herbicide exposure (OR=4.8, 95%CI=1.2, 19.4) in western Washington State (Woods et al, 1987), and in fencing (OR= 2.0, 95%CI=1.1, 2.8) and meat works operations (OR=1.8, 90%CI=1.2-2.6) in New Zealand (Pearce et al, 1988; Woods et al, 1987; Wiklund et al, 1987). Statistically non-significant increases in mortality from NHL were noted in a cohort of TCP and 2,4,5-T production workers

(SMR = 341, 95% CI - 69, 996) (Ott et al, 1987), but the risk was not increased in Swedish pesticide applicators (RR=1.01, 95% CI =0.63 - 1.54) (Wiklund et al, 1987) or in Swedish men employed in agriculture or forestry (Wiklund et al, 1988).

Incidence of Hodgkin's Disease was found significantly in excess among individuals reporting exposure to phenoxy herbicides in Sweden as fur farmers (RR=4.45, 95%CI=1.4, 10.1), and silviculturalists (RR=2.26, 95%CI=1.25, 3.90) (Wiklund et al, 1988) and slightly elevated in Swedish pesticide applicators (RR=1.20, 95%CI=0.60-2.16) (Wiklund et al, 1987). Proportionate mortality from HD among tree farmers (PMR=118), orchardists (PMR=196) and paper and pulpmill workers (PMR=194) in Washington state was also increased (Milham, 1982). Cohort mortality studies of Air Force Ranch Hand veterans showed no differences in mortality from NHL or HD (Lathrop et al, 1984; Lathrop et al, 1987).

Respiratory Cancers

Higher than expected mortality from respiratory and gastrointestinal cancers was found among individuals potentially exposed to 2,3,7,8-TCDD contaminated materials (Table 56). Cohort studies of chemical workers in the United States (5 observed vs. 3.02 expected) (Zack and Suskind, 1980), in Denmark (6 observed vs. 2.71 expected) (Lynge, 1985) and in West Germany (3 observed vs. 1.26 expected) (Theiss et al, 1982) and of pesticide applicators in

West Germany (exposed=35% vs. unexposed=24%) (Barthel, 1981) reported approximately two-fold statistically nonsignificant increases in mortality from lung cancer or in the incidence of lung cancer. None of these studies was able to account for other known causes of lung cancer, including cigarette smoking or occupational exposures and most of these investigations analyzed small numbers of deaths.

The incidence of nasopharyngeal cancers was significantly elevated (OR=6.7, 95%CI=2.8, 16.2) among cases in the Swedish Cancer Registry who reported exposure to phenoxy herbicides (Hardell et al, 1982). However, nasal cancer was not elevated, when adjusted for wood dust exposure, in cases from the Danish Cancer Registry who reported chlorophenol exposure (Relative Risk=0.6, 95% CI=0.3-1.2) (Olsen and Jensen, 1984) or significantly increased in cases from the Swedish Cancer Registry who reported phenoxy herbicide exposure (OR=2.1, 95% CI=0.9-4.7) (Hardell et al, 1982). No excesses of deaths from respiratory cancers were reported among Air Force Ranch Handers in the baseline study (1 observed vs 1 expected) (Lathrop et al, 1984). In the follow up study, five Ranch Handers and none of the comparison group had cancer of the oral cavity, brochus, pharynx and lung. These cancers were attributed to smoking alone and not to exposure (Lathrop et al., 1987).

Gastrointestinal cancers

Increased incidence of and mortality from stomach cancer has been reported in studies of chemical workers in the United States (6 observed vs. 3 expected) (Ott et al, 1987), in West Germany (3 observed vs 0.61-.70 expected) (Theiss et al, 1982) and in Denmark (12 observed vs 9.32 expected in males) (Lynge, 1985), and among Swedish pesticide applicators (3 observed vs 1.34 expected) (Axelson et al, 1980). (Table 57). None of the risk ratios were significantly elevated. Bond et al (1989) noted a statistically significant higher mortality rate from stomach cancer among workers exposed to processes contaminated with 2,3,7,8-TCDD and hexa-, hepta-, octa-, chlorinated dioxins compared to workers with no such exposure (no data shown). Malignancies of the colon were found to be 1.5 (OR=1.8; 95% CI=0.6-5.3) times higher than expected among Swedish residents reporting exposure to chlorophenols (10 observed vs 7.1 expected, 95% CI=67-259) or phenoxys (OR=1.3; 95% CI=0.6-2.8) (Hardell, 1981). Intestinal cancers were 40%, (SMR = 141; 95% CI = 67-259) in excess among U.S. workers (Ott et al, 1987) exposed to high levels of chlorinated dioxins in a Michigan chemical plant, and rectal cancers were 50% higher among Danish chemical workers (Lynge, 1985).

Other malignancies

Two studies reported increases in the occurrence of cancers of the genitourinary system (Table 58). Mortality from prostatic cancer was elevated among chemical workers with exposure to 2,3,7,8-TCDD and the higher chlorinated dioxin (8 observed vs 4.2 expected, 95% CI=82-375) (Ott et al, 1987). In a study of the same workers conducted after 5 additional years of follow-up, the mortality from prostatic cancer was statistically significantly increased when compared to unexposed workers (no data shown) (Bond et al, 1989) and the incidence of cervical cancer was higher than expected among Danish chemical workers (9 observed vs 7.15 expected) (Lynge, 1985).

In the 1984 baseline and the 1987 follow-up cross-sectional studies of Air Force Ranch Handers, the prevalence of histologically confirmed cases of basal cell carcinoma was elevated relative to non-Ranch Hand Air Force personnel included in the study (Lathrop et al, 1984; Lathrop et al, 1987).

The observed increases may be due to the selection of the cohort, to an exposure factor unique to the studied group or may be a true effect of exposure to 2,3,7,8-TCDD yet to be manifested in other populations.

Mortality from Causes Other Than Cancer

Mortality from nonmalignant causes of death has been reported most often for the classification "external causes of death" which includes deaths due to accidents, homicide, and suicide (Table 59). These causes of death could be important because excesses may reflect changes in mood and behavior reported in earlier studies and case reports of exposed workers (Suskind, 1953; Poland et al, 1971). In a cohort mortality study of a small number of forestry workers employed in Canada and who may have been exposed to 2,4-D and 2,4,5-T, deaths due to suicide were significantly elevated among individuals employed less than 14 years in the industry between 1950-1982 (11 observed vs 5.2 expected, 95% CI=126-298). Other factors which may have lead to suicide were not considered in this analysis.

Overall Summary of Human Health Effects

Although there is considerable literature reporting the effects of human exposure to 2,3,7,8-TCDD contaminated materials, the data do not describe one condition or a series of long-term health effects which are consistent among every exposed population. Results of clinical cross-sectional studies provide the most consistent information, suggesting that some effects are transient, particularly increased liver enzyme levels and urinary porphyrins, and that other effects may persist in some individuals,

particularly chloracne, and peripheral neuropathies and elevated lipid levels. However, these data are unable to determine the characteristics which distinguish individuals with persistent effects from those without.

Some of the case-control and cohort mortality studies suggest that there may be some association between incidence of NHL and HD, and soft-tissue sarcomas and exposure to phenoxy herbicides and chlorophenols. But the association is equivocal since other studies do not observe the associations. The studies are extremely limited in the ability to quantify the type, frequency, and duration of exposure to chemicals contaminated with 2,3,7,8-TCDD. Much of this information was obtained through interview of the case or the proxy respondent or estimated based on the types of pesticide used, in general, during the study members' potential period of exposure, e.g. forestry sprayers. Even with this information, the exposure information is insufficient to establish the relationship between STS, NHL, and HD and exposure to 2,3,7,8-TCDD contaminated 2,4,5-T. Other limitations of note include the lack of information on confounding exposures, particularly in the cohort mortality studies, and low participation in the cross-sectional investigations.

APPENDIX C

Medications, vitamin deficienceis, occupational exposures and systemic diseases related to peripheral nerve damage

Medication	Sensory	Motor	Reflexes	Autonomic	Source	Reference
EtOH	x	x		x	D	8
Chloramphenicol	x		--		D	1
Dapsone		x			D	2
Dilantin/ Phenytoin	x	x	--		D	2
Disulfuram	x	x	--		D	1
Ethambutol	x				D	2
Ethionamide	x				D	1
Gold	x	x			D	1
Glutethiamide	x		--		D	1
Hydralazine	x	x			D	1
Isoniazid	x		--		D	1
Metronidazole	x(flagyl)				D	1
Nitrofurantoin	x	x			D	2
Nitrous oxide	x		-- or ++		D	1
Perhexiline maleate	x	x	--	x	D	1
Platinum	x		--		D	1
Pyridoxine	x				D	1
Sodium cyanate	x		--		D	1

--hyporeflexia; ++hyperreflexia; N=data not obtained; ME= medical exam
D= NIOSH Demographic and Occupational History Questionnaire
[1]Schaumburg et al, 1983; [2]LeQuesne, 1984; [3]Windebank et al, 1984
[4]LeQuesne, 1980; [5]Seppalainen and Halta, 1980; [6]Politis et al, 1980; [7]O'Donoghue et al, 1985; [8]Amore, 1978.

Medication	Sensory	Motor	Reflexes	Autonomic		Source	Reference
Thallium	x	x			D	1	
Thalidomide		x		--		D	1
Vincristine		x	x	--	x	D	1
Deficiency							
Vit B12	x					ME	1
Thiamine	x	x				N	1
Folic acid	x					ME	1
Occupational Exposures							
Arsenic	x	x	x	x	x	D	3
Acrylamide	x		x		x	D	4
Carbon disulfide	x	x				D	5
Chloro-biphenyl	x					N	
Cyanide	x	+ visual ++	x			D	1
DMAPN	x					D	1
2,4-D	x		--	x		D	1
Ethylene oxide	x	x	--	x		D	1
n-hexane	x	x	--			D	1
Lead		x	--	x		D	1
Hexa-chlorophene	x	(visual) x				D	7
Methanol	x	(visual)				N	6
Methyl-n-butyl ketone	x	x	--			D	1
Methyl bromide	x		--	x		D	1
Mercury (inorganic)	x	x		x		D	3
Mercury (organic)				x	x	N	3
Organo-phosphates (TOCP)	x	x	--	x		D	1
Thallium	x	x	--	x	x	D	1
Trichloro-ethylene	x[8]					D	1

--hyporeflexia; ++hyperreflexia; N=data not obtained; ME= medical exam; D= NIOSH Demographic and Occupational History Questionnaire; [1]Schaumburg et al, 1983; [2]LeQuesne, 1984; [3]Windebank et al, 1984; [4]LeQuesne, 1980; [5]Seppalainen and Halta, 1980; [6]Politis et al, 1980; [7]O'Donoghue et al, 1985.

	Sensory	Motor	Reflexes	CNS	Autonomic	Source	Reference
Systemic disease							
Diabetes	x				x	ME	2
Uremia	x	x	x	x		ME	3
Proteinemia	x[a]				x	ME	4
Porphyria		x			x	ME	5
Hypo-thyroidism	x[a]					ME	6
Cancer							
carcinoma	x					ME	7
lymphoma	x	x				ME	8
multiple myeloma	x	x				ME	9
Inflammatory disease							
rheumatoid arthritis	x				x	MH	
lupus (SLE)	x	x				MH	
Injury	x	x	x	x		MH	1
Sarcoidosis	x[b]					MH	10
Stroke							

--hyporeflexia; ++hyperreflexia; N=data not obtained
D= NIOSH Demographic and Occupational History Questionnaire;
MH=medical history; [a]carpal tunnel; [b]cranial nerves;
[1]Schaumburg et al, 1983;[2]Dyck et al, 1980; [3]Alrey, 1986;
[4]McLeod & Pollard, 1984; [5]Ridley, 1984; [6]Bastron,
1984;[7]McLeod, 1984; [8]McLeod & Walsh, 1984; [9]McLeod et al, 1984.

APPENDIX D

SELF-REPORTED SYMPTOMS OF PERIPHERAL NERVE DYSFUNCTION COLLECTED IN THE MEDICAL HISTORY INTERVIEW

The following are questions included in the Medical History Questionnaire to elicit information on symptoms of peripheral nerve dysfunction. The questionnaire was administered by a trained nurse-interviewer. The number and the exact wording of the question is presented in this table. Each of the questions was preceded by the phrase "Have you ever had..."

- Multiple sclerosis
- Problems with nerves in hands or feet (numbing and tingling)
- Other problems with nerves in hands or feet
- Slipped disc
- Surgery on spine
- Carpal tunnel syndrome
- Sciatica
- Injury to nerves
- Problems with nerves due to illness other than from injury, including medications
- Severe cramping or weakness in legs
- Numbness in arms or legs
- Tingling sensation in arms or legs
- Burning sensation in arms or legs
- Weakness requiring assistance when getting out of a chair
- Finger or hand weakness so that it is difficult to button shirts or unscrew jars
- Numbness or loss of sensation so that it is difficult to pick up or handle small items
- Persistent twitching or rippling of muscles in arms or legs while at rest

SELF-REPORTED SYMPTOMS RELATED TO AUTONOMIC SYSTEM

The following are questions included in the Medical History Questionnaire to elicit information on symptoms of autonomic nerve dysfunction. The questionnaire was administered by a trained nurse-interviewer. The number and the exact wording of the question is presented in this table. Each of the questions was preceded by the phrase "Have you ever had..."

- Frequent vomiting and nausea after meals
- Fullness at least 2 hours after eating
- Sweating on arms legs and trunk and after meals
- Problems urinating
- Impotence
- Difficulty maintaining an erection
- Dizziness, like you are going to faint when you stand up quickly?

---

*Medical History Questionnaire: NIOSH Occupational Health Study

BIBLIOGRAPHY

BIBLIOGRAPHY

Abernethy DJ and Boreiko CJ. Promotion of C3H/10T1/2 morphological transformation by polychlorinated dibenzo-p-dioxin isomers. Carcinogenesis 8:1485-1490, 1987.

Abernethy DJ, Greenlee WF, Huband JC, et al. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) promotes the transformation of C3H/10T1/2cells. Carcinogenesis 6:651-653, 1985.

Albro PW, Corbett JT, Harriss, et al. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on lipid profiles in tissue of the Fischer rat. Chem Biol Interact 23:315-330, 1978.

Allen JR and Carstens LA. Light and electron microscopic observations in Macaca Mulatto Monkeys fed toxic fat. Am J Vet Res 28:1513-1526, 1967.

Allen JR, Barsotti DA, Van Miller JP, et al. Morphological changes in monkeys consuming a diet containing low levels of 2,3,7,8-tetrachlorodibenzodioxin. Food Cosmet Toxicol 15:401-410, 1977.

Alrey AC. Neurologic manifestations of renal diseases. In Asbury AK, McKhann GM, McDonald WI, (eds). Diseases of the nervous system. Ardmore:Philadelphia, 1986. pp 1483-1490.

American Diabetes Association. Report and Recommendations of the San Antonio Conference on Diabetic Neuropathy. Diabetes 37:1000-1004, 1988.

Andrews JS, Garrett WA, Patterson DG, et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in adipose tissue of persons with no known exposure and in exposed persons. Chemosphere, 18:495-502, 1989.

Appenzeller O and Atkinson R. Autonomic disorders: Assessment and management. In Peripheral nerve disorders. A practical approach. Asbury AK and Gilliatt RW (eds). Butterworths:Boston, 1984. pp 58-91.

Arezzo JC, Laudadio C, Schaumburg HH. The Optacon Tactile Tester and the Pfizer Thermal Tester: New devices for the detection of diabetic neuropathy. Diabetes 40:10, 1984.

Ashe WF and Suskind RR. Reports on chloracne cases, Monsanto Chemical Co. Nitro, West Virginia, October, 1949 and April 1950. Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio, 1950 (unpublished).

Assennato G, Cervino D, Emmet E, et al. Follow-up on subjects who developed chloracne following TCDD exposure of Seveso. Am J Ind Med 16:119-125, 1989.

Axelson O, Sundell L, Anderson K, et al. Herbicide exposure and tumor mortality. Scand J Work Environ Health 6:73-79, 1980.

Baader EW and Bauer HJ. Industrial intoxication due to pentachlorophenol. Ind Med Surg 20:286-290, 1951.

Balajaran R and Acheson E. Soft tissue sarcomas in agriculture and forestry workers. J Epidemiol Comm Health 38:113-116, 1984.

Barr ML. The human nervous system: an anatomic viewpoint. Harper & Row: Hagerstown, 1979.

Barthel E. Increased risk of lung cancer in pesticide-exposed male agricultural workers. J Toxicol Environ Health 8:1027-1040, 1981.

Bauer H, Schulz K, Spiegelburg W. Industrial poisoning in the manufacture of chlorophenol compounds. Arch Gewerbepath Gewerbehyg 18:538-555, 1961.

Beck H, Eckart K, Mathar W, et al. Levels of PCDD's and PCDF's in adipose tissue of occupationally exposed workers. Chemosphere 18:507-516, 1989.

Berkley MC, Magee KR. Neuropathy following exposure to a dimethylamine salt of 2,4-D. Arch Int Med 111:351-352, 1963.

Berry DL, DiGiovanni J, Juchou MR, et al. Lack of tumor-promoting ability of certain environmental chemicals in a two-stage mouse skin tumorigenesis assay. Res Commun Patholog Pharmacol 20:101-108, 1978.

Birnbaum LS, Weber H, Harris MW, et al. Toxic interaction of specific polychlorinated biphenyls and 2,3,7,8-tetrachloro-dibenzo-p-dioxin: increased incidence of cleft palate in mice. Toxicol Appl Pharmacol 77:292-302, 1985.

Bjorklund NE, Erne K. Toxicological studies of phenoxyacetic herbicides in animals. Acta Vet Scand 7:364-390, 1966.

Bleiberg J, Wallen M, Brodkin R, et al. Industrially acquired porphyria. Arch Dermatol 89:793-97, 1964.

Bond GG, McLaren EA, Brenner FE, et al. Incidence of chloracne among chemical workers exposed to chlorinated dioxins. J Occup Med 31:771-774, 1989.

Bond GG, Ott MG, Brenner FE, et al. Medical and morbidity surveillance findings among employees potentially exposed to TCDD. Br J Ind Med 40:318-324, 1983.

Bove F, Litwak MS, Arezzo JC, et al. Quantitative sensory testing in occupational medicine. Sem Occup Med 1:185-189, 1986.

Butler MG. Acneiform dermatosis produced by ortho (2 chlorophenyl) phenol sodium and tetrachlorophenol sodium. Arch Derm Syph 35:251-254, 1937.

Cam C and Nigogosyan G. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. JAMA 183:88-91, 1963.

Cantoni L, Dal Fiume D, Ferraroli A, et al. Different susceptibility of mouse tissues to porphyrogenic effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Letter 20:201-210, 1984.

Cantoni L, Salmona M, Rizzardini M. Porphyrogenic effect of chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin in female rats. Dose-effect relationship following urinary excretion of porphyrins. Toxicol Appl Pharmacol 57:156-163, 1981.

Cantoni L, Dal Fuime D, Ferraroli A et al. Different susceptibility of mouse tissues to porphyrogenic effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicolog Let 20:201-210, 1984.

Carlstedt-Duke JMB. Tissue distribution of the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Cancer Res 39:4653-4656, 1979.

Cavannah JB. Peripheral nervous system toxicity: a morphological approach. In Neurotoxicology. Drugs and Chemical Toxicology 3. Blum K and Manzo L, (eds). Marcel Dekker:New York, 1985. pp 1-44.

Centers for Disease Control Vietnam Experience Study. Health status of Vietnam Veterans. II Physical Health. JAMA 259:2708-2714, 1988.

Centers for Disease Veterans Health Studies. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in U.S. Army Vietnam-era veterans. JAMA 260:1249-1254, 1988.

Chastain JE and Pazdernik TL. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced immunotoxicity. Int J Immunopharmacol 7:849-856, 1985.

Clark DA, Gauldie J, Szewczuk MR, et al. Enhanced suppressor cell activity as a mechanism of immunosuppression by 2,3,7,8-tetrachlorodibenzo-p- dioxin. Proceedings of the Society for Experimental Biology and Medicine. 168:290-299, 1981.

Clark DA, Sweeney G, Safe E, et al. Cellular and genetic basis for suppression of cytotoxic T-cell generation by haloaromatic hydrocarbons. Immunopharmacol 6:143-153, 1983.

Cohen GM, Brachen WM, Lyer RB, et al. Anticarcinogenic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on benzo (a) pyrene and 7,12-dimethylbenz (a) anthracne tumor initiation and its relationship to DNA binding. Cancer Res 39:4027-4033, 1979.

Cook R, Townsend J, Ott G, et al. Mortality experience of employees exposed to 2,3,7,8-tetrachlorodibenzodioxin (TCDD). J Occup Med 22:530-532, 1980.

Cook RR, Bond GG, et al. Evaluation of the mortality experience of workers exposed to the chlorinated dioxins. Fifth International Conference on Dioxin, Bayreuth, West Germany, 1985.

Courtney KD and Moore JA. Teratology studies with 2,4,5-T and 2,3,7,8-TCDD. Toxicol Appl Pharmacol 20:396-403, 1971.

Courtney KD, Putnam JP, Andrews JE. Metabolic studies with TCDD (dioxin) treated rats. Arch Environ Contam Toxicol 7:385-396, 1978.

Courtney KD. Mouse teratology studies with chlorodibenzo-p-dioxins. Bull Environ Contam Toxicol 16:674-681, 1976.

Crow KD. Chloracne and its potential clinical implications. Clin Exp Dermatol 6:243-257, 1981.

Daube JR, Dandok BA, Reagan TJ, et al. Medical neurosciences: An approach to anatomy, pathology and physiology by systems and levels. Little, Brown & Co: Boston, 1978.

Dean JH and Lauer LD. Immunological effects following exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin: A review. In Public Health Risks of the Dioxins. Lourance WW (ed). Los Altos: Kaufmann, 1984. pp 275-293.

Dean JH, Juster MI, Boorman, et al. Assessment of immunotoxicity induced by the environmental chemicals 2,3,7,8-tetrachlorodibenzo-p-dioxin, diethylstilbesterol and benzo(a)pyrene. In Advances in Immunopharmacology. Hadden J, Chedid L, Mullen P, (eds). Pergamon Press:New York, 1981. pp 37-50.

DeCaprio AP, McMartin DN, O'Keefe PW, et al. Subchronic oral toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the guinea pig. Comparisons with a PCB-containing transformer fluid pyrolysate. Fund Appl Toxicol 6:454-463, 1986.

DeJesus PV, Hausmanowa-Petruseiwicz I, Barchi RL. The effect of cold on nerve conduction of human slow and fast nerve fibers. Neurology 23:1182-1189, 1973.

Dencker L and Pratt RM. Association between the presence of the Ah-receptor in embryonic murine tissues and sensitivity to TCDD induced cleft palate. Teratol Carcinogen Mutagen 1:399-406, 1981.

DeVerneuil H, Sassa S, Kappas A. Effects of polychlorinated biphenyl compounds, 2,3,7,8-tetrachlorodibenzo-p-dioxin, phenobarbital and iron on hepatic uroporphyrinogen decarboxylase. Biochem J 214:145-151, 1983.

Di Giovanni J, Viajl A, Berry DL, et al Tumor-initiating ability of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Arochlor 1254 in a two-stage system of mouse skin carcinogenesis. Bull Environ Contam Toxicol 18:552-556, 1977.

Dorfman LJ and Bosley TM. Age-related changes in peripheral and central nerve conduction in man. Neurology 29:38-44, 1979.

Doss M, Schermuly E, Koss G. Hexachlorobenzene porphyria in rats as a model for human chronic hepatic porphyrias. Ann Clin Res 8(Suppl) 17:171-181, 1976.

Doss M, Sauer H, Von Tiepermann R, et al. Development of chronic hepatic porphyria (porphyria cutanea tarda) with inherited uroporphyrinogen decarboxylase deficiency under exposure to dioxin. Int J Biochem 16:369-373, 1984.

Dunagin, WG. Cutaneous signs of toxicity due dioxins. J Am Acad Dermatol 10:688-700, 1984.

Dyck PJ, Thomas PK, Lambert EH, et al, (eds). Peripheral Neuropathy. Saunders: Philadelphia, 1984.

Dyck PJ, Windbank A, Yasuda H, et al. Diabetic Neuropathy. Adv Exp Med Biology 189:305-320, 1985.

Erickson M, Hardell L, Berg ND, et al. Soft tissue sarcomas and exposure to chemical substances: a case-referent study. Br J Ind Med 38:27-33, 1981.

Esposito MP, Tiernan TO, Dryden FE. Dioxins. EPA-600/2-80-197, U.S. Environmental Protection Agency. November, 1980.

Evans GR, Webb KB, Knutsen AP, et al. A medical follow-up of the health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch Environ Health 43:273-278, 1988.

Faith RE and Moore JA. Impairment of thymus-dependent immune functions by exposure of the developing immune system to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J Toxicol Environ Health 3:451-464, 1977.

Fee DC, Hughes BM, Tiernan TO. Analytical methods for herbicide Orange, Vol II: Determination of origin of USAF stock. USAFARL 75-00110, Vol II., 1975.

Filippini G, Bordo B, Crenna P, et al. Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8 - tetrachlordibenzo-dioxin. Scand J Work Environ Health 7:257-262, 1981.

Fingerhut MA, Halperin WE, Honchar P, et al. An evaluation of reports of dioxin exposure and soft tissue sarcoma pathology in U.S. chemical workers. Scand J Work Environ Health 10:299-303, 1984.

Fingerhut MA, Sweeney MH, Halperin WE, et al. Epidemiology of populations exposed to dioxins. In: Exner JH (eds.), Solving hazardous waste problems. ACS Symposium Series 338. American Chemical Society, Washington, DC, 1987.

Fingerhut MA, Sweeney MH, Patterson DG, et al. Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the serum of U.S. chemical workers exposed to dioxin contaminated products: Interim results. Chemosphere 19:835-840, 1989.

Gasiewicz TA and Neal RA. 2,3,7,8-tetrachlorodibenzo-p-dioxin tissue distribution, excretion, and effects on clinical chemical parameters in guinea pigs. Toxicol Appl Pharmacol 51:329-339, 1979.

Gasiewicz TA and Rucci G. Cytosolic Receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Evidence for a homologous nature among various mammalian species. Mol Pharmacol 26:90-98, 1984.

Gasiewicz TA, Holscher MA, Neal RA. The effect of total parenteral nutrition on the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Toxicol Appl Pharmacol 54:469-488, 1980.

Giavinni E, Prati M, Vismara C. Embryotoxic effects of 2,3,7,8-tetrachlordibenzo-p-dioxin administered to female rats before mating. Environ Res 31:105-110, 1983.

Goldman PJ. Critically acute chloracne caused by trichlorophenol decomposition products. Arbeitsmed Sozialmed Arbeitshygiene 7:12-18, 1972.

Goldstein JA and Safe S. Mechanism of action and structure-activity relationships for the chlorinated dibenzo-p-dioxins and related compounds. In Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Kimbrough RD and Jensen AA (eds). Elsevier: New York, 1989.

Goldstein JA, Hickman P, Bergman H, et al. Hepatic porphyria induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Res Com Chem Path Pharmacol 6:91928, 1973.

Goldstein JA, Linko P, Bergman H. Induction of porphyria in the rat by chronic versus acute exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Biochem Pharmacol 31:1607-1613, 1982.

Goldstein NP, Jones, PH, Brown JR. Peripheral neuropathy after exposure to an ester of dichlorophenoxyacetic acid. JAMA 171:1306-1309, 1959.

Green LM. Suicide and exposure to phenoxy acid herbicides. Scand J Work Environ Health 13:460, 1988.

Greig JB, Jones G, Butler WH, et al. Toxic effects of 2,3,7,8-tetrachloro- dibenzo-p-dioxin. Fd Cosmet Toxicol 11:585-595, 1973.

Gupta BN, Vos JG, Moore JA, et al. Pathologic effects of 2,3,7,8-TCDD in laboratory animals. Environ Health Perspect 5:125-140, 1973.

Hansen WH, Quaife ML, Habermann RT, et al. Chronic toxicity of 2,4-dichlorophenoxyacetic acid in rats and dogs. Toxicol Appl Pharmacol 20:122-129, 1971.

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

Hardell L, Erickson 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.

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

Hardell L. Relations of soft tissue sarcoma malignant lymphoma and colon cancer to phenoxy acids or chlorophenol and other agents. Scand J Work Environ Health 7:119-130, 1981.

Hardell LM. Malignant mesenchymal tumors and exposure to phenoxy acids-a clinical observation. Lakartidningen 74:2853, 1977.

Hardell LM. Soft tissue sarcomas and exposure to phenoxyacetic acids-a clinical observation. Lakartidningen 74:2753-2754, 1977.

Harris MW, Moore JA, Vos JG, et al. General biological effects of TCDD in laboratory animals. Environ Health Perspect 5:101-109, 1973.

Hassoun EM and Dencker L. TCDD embryotoxicity in the mouse may be enhanced by beta-naphthflovone, another ligand of the Ah-receptor. Toxicol Lett 12:191-198, 1982.

Hay A. The mutagenic properties of 2,3,7,8-tetrachloro-dibenzo-p-dioxin. In Chlorinated dioxins and dibenzofurans in the total environment II. Keith HH, Rappe C and Choudary G (eds). Butterworth: Boston, 1985.

Hill EV and Carlisle H. Toxicity of 2,4-dichlorophenoxyacetic acid for experimental animals. J Ind Hyg Toxicol 29:85-95, 1947.

Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicides and risk of lymphoma and soft-tissue sarcoma. JAMA 256:1141-1147, 1986.

Hoffman RE, Stehr-Green PA, Webb KB, et al. Health Effects of long-term exposure to 2,3,7,8-tetrachlorodibenzodioxin. JAMA 255:2031-2038, 1986.

Holder JW and Menzel HM. Analysis of 2,3,7,8-TCDD tumor promotion activity and its relationship to cancer. Chemosphere 19:861-868, 1989.

Holsapple MP, McCay JA, Barnes DW. Immunosuppression without induction by subchronic exposure to 2,7-dichlorodibenzo-p-dioxin in adult female B6C3F1 mice. Toxicol Appl Pharmacol 83:445-455, 1986.

Hornung RW, Reed LD. Estimation of average concentration in the presence of nondetectable values. Appl Ind Environ Hyg 5:46-51, 1990.

IARC. Evaluation of the carcinogenic risk of chemicals to humans. Some halogenated hydrocarbons and pesticide exposures. IARC Technical Report No 781001. International Agency for Research on Cancer. Lyon, Volume 41, 1986.

IARC. Long Term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans. IARC Technical Report No 781001. International Agency for Research on Cancer. Lyon, 1978.

Ideo G, Ballati G, Bellobuno A, et al. Urinary D-glucaric excretion in the Seveso area, polluted by tetrachlorodibenzo-p-dioxin (TCDD): five years of experience. Environ Health Perspect 60:151-157, 1985.

Jacobs JM. Vascular permeability and neural injury. In Experimental and clinical neurotoxicology. Spencer PS and Schaumburg HH, (eds). Williams and Wilkins: Baltimore, 1980. pp 102-117.

Jennings AM, Wild G, Ward JD, et al. Immunological abnormalities 17 years after accidental exposure to 2,3,7,8-tetrachlorodibenzo -p-dioxin. Br J Ind Med 45:701-704, 1988.

Jirasek L, Kalensky J, Kulec K. Chloracne and porphyria cutanea tarda in association with the production of herbicide. Cesk Derm 48:306-317, 1973.

Jirasek L, Kalensky K, Kubec K, et al. Chronic poisoning by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Cesk Dermatol 49:145-157, 1974.

Jones EL and Kizek H. A technique for testing acnegenic potency in rabbits, applied to the potent acnegen, 2,3,7,8-tetrachloro-dibenzo-p-dioxin. J Invest Dermatol 9:511-517, 1962.

Jones G and Greig JB. Pathological changes in the liver of mice given 2,3,7,8-TCDD. Experientia 31:1315-1317, 1975.

Jones KG and Sweeney GD. Dependence of the porphyrigenic effect of 2,3,7,8-tetrachlorodibenzo-(p)-dioxin upon inheritance of aryl hydrocarbon hydroylase responsiveness. Toxicol Appl Pharmacol 53:42-49, 1980.

Jones KG, Cole FM, Sweeney GD. The role of iron in the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol Appl Pharmacol 61:74-88, 1981.

Jones RE and Chelsky M. Further discussion concerning porphyria cutanea tarda and TCDD exposure. Arch Environ Health 41:100-103, 1986.

Kay JH, Palazzolo RJ, Calandra JC. Subacute dermal toxicity of 2,4-D. Arch Environ Health. 11:648-651, 1965.

Khera KS and Ruddick JA. Polychlorinated dibenzo-p-dioxins: Perinatal effects and the dominant lethal test in Wistar rats. In Chlorodioxins--Origins and fate. Blair EH (ed). Adv Chem Ser No. 120. Am Chem Soc. Washington, DC.(1973)

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

Kimbrough RD. Review of the toxicity of hexachlorophene. Arch Environ Health 23:119-122, 1971.

Kimmig J and Schulz KH. Chlorinated aromatic cyclic ethers as the cause of so-called chloracne. Naturwissenshaften 44:337-338, 1957a.

Kimmig J and Schulz KH. Occupational chloracne caused by aromatic cyclic ethers. Dermatologica 115:540-546, 1957b.

Kimura J. Electrodiagnosis in diseases of nerve and muscle: principles and practice. Davis: Philadelphia, 1983.

Kociba RJ and Schwetz BA. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Drug Metab Rev 13:387-406, 1982.

Kociba RJ, Keeler CN, Park CN, et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin: results of a 13 week oral toxicity study in rats. Toxicol Appl Pharmacol 35:553-574, 1976.

Kociba RJ, Keyes DG, Beger JE, 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.

Kouri RE, Rude TH, Joglekar R, et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin as cocarcinogen causing 3-methylcholanthrene-initiated subcutaneous tumors in mice genetically "nonresponsive" at Ah locus. Cancer Res 38:2777-2783, 1978.

Krarup C and Buchthal F. Conduction studies in peripheral nerves. Neurobehav Toxicol Teratol 7:319-323, 1985.

Kristensson K and Olsson Y. Retrograde axonal transport of protein. Brain Res 29:363, 1971

Kuratsune M, Yoshimura T, Matsuzaka J et al. Epidemiologic study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. Environ Health Perspect 1:119-128, 1972.

Kuratsune M. Yusho, with reference to Yu-cheng. In Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Kimbrough RD and Jensen AA (eds). Elsevier: New York, 1989. pp 381-400.

Lathrop GD, Wolfe WH, Albanese RA, et al. An epidemiologic investigation of health effects in air force personnel following exposure to herbicides. Baseline morbidity study results. U.S. Air Force School of Aerospace Medicine, Aerospace Medical Division, Brooks Air Force Base, Texas, 1984 (unpublished).

Lathrop GD, Wolfe WH, Michalek JE, et al. An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides. First follow-up examination results. January 1985-September, 1987. U.S. Air Force School of Aerospace Medicine, Aerospace Medical Division, Brooks Air Force Base, Texas, 1987 (unpublished).

LaVecchio FA, Pashayan HM, Singer W. Agent orange birth defects. N Eng J Med 308:719-720, 1983.

LeQuesne PM. Acrylamide. In Experimental and Clinical Neurotoxicology. Spencer PS and Schaumburg HH (eds). Williams and Wilkins: Baltimore, 1980.

LeQuesne PM. Neuropathy due to drugs. In Periheral neuropathy. Dyck PJ, Thomas PK, Lambert EH, et al (eds). WB Saunders: Philadelphia, 1984.

Lesca P. Modulating effects of 2,3,7,8,-tetrachlorodibenzo-p-dioxin on skin carcinogenesis initiated by 7, 12-dimethylbenz(a)anthracne in CF-1 Swiss mice. In Extrahepatic drug metabolism and chemical carcinogenesis: Proceedings of an International Meeting. Rydatroem J, Monteliens J and Bengtsson M, (eds). Elsevier Science Publishers: Amsterdam , 1983.

Light AR and Edward RP. Peripheral Sensory systems. In Peripheral Neuropathy. Dyck PJ, Thomas PK, Lambert EH, et al (eds). Saunders: Philadelphia, 1984. pp 210-230.

Luster MI, Dean JA, Boorman GA. Altered immune functions in rodents treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin, phorbol-12-myristate-13-acetate, and benzo (a) pyrene. In Banbury Report 11: Environmental Factors in Human Growth and Development. 1982. pp 199-215.

Luster MI, Hong LH, Boorman GA. Acute myelotoxic responses to mice exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol Appl Pharmacol 81:156-165, 1985.

Lutz WD, Weber LWD, Greim H, et al. Metabolism and distribution of (14C) glucose in rats treated with 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). J Toxicol Environ Health 22:195-206, 1987.

Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br J Cancer 52:259-270, 1985.

Ma DM and Liveson JA. Nerve conduction handbook. Davis: Philidelphia, 1983.

Marlow D, Fingerhut M, Hearn S, et al. Dioxin Registry Report: Report Prepared by review of documents received from Syntex (U.S.A.), Incorporated and site visits. Verona, Missouri, Springfield Missouri, May, 1987 (unpublished).

Martin JV. Lipid abnormalities in workers exposed to dioxin. Br J Ind Med 41:254-256, 1984.

Mason ME and Okey AB. Cytosolic and nuclear binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin to the Ah receptor in extra-hepatic tissues of rats and mice. Eur J Biochem. 123:209-215, 1982.

Mastroiacovo P, Spagnolo A, Marni E, et al. Birth defects in the Seveso area after TCDD contamination. JAMA 259:1668-1672, 1988.

Masuda Y. Health status of Japanese and Taiwanese after exposure to contaminated rice oil. Environ Health Perspect 60:321-325, 1985.

Mattsson JL, Johnson KA, Alber RR. Lack of neuropatholic consequences of repeated dermal exposure to 2,4-D in rats. Fund Appl Toxicol 6:175-181, 1986.

May G. Chloracne from the accidental production of tetrachlorodibenzo-dioxin. Br J Ind Med 30:276-283, 1973.

May G. Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. Br J Ind Med 39:128-135, 1982.

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, 1978a.

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, 1978b.

McConnell EE. Acute and chronic toxicity and carcinogenesis in animals. In Halogenated biphenyls, terphenyls, naphtyalines dibenzodioxins and related products. Kimbrough RD and Jensen AA (eds). Elsevier: New York, 1989.

McLeod JG and Pollard JD. Neuropathies in systemic diseases: hidden and overt. In Asbury Ak and Gilliatt RW, (eds). Peripheral nerve disorders. Butterworths:Boston, 1984. pp 92-99.

McLeod JG and Walsh JC. Peripheral neuropathy associated with lymphomas and other reticuloses. In Dyck PJ, Thomas Pk, Lambert EH et al ((eds)). Peripheral Neuropathy. Saunders:Philadelphia, 1984. pp 2192-2203.

McLeod JG, Walsh JC and Pollard JD. Neuropathies associated with paraproteinemias and dysproteinemias. In Dyck PJ, Thomas Pk, Lambert EH et al (eds). Peripheral Neuropathy. Saunders:Philadelphia, 1984. pp 1847-1865.

McLeod JG. Autonomic dysfunction in peripheral nerve disease. In Autonomic failure. A textbook of clinical disorders of the autonomic system. Bannister R. (ed), Oxford University Press:New York, 1988. pp 607-623.

McLeod JG. Carcinomatous Neuropathy. In Dyck PJ, Thomas Pk, Lambert EH et al (eds). Peripheral Neuropathy. Saunders:Philadelphia, 1984. pp 2180-2191.

McNulty WP. Fetocidal and teratogenic actions of TCDD. In Pubic Health Risks of the Dioxins. Lourance WW (ed). William Kaufmann: Los Altos, 1984.

McNulty WP. Toxicity of 2,3,7,8-tetrachlordibenzo-p-dioxin for Rhesus monkeys: Brief report. Bull Environ Contam Toxicol 18:108-109, 1977.

Milham S. Herbicides, occupation, and cancer. Lancet i:1464-1465, 1982.

Miyata H, Takayama K, Ogaki J et al. Levels of PCDDs, coplanar PCBs and PCDFs in patients with Yusho disease and Yusho oil. Chemosphere 18:407-416, 1989.

Mocarelli P, Marocchi A, Brambilla P, et al. Clinical laboratory manifestations of exposure to dioxin in children. A six year study of the effects of an environmental disaster near Seveso, Italy. JAMA 256:2687-2695, 1986.

Mocarelli P, Pocchiari F, Nelson N, et al. Preliminary report: 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Exposure to Humans-Seveso, Italy. MMWR 37:733-736, 1988.

Moody L, Arezzo J, Otto D. Screening occupational populations for asymptomatic or early peripheral neuropathy. J Occup Med 28:975-986, 1986.

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

Moore JA, McConnell, Dalgard DW, et al. Comparative toxicity of three halogenated dibenzofurans in guinea pigs, mice and rhesus monkeys. Ann NY Acad Sci 320:151-163, 1979.

Moore RW, Potter Cl, Theobald HM, et al. Androgenic deficiency in male rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol App Pharmacol 79:99-111, 1985.

Moses M, Lilis R, Crow KD, et al. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid. Comparison of findings with and without chloracne. Am J Ind Med 5:161-182, 1984.

Moses M and Prioleau PG. Cutaneous histologic findings in chemical workers with and without chloracne with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Am Acad Dermatol 12:497-506, 1985.

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

National Toxicology Program (NTP). Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (CAS No. 174 01-6) in Osborne-Mendel rats and B7CF$_1$ mice (gavage study). NTP Technical Report Series No. 209. Washington, DC. DHEW Publication No. (NIH) 82-1765, 1982a.

National Toxicology Program (NTP). Carcinogenesis bioassay 1 of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Swiss-Webster mice (dermal study). Technical Report Series No. 201. Washington, D.C. DHEW Publication No. (NIH) 82-1757, 1982b.

Neal RA, Olson TA, Gasiewicz TA, et al. The toxicokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian systems. Drug Met Rev 13:355-385, 1982.

Neal RA. Mechanisms of the biological effects of PCB's, polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans in experimental animals. Environ Health Perspect 60:41-46, 1985.

North Atlantic Treaty Organization. Pilot study on international information exchange on dioxins and related compounds. Formation of Dioxins and Related Compounds in Industrial Processes. Report No. 173, 1988.

North Atlantic Treaty Organization. Pilot Study on International Information Excahnge on Dioxins and Related Compounds. Emissions of Dioxins and Related Compounds from Combustion and Incineration Sources. Report No. 172, 1988.

O'Donoghue JL (ed). Neurotoxicity of Industrial and Commercial Chemicals, Vol I and II, CRC: Boca Raton, 1986.

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

Olsen JH and Jensen OM. Nasal cancer and chlorophenols. Lancet II:47-48, 1984.

Olson JR, Holscher MA, Neal RA. Toxicity of 2,3,7,8-tetrachlorodibenzo- p-dioxin in the Golden Syrian hamster. Toxicol Appl Pharmacol 55:67-78, 1980.

Olsson Y. Vascular permeability in the peripheral nervous. In Peripheral Neuropathy. Dyck PJ, Thomas PK, Lambert EH, et al (eds). Saunders: Philadelphia, pp 579-597, 1984.

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

Ott, MG, Olson RA, Cook RR et al. Cohort mortality study of chemical workers with potential exposure to the higher chlorinated dioxins. J Occup Med 29:422-429, 1987.

Patterson DG, Fingerhut MA, Roberts DW, et al. Levels of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. AM J Ind Med 16:135-146, 1989.

Patterson DG, Hoffman RE, Needham LL, et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in adipose tissue of exposed and control persons in Missouri. JAMA 256:2683-2686, 1986.

Patterson DG, Holler JS, Lapeza CR, et al. High-resolution gas chromatography/ high-resolution mass spectrometric analysis of human adipose tissue for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Anal chem 58:705-713, 1986.

Patterson DG, Turner WE, Alexander LR, et al. The analytical methodology and method performance for the determination of 2,3,7,8-TCDD in serum for the Vietnam Veteran Agent Orange Validation Study, the Ranch Hand Validation and Half-life Validation Studies, and selected NIOSH Worker Studies. Chemosphere 18:875-882, 1989.

Patterson DG, Needham LL, Pirkle JL et al. Correlation between serum and adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 50 persons from Missouri. Arch Environ Contam Toxicol 17:139-143, 1988.

Pazderova-Vejlupkova J, Nemcova M, Pikova J, et al. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-doxin in men. Arch Environ Health 36:5-11, 1981.

Pearce NE, Smith AH, Howard JK, et al. Non-Hodgkin's lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: a case control study. Br J Ind Med 43:75-83, 1986.

Pearce NE, Smith AH, Fisher DO. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand Cancer Registry-based study. Am J Epidemiol 121:225-237, 1988.

Percy C, Stanek E, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. Am J Pub Health 71:242-250, 1981.

Pirkle JL, Wolfe WH, Patterson DG Jr, et al. Estimates of the half-life of 2,3,7,8-TCDD Vietnam weterans of Operation Ranch Hand. J Toxicol Environ Health 27:165-171, 1989.

Pitot HC, Goldsworthy T, Campbell HA, et al. Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzodioxin of hepatocarcinogenesis from diethylnitrosamine. Cancer Res 40:3616-3620, 1980.

Pleasure D, Towfighi J, Silberberg D et al. The pathogenesis of hexachlorophene neuropathy: In vivo and in vitro studies. Neurology 24:1068-1075, 1974.

Pocchiari F, Silvano V, Zampieri A, et al. Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. Ann NY Acad Sci 77:311-320.

Poiger H and Schlatter C. Pharmacokinetics of 2,3,7,8-TCDD in man. Chemosphere 15:1489-1494, 1985.

Poiger H, Schlatter C, Wendling JM. Toxicokinetics of 2,3,7,8-TCDD in man: an update. Presented at Dioxin '88. The 8th International Symposium on Chlorinated Dioxins and Related Compounds. August 21-26, 1988, Umea, Sweden.

Poland A and Glover E. A model for the mechanism of action of 2,3,7,8-TCDD. In Estrogens in the Environment. McClachlan J (ed). Elsevier: Netherlands, 1980.

Poland AP and Glover E. 2,3,7,8-tetrachlorodibenzodioxin. Segregation of toxicity with Ah locus. Mol Pharmacol 17:86-94, 1980.

Poland A and Glover E. An estimate of the maximum in vivo covalent binding of 2,3,7,8-tetrachlorodibenzodioxin to rat liver protein, ribosomal RNA, and DNA. Cancer Res 39:3341-3344, 1979.

Poland A and Glover E. Comparison of 2,3,7,8-tetrachloro-dibenzo-p-dioxin a potent inducer of aryl hydrocarbon hydroxylase, with 3-methylcholanthrene. Mol Pharmacol 10:349-359, 1974.

Poland A and Glover E. 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 9:736-747, 1973.

Poland A, Glover E, Kende AS. Stereospecific, high affinity binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin by hepatic cytosol. J Biol Chem 251:4936-4946, 1976.

Poland A, Palen D, Glover E. Tumour promotion by TCDD in skin of HRS/J hairless mice. Nature 300:271-273, 1982.

Poland AP and Knutsen JC. 2,3,7,8-TCDD and related halogenated aromatic hydrocarbons: Examination of the mechanisms of toxicity. Ann Rev Pharmacol 22:517-554, 1982.

Poland AP, Smith D, Metter G, et al. A health survey of workers in a 2,4-D and 2,4,5-T plant. Arch Environ Health 22:316-27, 1971.

Poli A, Francheschini L, Puglist L, et al. Increased total and high-density lipoprotein cholesterol with apoprotein changes resembling streptozotoxin diabetes in tetrachlorodibenzodioxin (TCDD) treated rats. Biochem Pharmacol 29:835-838, 1980.

Politis MJ, Schaumburg HH, Spencer PS. Neurotoxicity of selected chemicals. In Experimental and Clinical Neurotoxicology. Spencer PS and Schaumburg HH (eds). Williams and Wilkins: Baltimore, 1980. pp 613-629.

Price DL and Griffin JW. Neurons and ensheathing cells as targets of disease processes. In Experimental and clinical neurotoxicology. Spencer PS and Schaumburg HH (eds). Williams and Wilkins: Baltimore, 1980. pp 2-23

Puntoni R, Merlo F, Fini A, et al. Soft tissue sarcoma in Seveso. Lancet II:525, 1986.

Rao MS, Subbarao V, Prasad JD et al. Carcinogenicity of 2,37,8-tetrachlorodibenzo-p-dioxinin the Syrian golden hamster. Carcinogenesis 9:1677-1679, 1988.

Rappe C and Buser HR. Chemical properties and analytical methods. In Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins. Kimbrough R (ed). Elsevier/North Holland: New York, 1980. pp 41-76.

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

Reggiani G. Medical Problems Raised by the TCDD Contamination in Seveso, Italy. Arch Toxicol 40:161-188, 1978.

Riihimaki V, Asp S, Hernberg S, et al. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland. Scand J Work Environ Health 8:37-42, 1982.

Rogan W. Yu-Cheng. In Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Kimbrough RD and Jensen AA (eds). Elsevier: New York, 1989. pp 401-415.

Russell WO, Cohen J, Enzinger F, et al. A clinical and pathological staging system for soft tissue sarcomas. Cancer 40:1562-1570, 1977.

SAS Institute Inc. SAS Procedures Guide, Release 6.03 Edition. Cary, NC:SAS Institute Inc., 1988.

SAS Institute Inc. SUGI Supplemental Library User's Guide, 1987 Edition. Cary, NC:SAS Institute, 1987.

Schantz SL, Barsotti DA, Allen JR. Toxicological effects produced in non-human primates chronically exposed to fifty parts per trillion 2,3,7,8- tetrachlorodibenzo-p-dioxin (TCDD). Toxicol Appl Pharmacol 48:A181, 1979.

Schaumberg HH, Spencer PS, Thomas PS, et al. In Disorders of the peripheral nervous system. Davis: Philadelphia, 1983.

Schaumburg HH and Spencer PS. Human toxic neuropathy due to industrial agents. In Experimental and clinical neurotoxicology. Spencer PS and Schaumburg HH (eds). Williams and Wilkins: Baltimore, 1980. pp 2115-2131.

Schiller CM, King MW, Walden R. Alterations in lipid parameters associated with changes in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced mortality in rats. In Chlorinated dioxins and dibenzofurans in perspective. Rappe C, Choudhary G, Keith HH, et al (eds). Lewis: Ann Arbor, 1986. pp 285-302.

Schwetz BA, Norris JM, Sparcchu CL, et al. Toxicology of chlorinated dibenzo-p-dioxins. Environ Health Perspect 5:87-99, 1973.

Seppalainen AM and Haltia M. Carbon disulfide. In Experimental and clinical neurotoxicology. Spencer PS and Schaumburg HH (eds). Williams and Wilkins: Baltimore, 1980. pp 356-373.

Shu HP, Paustenbach DE, Murray FJ. A critical evaluation of the use of mutagenesis, carcinogenesis, and tumor promotion data in a cancer risk assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Regul Toxicol Pharmacol 7:57-88, 1987.

Silbergeld E and Gasiewicz TA. Dioxins and the Ah receptor. Am J Ind Med 16:455-474, 1989.

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.

Skene SA, Dewhurst IC, Greenberg M. Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans: The risk to human health. A review. Human Toxicol 8:173-203, 1989.

Smith AG, Francis JE, Kay SJE, et al. Hepatic toxicity and uroporphyrinogen decarboxylase activity following a single dose of 2,3,7,8-tetrachloro- dibenzo-p-dioxin to mice. Biochem Pharmacol 30:2825-2830, 1981.

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

Smith AH, Pearce NE, Fisher DO, et al. Soft tissue sarcoma and exposure to phenoxyherbicides and chlorophenols in New Zealand. J Nat Cancer Inst 73:1111-1117, 1984.

Smith FA, Schwetz BA, Nitschke KD, et al. Teratogenicity of 2,3,7,8-tetrachlorodibenzodioxin in CF-1 mice. Toxicol Appl Pharmacol 38:517-523, 1976.

Sobel W, Bond GG, S Kowronski BJ, et al. Soft-tissue sarcoma: Case-control study (letter). J Occup Med 28:804-808, 1986.

Sonawane BR, Smialowiez RJ, Luebke, Immunotoxicity of 2,3,7,8-TCDD: Review, issues and uncertainties. Risk Assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin. U.S. Environmental Protective Agency, Office of Research and Development, 1988.

Spencer PS, Arezzo JC, Schaumberg HH. Chemicals causing diseases of neurons and their processes. In Neurotoxicity of industrial and commercial chemicals. O'Donoghue J (ed). CRC: Boca Raton, 1984. pp 3-9.

Squibb RE, Tilson HA, Mitchell CL. Neurobehavioral assessment of 2,4-dichlorophenoxyacetic acid (2,4-D) in rats. Neurobehav Toxicol Teratol 5:331-35, 1983.

Steinberg KK, MacNeil ML, Karon JM, et al. Assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure using a modified d-glucaric acid assay. J Toxicol Environ Health 16:743-752, 1985.

Sternman AB and Schaumburg HH. Neurotoxicity of selected drugs. In Experimental and clinical neurotoxicity. Spencer PS and Schaumburg HH (ed). Williams and Wilkins: Baltimore, 1980. pp 593-611.

Stockbauer JW, Hoffman RE, Schramm WF, et al. Reproductive outcomes of mothers with potential exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Am J Epidemiol 128:410-419, 1988.

Strik JJTWA. The occurrence of chronic-hepatic porphyria in man caused by halogenated hydrocarbons. In Chemical Porphyria in man. Strik JJTWA and Koeman JH (eds). Elsevier/North-Holland: New York, 1979. pp 3-9.

Suskind R, Cholak J, Schater LJ, et al. Reports on clinical and environmental surveys at Monsanto Chemical Co. Nitro, West Virginia, 1953. Department of Environmental Health, University of Cincinnati. (Unpublished).

Suskind RR and Hertzberg VS. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 251:2372-2380, 1984.

Sweeney GD. Porphyria cutenea tarda, or the uroporphyrinogen decarboxylase deficiencey disease. Clin Biochem 19:3-15, 1986.

Sweeney GD. Iron deficiency prevents liver toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Science 204:332-335, 1979.

Sweeney MH, Fingerhut MA, Patterson DG, et al. Serum levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) in New Jersey and Missouri chemical workers exposed to dioxin-contaminated processes: interim report. Chemosphere : , 1990.

Sweeney MH, Fingerhut MA, Connally LB, et al. Progress of the NIOSH cross-sectional medical study of workers occupationally exposed to chemicals contaminated with 2,3,7,8-TCDD. Chemosphere 19:973-977, 1989.

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.

Thomas PK. The peripheral nervous system as a target for toxic substances. In Experimental and clinical neurotoxicology. Spencer PS and Schaumburg HH (eds). 1980. pp 35-47.

Thomas PT and Hinsdill RD. The effect of perinatal exposure to tetrachlorodibenzo-p-dioxin on the immune response of young mice. Drug Chem Toxicol 2:77-78, 1979.

Thunberg T, Ahlborg G, Johnsson H. Vitamin A (retinol) status in the rat after a single oral dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch Toxicol 57:13-16, 1985.

Toth K, Somafai-Relle S, Sugar J, et al. Carcinogenicity testing of herbicide 2,4,5-trichlorphenoxyethanol containing dioxin and of pure dioxin in Swiss mice. Nature 278:548-549, 1979.

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

Toyoshima E, Mayer RF, Max SR, et al. 2,4-Dichlorophenoxy acetic acid (2,4-D) does not cause polyneuropathy in the rat. J Neurol Sci 70:225-229, 1985.

Tucker AN, Vore SJ, Luster MI. Suppression of B cell differentiation by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Mol Pharmacol 28:372-377, 1986.

Turner WE, Isaacs S, Alexander LR, et al. A quality assurance program for large-scale studies measuring 2,3,7,8-tetrachlorodibenzo-p-dioxin in human serum. Chemosphere 18:1009-1016, 1989.

U.S. EPA. Health assessment document for polychlorinated dibenzo-p-dioxins. EPA/600/8-84/014F. Office of Health and Environmental Assessment, Washington, DC, 1985.

U.S. Environmental Protection Agency. Interim procedures for estimating risks associated with exposures to mixtures of chlorinated dibenzo-p-dioxins and -dibenzofurans (CDDs and CDFs) and 1989 update. Risk Assessment Forum, U.S.E.P.A., Washington, D.C., 20460, 1989.

Van Houdt JJ, Fransman LG, Strik JJTWA. Epidemiologic case control study in personnel exposed to 2,4,5-T. Chemosphere 12(4/5):575, 1983.

Van Miller JP and Allen JR. Chronic toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Fed Proc Am Soc Exp Biol 36:396, 1977.

Van Miller JP, Lalich JJ, Allen JR, et al. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzodioxin. Chemosphere 10:625-632, 1977.

Van den Berg M, Heeremans C, Veenhoven E, et al. Transfer of polychlorinated dibenzo-p-dioxins and dibenzofurans to fetal and neonatal rats. Fund Appl Toxicol 9:635-644, 1987.

Vecchi A, Graziani A, Sironi M, et al. Simultaneous administration of TCDD and TCDF at different ratios induces different effects. Chemosphere 14:957-961, 1985.

Vecchi A, Sironi M, Canegrati MA, et al. Immunosuppressive effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in strains of mice with different susceptibility to induction of aryl hydrocarbon hydroxylase. Toxicol Appl Pharamcol 68:434-441, 1983.

Vecchi A, Sironi M, Sfreddo-Gallotta E, et al. Effect of inducers of P-450 cytochrome isoenzymes on TCDD immunosuppression activities. Chemosphere 15:1707-1714, 1986.

Vineis P, Benedetto T, Ciccone G, et al. Phenoxy herbicides and soft-tissue sarcomas in female rice weeders. A population-based case-referent study. Scand J Work Environ Health 13:9-17, 1986.

Vos JG and Luster MI. Immune alterations. In Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Kimbrough RD and Jensen AA (eds). New York: Elsevier, 1989. pp295-322.

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

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.

Vos JG. Dioxin induced thymic atrophy and suppression of thymus dependent immunity. In Banbury Report 18: Biological Mechanisms of Dioxin Action. Poland A, Kimbrough RD, (eds). New York: Cold Spring Harbor, 1984. pp 401-409.

Wasson JS, Huff, JE, Lopriano NA. A review on the genetic toxicology of chlorinated dibenzo-p-dioxins. Mut Res 47:141-160, 1977.

Webb K, Evans G, Stehr P, et al. Pilot study on health effects of environmental 2,3,7,8-TCDD in Missouri. Am J Ind Med 11:685-691, 1987.

Webb KB, Evans RG, Knudsen DP, et al. Medical evaluation of subjects with known body levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. 1989 (unpublished).

Weber H, Harris MW, Haseman JK, et al. Teratogenic potency of TCDD, TCDF and TCDD-TCDF combinations in C57BL/6N mice. Toxicol Let 26:159-167, 1985.

Weissberg JB and 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.

White KL, Lysy HH, McCay JA, et al. Modulation of serum complement levels following exposure to polychlorinated dibenzo-p-dioxins. Toxicol Appl Pharmacol 84:209-219, 1986.

Wiklund K and Holm L. Soft tissue sarcoma risk in Swedish agricultural and forestry workers. J Nat Cancer Inst 76:229-234, 1986.

Wiklund K, Dich H, Holm LE. Risk of malignant lymphoma in Swedish pesticide appliers. Br J Cancer 56:505-508, 1987.

Wiklund K, Lindefors BM, Holm LE. Risk of malignant lymphoma in Swedish agricultural and forestry workers. Br J Ind Med 45:19-24, 1988.

Windebank AJ, McCall JT, Dyck PJ. Metal neuropathy. In Peripheral neuropathy. Dyck PJ, Thomas PK, Lambert EH, et al, (eds). Saunders: Philadelphia, 1984. pp 2133-2161.

Wipf HK and Schmidt J. Seveso: An environmental assessment. In Human and environmental risks of chlorinated dioxins and related compounds. Tucker RE, Young AL, Gray AP (eds). Plenum: New York, 1983. pp 255-276.

Wolfe WH, Michalek JE, Miner JC et al. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in Air Force Health Study participants- Preliminary report. MMWR 37:309-310, 1988.

Woods JS, Polissar L, et al. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. J Natl Cancer Inst 78:899-910, 1987.

Young AL, Kang HK, et al. Chlorinated dioxins as herbicide contaminants. Environ Sci Technol 17:530A-540A, 1983.

Zack JA and Gaffey WR. A mortality study of workers employed at the Monsanto Company plant in Nitro, West Virginia. Environ Sci Res 26:575-591, 1983.

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

Zinkl JG, Moore JA, Gupta BN. Hematologic and clinical chemistry effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Environ Health Perspect 5:111-118, 1973.