Mortality Among U.S. Workers Employed in the Production of Chemicals Contaminated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

FINAL REPORT

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Abstract

To examine the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on mortality, a retrospective cohort mortality study was conducted of 5172 chemical workers from 12 U.S. plants. Occupational exposure was documented by a review of process descriptions and job duties and by measurement of serum TCDD levels in a sample of 253 workers from 2 plants. The serum TCDD levels in the sample of workers, with a range up to 3400 parts per trillion, were highly correlated with years worked in TCDD-contaminated processes ($r=.72$, $p<.0001$). Therefore, the number of years worked in these processes was used as a surrogate for cumulative TCDD exposure in the cohort study.

Mortality from several rare cancers previously associated with chemicals contaminated with TCDD was not statistically significantly elevated in the cohort. This included cancer of the stomach (SMR 103, 95% CI 50-190), cancer of liver, biliary passages and gallbladder (SMR 116, 95% CI 42-252), Hodgkin's Disease (SMR 119, 95% CI 25-349), and non-Hodgkin's lymphoma (SMR 137, 95% CI 66-254). Mortality from soft tissue sarcoma (STS) was nonsignificantly elevated in the overall cohort, based upon 4 deaths which had been described in earlier reports (SMR 338, 95% CI 92-865). In a subcohort of 1520 workers with more than one year of exposure and more than 20 years of latency, STS mortality was significantly elevated (3 deaths, SMR 922, 95% CI 190-2695). However, only two of the deaths were confirmed as STS by review of tissue specimens. In the same subcohort, respiratory system cancer was significantly elevated (SMR 142, 95% CI 103-192). Mortality due to "all cancers combined" was significantly elevated both in the cohort (SMR 115, 95% CI 102-130) and in the subcohort (SMR 146, 95% CI 121-176). Mortality due to "all accidents" was significantly elevated in the cohort (SMR 128, 95% CI 104-154).

This study does not confirm the high relative risks for several rare cancers reported in previous studies. Conclusions about STS should be tempered due to the small number of deaths and to misclassification of cause of death on the death certificates of the workers and of the national comparison population. Excess mortality from "all cancers combined", respiratory cancer and soft tissue sarcoma, expecially in the subcohort with more than one year of exposure, is consistent with TCDD being a carcinogen. However, the study could not completely exclude a possible contribution from factors such as other occupational chemicals or smoking. Surveillance of this substantially exposed cohort of workers will be continued.

Key words: dioxins, NIOSH, occupation, epidemiology, cancer, cohort studies, serum TCDD levels, phenoxy herbicides, 2,4,5-trichlorophenoxyacetic acid, trichlorophenol.

I. INTRODUCTION

An etiologic association between cancer excess and exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), or the chemicals it contaminates, has been suggested by several epidemiologic studies. These cancers, which include soft-tissue sarcoma (STS), Hodgkin's Disease (HD), non-Hodgkin's lymphoma (NHL), stomach, liver, and nasal cancer, comprise the a priori hypotheses for the study described here. The relative risks reported in the positive studies are listed in Table 1. In other studies, statistically significant elevations were not found for STS (Smith, 1984; Wiklund, 1986); NHL (Pearce, 1987; Wiklund, 1987); HD (Persson, 1989); liver (Hardell, 1984); or nasal cancer (Olsen, 1984). The inconsistent epidemiologic evidence has been extensively reviewed (Fingerhut, 1986; Ad Hoc Panel, 1988; Johnson, 1989). Interpretation of the studies has been complicated by possible confounding from other occupational chemical exposures, and also by small population size and limited latency periods.

TCDD was shown to be a tumor promoter in animal test systems of rat liver carcinogenesis and hairless mouse skin tumorigenesis (Pitot, 1980; Poland, 1982). In two long-term feeding studies, TCDD produced statistically significant increases in liver tumors, prompting the a priori hypothesis tested in this study (Kociba, 1978; NTP, 1982). Histiocytic lymphomas, fibrosarcomas, and tumors of hard palate, nasal turbinates, tongue, lung, thyroid, and skin have also been found (Kociba, 1978; NTP, 1982; Rao, 1988; Poland, 1982). Although there is general agreement that TCDD is a promoter in animals, conflicting views exist regarding its role as a complete carcinogen (Poland, 1982; Shu, 1987; Rao, 1988).

TCDD is considered to be the most toxic of the 75 isomers of dioxin, based upon animal studies. In the United States, the unintentional formation of TCDD occurred primarily during the production of 2,4,5-trichlorophenol (TCP) when two sodium 2,4,5-trichlorophenate (NaTCP) molecules reacted with each other to form TCDD (Figure 1). TCDD was carried as a contaminant into the subsequent herbicide production processes (Esposito, 1980). The herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), which is synthesized from TCP, was widely used to kill brush on residential and commercial property in the United States, and it was also a constituent of defoliants, such as Agent Orange, used by the military in the Vietnam war.

Interest in occupational and environmental exposure to TCDD derives from its toxicity in animals, the variety of populations exposed to it, and its wide dispersion in the environment. Populations exposed to TCDD include chemical workers exposed during routine production and during occupational incidents with sudden unintentional releases, community residents exposed in Seveso, Italy, after an industrial explosion (Reggiani, 1978), community residents in Missouri, U.S.A., exposed to soil contaminated with industrial wastes (Kimbrough, 1977), and military personnel exposed to Agent Orange during the Vietnam war (Wolfe, 1990). The general public in industrialized countries has low level exposure to TCDD primarily through the food chain and also from general environmental exposures, including municipal incinerator emissions and bleached paper products (Amendola, 1989; Ryan, 1988; Vainio, 1989).

In 1978, researchers at the National Institute for Occupational Safety and Health (NIOSH) initiated an effort to identify the exposed workers at all U.S.

chemical plants which produced TCDD-contaminated products. As a result, the NIOSH Dioxin Registry was established. It includes demographic and work history information for all workers assigned to the production of products contaminated with certain isomers of dioxin. The workers in this study were employed at 12 U.S. plants. They have records of assignment to jobs in the production of TCP or its derivatives, which were contaminated with TCDD (Table 2). To evaluate the effect of exposure to TCDD-contaminated materials on mortality, particularly non-Hodgkin's lymphoma, soft tissue sarcoma, stomach cancer, liver cancer, Hodgkin's Disease, and nasal cancer, NIOSH researchers have conducted a retrospective cohort mortality study among these workers.

This report describes the first analysis of mortality in the cohort of U.S. workers exposed to TCDD. In this study, duration of assignment in the processes making the TCDD-contaminated products was used as a surrogate for cumulative exposure. A subsequent mortality analysis of this cohort will utilize an exposure matrix constructed from historic process descriptions, analytic measurements of TCDD and industrial hygiene data. Future analyses based upon data in the NIOSH Dioxin Registry will evaluate mortality among workers whose medical records show a history of chloracne and among workers exposed to pentachlorophenol. NIOSH researchers have also conducted a cross-sectional medical study of living workers from two plants and an unexposed comparison group, during which serum TCDD levels were measured for 253 workers (Sweeney, 1989).

II. METHODS:

Identification of Companies

Thirteen chemical facilities, located throughout the United States, synthesized TCP or its derivatives. These companies were identified by reviewing indices of commercial producers and by interview of producers. Twelve plants were included in the NIOSH Dioxin Registry (Table 2). One company owned plants 7 and 8, but the other plants were operated by separate companies. One small pesticide formulating company was excluded because it synthesized 2,4,5-T for an undetermined period, and it had no records to describe the process or to identify workers assigned to it.

At the 12 plants the products contaminated with TCDD were 2,4,5-trichlorophenol (TCP), its sodium salt, and several derivatives: the herbicides 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2-[2,4,5-trichlorophenoxy]propionic acid (Silvex) and 2-[2,4,5-trichlorophenoxy]ethyl-2,2-dichloropropionate (Erbon); the insecticide, o,o-dimethyl-o-[2,4,5-trichlorophenyl]phosphorothioate (Ronnel); and the bactericide/fungicide, 2,2-methylene-bis[3,4,6-trichlorophenol] (hexachlorophene) (Table 2).

Identification of Exposed Workers

Workers from the 12 plants were included in the cohort if: 1) upon review of company personnel records or payroll records, NIOSH staff identified a work record documenting an assignment to a production or maintenance job in a process in which substances contaminated with TCDD were made (N=5000); or 2) the worker did not have a work record, but was identified in a previously

published study based upon exposure to TCDD (N=172, from Plant 8) (Suskind, 1984). The second criterion was placed in the study protocol as an a priori stipulation because the quality of company records for identification of TCDD-exposed workers was unknown at the time.

Personnel records for these 172 workers did not show duration of assignment to TCDD-contaminated processes; therefore, they were included in the overall mortality analysis, but were excluded from analyses by duration of exposure. Also excluded from analyses using duration of exposure were 30 maintenance workers identified in a 1949 company memo as having worked for several days in the cleanup process following the 1949 trichlorophenol reactor explosion at Plant 8. Because company records did not list the specific assignments of maintenance workers, it was not possible to know the total time the workers might have worked in TCDD-contaminated production areas during this employment at the plant. Sixty-seven females are not included in this report. Among them there were 10 deaths, including one cancer death (lung cancer).

Exposure Assessment

At each plant a thorough review was made of the process operating conditions, the employee job duties, and analytical records of TCDD levels in industrial hygiene samples, process streams, products, and wastes. The review provided clear evidence of potential daily exposure to TCDD for the members of the cohort. Production at the various plants involved similar raw materials, process steps, and job duties. Detailed descriptions are contained in twelve site visit reports prepared by the authors (Fingerhut, 1983; Piacitelli, 1990; Marlow, 1990 a-e, 1989, 1987, 1986, 1984). A listing of the dioxin-contaminated products made at each plant is presented in Table 2. Of the eight sites which produced TCP, seven used the same raw materials (1,2,4,5-tetrachlorobenzene, methanol, and caustic), similar process steps, and job duties. Using similar processes, six sites produced 2,4,5-T acid from the raw materials of TCP, monochloroacetic acid and caustic. Eight of nine sites made 2,4,5-T esters by similar process steps from 2,4,5-T acid and alcohols. Two of these companies, as well as the ninth ester producer, also made 2,4,5-T esters by a second method, using TCP, caustic, and alcohol esters. Both of the hexachlorophene producers used purified TCP for production. Three plants also produced pentachlorophenol, which is contaminated with hexa-, hepta-, and octachlorinated dioxins and furans, but which in the United States did not contain TCDD (Esposito, 1980).

Occupational exposure to TCDD-contaminated processes was confirmed by measuring serum TCDD levels in 253 surviving cohort members from Plants 1 and 2. These workers were participants in a related NIOSH cross-sectional medical study, during which serum TCDD levels (lipid-adjusted) were measured (Sweeney, 1989). Both plants produced TCP and 2,4,5-T (Table 2). Methods for serum collection (Fingerhut, 1989), chemical analysis and lipid-adjustment (Patterson, 1987; Lapeza, 1986), calculation of half-life extrapolated levels, and preliminary results of the serum measurements (Sweeney, 1990) have been described previously.

Life Table Analysis

The vital status of the members of the cohort was determined as of December 31, 1987, from records of the Social Security Administration, Internal Revenue

Service, or the National Death Index (Stampfer, 1984). All death certificates were independently coded by two nosologists according to the rules of the revision of the International Classification of Disease in effect on the date of death. Discrepancies were resolved by a senior nosologist at the National Center for Health Statistics (NCHS). All nosologists were blind to the nature of the study and the outcomes of interest.

Lifetable analysis methods were used to evaluate mortality in the cohort (Waxweiler, 1983; Steenland, 1990). Person-years-at-risk (PYAR) at each plant were accumulated from the first date when records systematically documented assignment to a TCDD-contaminated process until the date of death or the study end date of December 31, 1987, whichever occurred first. Individuals whose vital status was unknown were assumed to be alive until the end of the study. In the lifetable analysis program, the PYAR were stratified by race, five-year age and calendar time periods, duration of exposure, and time-since-first-exposure (latency). Each death was counted in the stratum of longest duration and latency achieved by the cohort member. PYAR within each stratum were multiplied by the appropriate race-, age-, calendar time- and cause-specific mortality rates of the U.S. population to yield the number of expected deaths. Total expected deaths for a given cause were obtained by summing across strata. Standardized mortality ratios (SMRs) were computed for each stratum by dividing the observed number of deaths by the expected number and multiplying the ratio by 100. Two sided 95% confidence intervals (CI) were constructed for each cause-specific SMR using the Byar approximation for eight or more deaths and the Fisher exact method for fewer than eight deaths (Rothman, 1979).

The U.S. male population was the reference group. National rates were used as comparison rates for all plants because of their dispersion in ten states across the U.S. (Table 2). To estimate whether the use of local rates would have yielded different results, state and (separately) county mortality rates for all cancers combined among white males between 1970-1979 (EPA/NCI, 1983) were weighted by the person-year contribution of each of the 12 plants. The weighted average mortality rate for all cancers combined was compared with the U.S. rate for that time period. This estimation indicated that the use of state rates would have increased the expected number of all cancers combined by 1.8% and the use of county rates would have increased the expected number by 4%. Thus, the use of local rates would not have changed the results of the study substantially. Additionally the use of national rates avoids the problems associated with the use of county rates, including instability due to small numbers, the need for workers to reside in the counties where they worked (about which we have no information), and the possibility that some county rates were influenced by deaths at the study plants, because the study plants were major employers.

A modification was made of the existing NIOSH lifetable program to evaluate non-Hodgkin's lymphoma (NHL) (ICD 200, 202). In the NIOSH standard program, ICD 200 constitutes a death category, but ICD 202 is contained in a category with ICD 203. (Waxweiler, 1983). To evaluate mortality due to NHL, separate comparison rates were created for ICD 200 and 202 from computer tapes of the National Center for Health Statistics (NCHS). Because the ICD 200 and 202 rates on the NCHS tapes begin in 1960, the observed deaths were collected and the PYAR were calculated for NHL from 1960. No deaths due to NHL occurred before 1960 in the cohort.

Analyses by Duration of Exposure and Employment

"Duration of exposure" was defined as the number of years worked in processes contaminated with TCDD. The use of duration of exposure as a surrogate for cumulative exposure was based upon the high correlation of the logarithm of serum TCDD levels in a sample of workers from two plants with the logarithm of the number of years assigned to TCDD-contaminated processes (Pearson product moment correlation coefficient (r) = .72, p <.0001)(Figure 2), and the assumption that the production processes and the exposures to workers were similar in the 12 plants. However, there were inter-job and inter-plant differences in the extent of TCDD exposures. Consequently, for some members of the cohort the use of the length of time worked in TCDD-contaminated processes as a surrogate for cumulative TCDD exposure may have misclassified their exposure levels. In a subsequent report, a dioxin exposure matrix constructed from historic process descriptions, analytic measurements of TCDD and industrial hygiene data will be used to develop the relative ranking of workers exposed to TCDD.

Personnel records were used to calculate duration of exposure. These records were available for all years of production at all plants, with two exceptions: 1) The last year of exposure in hexachlorophene production at Plant 11 was not coded, because the records were obtained one year before production ended; and 2) At five plants systematic records were not available to identify some workers as exposed in the earliest years of production (Table 2). For those workers for whom job assignment records were available in the early years at these 5 plants, all periods of assignment to TCDD-contaminated processes were included in the analyses by duration of exposure. The PYAR for workers in these five plants began on the date when systematic company records identified individuals assigned to TCDD-contaminated processes.

Prior to analysis, duration of exposure was stratified into categories of less than 1 year, 1 - <5, 5 - <15, and 15+ years, in order to have several strata of duration longer than one year. For some analyses, the cohort was divided into two groups of less than and greater than one year of exposure. Mortality was also examined by latency in periods of 0 - <10, 10 - <20 and 20+ years, which reflect induction-latency periods that have been observed for occupational cancers (Cole, 1975).

To evaluate cancer mortality among a subcohort of workers who had experienced substantial exposure and adequate latency for expression of some cancers, a "high exposure" subcohort was identified. One year was chosen as a cutpoint for the high exposure subcohort, because 100% of the workers with more than one year of TCDD exposure in the subgroup of 253 surviving cohort members from plants 1 and 2 had serum TCDD levels higher than the unexposed referent group mean of 7 parts per trillion (ppt) (Figure 2). A cut point of twenty years of latency was chosen because that time period permits development of some cancers. PYAR for this subcohort were accumulated from the date that the individuals attained both 20 years of latency and one year of exposure. All plants contributed person-years to the subgroup of workers with more than 20 years of latency, except plant 2, which began production of relevant products less than twenty years before the study end date.

Most of the plants were large U.S. chemical manufacturing sites, which produced thousands of chemicals. Complete documentation of all exposures

experienced by each worker was not possible. Therefore, a separate measure called "duration of employment" was defined as the total time that each worker was employed at the study plant. Because of the long total employment at the plants, the analyses by duration of employment were stratified into periods of less than 5 years, 5 - <10, 10 - <15, 15 - <20, 20 - <25, 25 - <30, and 30+ years. For these analyses latency was defined as time since first employment. PYAR began on the same date used in the analyses of duration of exposure. The Spearman correlation coefficient (r_s) was used to evaluate the correlation between duration of exposure and duration of employment (Snedecor, 1972).

When the SMRs showed an apparent trend with exposure and employment and the observed numbers of deaths were sufficiently large, internal comparisons were conducted using directly standardized rate ratios (SRRs) and tests for trend (Rothman, 1986). For the SRRs, the cause-specific mortality rate in each of the longer duration categories was compared with the rate in the shortest category. The SRRs were adjusted for the effects of age, race and calendar time by using standardized weights (the total person-years for the cohort) to weight the rates in each duration category. The use of SRRs avoided the potential bias which could occur in the comparison of SMRs across duration categories if the categories had differences in age, race or calendar time of exposure.

Pathologic Confirmation of Cause of Death on Death Certificates

To verify the causes of death for cancers of a priori interest, pathology reports were requested. However, the underlying causes of death as coded from the death certificates were not changed for any of the lifetable analyses.

To identify and describe all deaths from soft tissue sarcomas which might have occurred in the worker cohort, all death certificates were reviewed on which a malignancy was identified as an underlying or contributory cause, or as a significant condition. For malignancies without a specified primary site noted on the death certificate, and for malignancies in organs where soft tissue sarcomas comprise 2% or more of tumors at diagnosis (NCI, 1981), hospital and pathology reports were obtained and reviewed to identify the histology of the tumors. The sites included stomach, small intestine, retroperitoneum, bones and joints, eye and orbit, parts of the respiratory and male genital systems, and cancers with unknown primary sites. There are no comparison rates for this type of information; the intent was to describe all soft tissue sarcomas in the worker cohort.

Smoking Adjustment

Although smoking data were not available for the entire cohort, lifetime smoking histories were obtained in 1987 by interview of 223 living workers from Plants 1 and 2 who were 20 years or older in 1965 and who participated in a related NIOSH medical study of TCDD-exposed workers (Sweeney, 1989). The sample comprised 5.4% of the total cohort. Smoking status in 1965 was estimated for the entire cohort from the smoking histories of the sample of living workers. The year 1965 was selected because it was the approximate mid-point of the observation period for the cohort mortality study, and because age-stratified smoking status was available for the national population in the 1965 Health Promotion Survey (NCHS, 1981). To estimate the

contribution from smoking, an adjustment was made of the SMR for mortality from cancers of trachea, bronchus and lung (Axelson, 1978). The procedure is described in detail in Steenland (1989). Smoking data were restricted to cigarette smoking, and nonsmokers were defined as those who had never smoked more than 100 cigarettes. The adjustment assumed relative risks for lung cancer of 1.0 for nonsmokers, 4.7 for former smokers and 10.9 for smokers (Kahn, 1966). A similar adjustment was made for the subcohort of workers with over one year of exposure and more than 20 years of latency. This adjustment was based upon a subsample of 87 workers who were in the high exposure subcohort and in the smoking survey.

III. RESULTS

Description of the Cohort

The cohort of 5172 male workers, contributed 116,748 person-years. A total of 5000 workers (97%) met the first entry criterion of assignment to TCDD-contaminated processes. An additional 172 workers (3%) from Plant 8 met only the second entry criterion: identified as exposed in a published study (Suskind, 1984).

The distribution of the cohort by plant, exposure, vital status, race, duration of exposure, duration of employment, latency, and time since last exposure is presented in Tables 2 and 3. Through December 31, 1987, the vital status of 98% of the cohort was successfully traced: 4043 (78%) workers were alive, and 1052 (20%) workers were deceased. Only 77 (2%) individuals were lost-to-followup. Death certificates were obtained for 99% of all deaths. Of the 5172 males in the cohort, 4590 (89%) were white, 385 (7%) were races other than white, and 197 (4%) were of unknown race. For approximately 60% of the workers, 20 years or more had elapsed between first exposure and the date of death or the study end date of December 31, 1987. For 55% of the workers, 20 years or more had elapsed between last exposure and the study end date (Table 3). The mean age of the overall cohort as of December 31, 1987, was 56 years. Among the workers with over 20 years of latency, the mean ages at the study end date were 56 and 63, respectively, for those with under and over one year of exposure to TCDD-contaminated processes.

Mortality Experience of the TCDD Cohort

Overall Mortality

The results from the lifetable analysis for all causes of death are presented in Table 4. Overall mortality for all males from all causes was similar to mortality in the U.S. comparison rates (1052 deaths, SMR 99, 95% CI 93-105). Heart disease mortality (393 deaths, SMR 96, 95% CI 87-106) and deaths from diseases of the respiratory system (59 deaths, SMR 94, 95% CI 72-122) were also similar to national rates. Significant deficits were observed for deaths from diseases of the circulatory system (67 deaths, SMR 77, 95% CI 60-98), primarily due to cerebrovascular diseases (ICD 430-438) (43 deaths, SMR 75, 95% CI 54-101), and for deaths from diseases of the digestive system (38 deaths, SMR 69, 95% CI 49-96), primarily due to cirrhosis (ICD 571) (22 deaths, SMR 72, 95% CI 45-108). There was also a significant deficit for deaths from alcoholism and personality disorders (2 deaths, SMR 23, 95% CI 3-87). The deficit in circulatory disease mortality may be a reflection of

the "healthy worker" effect: that worker cohorts die at lower rates than the general populations, particularly of causes other than cancer (Fox, 1976). The deficits for cirrhosis and alcoholism may indicate that this cohort consumed less alcohol than the general population. Deficits may also have occurred simply by chance, because of the multiple comparisons which were made between the cohort and the U.S. population.

Deaths from injury in the category of "all accidents" were significantly elevated in the cohort (106 deaths, SMR 128, 95% CI 104-154) (Table 4). A significant excess was observed from mortality in the subcategory "accidental poisoning" (9 deaths, SMR 222, 95% CI 101-421). Five of the deaths occurred at work at the study plants. On the death certificate for one of these deaths, the agent was identifed as monochloroacetic acid, a chemical which is used in 2,4,5-T processes. A significant excess was also found from mortality in the category of "other accidents", which includes fatal injury from causes other than falls, unintentional poisonings and transportation incidents (41 deaths, SMR 182, 95% CI 131-248). Ten of the 12 plants in the TCDD cohort had elevated mortality due to "other accidents". Notations on the 41 death certificates indicated that 20 deaths occurred while the individual was at work. Of these, 12 deaths occurred at study plants, including four in TCP processes: three in 1959 due to a TCP reactor explosion at one plant, and one death in 1963 at another plant due to severe burns from a spill of hot TCP.

It was of interest to evaluate whether the work-related deaths from fatal injury were in excess. Although population-based or chemical industry comparison data were not readily available, the proportion of deaths in this category which could be expected to be work-related was estimated using population-based data from two sources. The number of work-related deaths (1980-85) within the category of "other accidents" was available for U.S. males aged 20 to 64 from the NIOSH National Traumatic Occupational Fatalities database (NIOSH, 1989), and the total number of deaths of U.S. males aged 20-64 for 1980-85 was abstracted from a National Center for Health Statistics (NCHS) table of "Deaths for 282 Selected Causes, 1979-86" (NCHS, 1988). The NSHS dataset included unemployed men. Based upon these data, 23% of the deaths among U.S. males which occurred between 1980 and 1985 in the category "other accidents" were expected to be work related, while 49% of deaths in the cohort were observed to be work related. This suggests that the workers in this study were at increased risk of fatal injury on the job, although a review of the death certificates showed that the jobs were not necessarily in TCDD-contaminated processes or even at the study plants. Because no data are available for earlier periods, it is not known whether the results for work-related deaths would have been different if comparison data for 1940-1987 had been used.

Cancer Mortality

Table 5 presents the SMRs for cancer deaths experienced by the entire cohort(N=5172). The table also shows the SMRs for 3036 workers with more than 20 years of latency, who are divided into two subcohorts with less than or greater than one year of exposure to TCDD-contaminated processes. The subcohort of 1520 workers with greater than one year of exposure and more than 20 years of latency is referred to as the "high exposure" subcohort.

Cancers of A Priori Interest

The term soft tissue sarcoma describes a group of rare malignant neoplasms arising from supportive tissue other than bone (Suit, 1978). Analysis of mortality due to soft tissue sarcoma (STS) is restricted to those soft tissue sarcomas coded as underlying cause of death from death certificates into the ICD category, "malignant neoplasms of connective and other soft tissue". In the overall cohort, mortality from STS was nonsignificantly elevated (4 deaths, SMR 338, 95% CI 92-865). The deaths occurred at 2 of the 12 plants, with a statistically significant elevation at Plant 8 (2 deaths, SMR 1516, 95% CI 183-5474) (Table 6). Only two of the four deaths (cases 1 and 4, Table 7) were confirmed as STS upon pathologic review of tissue specimens (Fingerhut, 1984). In the high exposure subcohort, mortality from STS was significantly elevated (3 deaths, SMR 922, 95% CI 190-2695) (Table 5).

Two other deaths in the cohort (cases 5 and 6) were attributed to soft tissue sarcoma by hospital records, and one (case 5) was confirmed by a review of a tissue specimen. These two deaths did not contribute to STS mortality in the lifetable analysis, because their deaths were coded from death certificates into other ICD categories. Cases 5 and 6 were in the group of 202 workers from Plant 8 excluded from analyses involving duration of exposure because their work records did not indicate this information. Case 5 had been identified by the company for inclusion in a previous medical study (Suskind, 1984) because he had "intermittent" exposure to TCDD, but the company record did not cite dates of exposure. Case 6 was identified in a 1949 company memo as a maintenance worker who worked 2 days in cleanup following a trichlorophenol reactor explosion. Since records of maintenance workers do not specify the departments where they worked, it was not possible to assess whether he had additional exposure to TCDD during his employment.

Five of the STS deaths from this cohort had been described previously (Fingerhut, 1984). The sixth STS death was identified during the review of hospital records in the current study (case 6, Table 7).

SMRs for the other cancers of a priori interest were elevated but not statistically significant in the cohort: cancer of the stomach (10 deaths, SMR 103, 95% CI 50-190); cancer of the liver, biliary passages, and gallbladder (6 deaths, SMR 116, 95% CI 42-252); Hodgkin's Disease (3 deaths, SMR 119, 95% CI 25-349); and non-Hodgkin's lymphoma (10 deaths, SMR 137, 95% CI 66-254) (Table 5). No deaths from nasal cancer occurred in the cohort, with approximately one expected. In the high exposure subcohort, the SMRs were elevated but not statistically significant for stomach cancer (4 deaths, SMR 138, 95% CI 38-353), and Hodgkin's Disease (1 death, SMR 276, 95% CI 7-1534) and were lower than expected for NHL (2 deaths, SMR 93, 95% CI 11-337) and for cancer of the liver, biliary passages, and gallbladder (1 death, SMR 59, 95% CI 1-327).

For the 29 deaths in the cohort which were due to cancers of a priori interest, the underlying cause of death was confirmed for all 22 death certificates for which hospital records were available. Records could not be obtained for 4 of the 10 stomach cancer deaths, 1 of the 3 Hodgkin's Disease deaths and 2 of the 10 NHL deaths. Table 6 shows the plant-specific results for mortality due to cancers of a priori interest.

A Posteriori Findings:

A statistically significant excess of mortality in the category of all cancers combined was observed in the entire cohort (265 deaths, SMR 115, 95% CI 102-130) (Table 5). Mortality due to all cancers combined in the high exposure subcohort was significantly elevated (114 deaths, SMR 146, 95% CI 121-176). Mortality for all cancers combined was elevated at nine of the 12 plants in the cohort, including a statistically significant excess at Plant 10 (30 deaths, SMR 181, 95% CI 122-259) (Table 6).

Although mortality for many cancer categories was nonsignificantly elevated in the cohort, the only statistically significant elevation occurred in the category "cancer of unspecified sites" (ICD 194-199) (24 deaths, SMR 162, 95% CI 104-241) (Table 5). This category includes rare cancers not included in a specific NIOSH lifetable cancer category and deaths for which no primary cancer site was listed on the death certificate. Hospital records were obtained for 23 (96%) of these deaths. Five deaths were due to lung cancer, and single deaths were due to cancer of the femur, breast, liver, pharynx, prostate, neck, adrenal gland, and mesothelioma of peritoneum. The primary site was not specified on the hospital records for ten deaths (including carcinomatosis listed on the death certificate for Case 5, Table 7). The record for one death could not be obtained. In the high exposure subcohort, deaths coded in the category "unspecified sites" and those coded as soft tissue sarcomas were primarily responsible for the significant elevation in the larger category of "other sites" (ICD 170-173, 190-199) (18 deaths, SMR 201, 95% CI 118-316) (Table 5).

The cohort experienced a nonsignificant elevation in mortality from cancers of the trachea, bronchus and lung (ICD 162) (89 deaths, SMR 111, 95% CI 89-137) (Table 5). The SMR was 106 for white males (81 deaths, 95% CI 84-132), and 201 for males other than white (8 deaths, 95% CI 87-397). Mortality from this cause was elevated in 9 plants, including a significant excess at Plant 10 (13 deaths, SMR 214, 95% CI 114-366) (Table 6). In the high exposure subcohort, mortality from cancer of the trachea, bronchus and lung (ICD 162) was nonsignificantly elevated (40 deaths, SMR 139, 95% CI 99-189). Of the 11 plants contributing to the high exposure subcohort, 4 had significantly elevated mortality and 4 had nonsignificantly elevated mortality from this cause. Mortality from cancers of the respiratory system (ICD 160-165) was significantly elevated (43 deaths, SMR 142, 95% CI 103-192) in the high exposure cohort.

Information on smoking prevalence in the sample of 223 workers from two plants was used to conduct a limited adjustment of the results for lung cancer mortality in the cohort. The sample included 24.7% nonsmokers, 11.2% former smokers, and 64.1% smokers in 1965. The age-adjusted smoking status of the U.S. male population in 1965 included 24.3% nonsmokers, 17.6% former smokers and 58.1% current smokers. Adjustment for smoking status in the cohort, based upon the data from two plants, increased the number of expected lung cancers by 5%, thus reducing the SMR for cancer of the trachea, bronchus, and lung in the cohort from 111 to 105 (95% CI 85-130).

A limited smoking adjustment was also applied to lung cancer mortality in the high exposure cohort. The smoking status of the sample of 87 workers with more than 1 year of exposure and more than 20 years of latency was 27.6%

nonsmokers, 13.8% former smokers and 58.6% smokers. The age-adjusted smoking status of U.S. males in 1965 included 23.5% nonsmokers, 19.4% former smokers and 57.1% smokers. The smoking adjustment increased the expected number of lung cancers in the high exposure subcohort by 1%, thus reducing the SMR from 139 to 137 (95% CI 98-187).

Analyses by Duration of Exposure and Employment

On average, the entire cohort worked about five times longer in all chemical operations at the plants (mean 12.6 years) than in TCDD-contaminated processes (mean 2.7 years) (Table 2). Workers with less than one year of exposure to TCDD-contaminated processes had a mean exposure of 0.3 year but a mean employment of 8.3 years. Workers with more than one year of exposure had a mean exposure of 5.8 years but a mean total employment or 16.5 years. Among workers with over 20 years of latency, those with less than one year of exposure to TCDD had a mean exposure of 0.3 years and a mean employment of 10.7 years. Those with over one year of exposure (the high exposure subcohort) had a mean of 6.8 years of exposure to TCDD and a mean of 19.2 years of total employment at the plants (Table 5).

Table 8 shows the distribution of deaths for the a priori cancers of interest by latency and duration of exposure to TCDD-contaminated processes. The number of observed deaths for each of the cancers of a priori interest was too small to conduct meaningful tests for trend.

Table 9 shows the distribution of mortality due to all cancers combined and to cancers of the trachea, bronchus and lung with increasing duration of exposure to TCDD-contaminated products. Although the SRRs were elevated in the strata of longer duration for both outcomes, significant linear trends were not found for either outcome with increasing exposure. Mortality increased with increasing latency for both outcomes. To examine whether the elevated mortality in the longer duration stratum was significantly different from mortality in the stratum of under one year of exposure, the cohort was also divided into two strata of under and over one year of exposure to TCDD-contaminated substances. For workers with more than one year of exposure, a statistically significant SRR of 127 was observed for all cancers combined (95% CI 100-160); for the same workers, the SRR was 135 (95% CI 79-229) for cancers of trachea, bronchus and lung.

Table 10 shows the distribution of mortality for the same outcomes with increasing duration of total employment at the plants. Significant linear trends were not observed for either outcome with increasing employment, although SRRs were elevated in several strata of employment longer than 20 years. Mortality increased with increasing latency for both outcomes. When the cohort was divided into two strata with under and over 5 years of total employment at the plants, the SRR for the over 5 year stratum was 94 (95% CI 74-120) for all cancers combined and 127 (95% CI 75-215) for cancers of trachea, bronchus and lung.

Serum Levels of 2,3,7,8-TCDD

The mean serum TCDD level (lipid-adjusted) in the sample of 253 workers from Plants 1 and 2 was 233 parts per trillion (ppt) (median 76 ppt) ranging from 2 to 3400 ppt (Figure 2). A mean of 7 ppt (median 6 ppt) was found in the

comparison group of 79 nonexposed persons, whose levels ranged from less than the limit of detection to 20 ppt, a range found in other nonexposed populations (Patterson, 1989). Workers with less than one year of exposure to TCDD-contaminated products had a mean serum TCDD level of 69 ppt (median 24 ppt). The mean for those exposed longer than one year was 418 ppt (median 231 ppt). In the latter group, 119 workers (100%), had levels higher than the mean level of 7 ppt observed in the unexposed comparison population (Figure 2). Among the 176 workers in the sample who had at least 20 years of latency, those with under one year of exposure (N=81) had a mean serum TCDD level of 78 ppt, and those with over one year of exposure (N=95) had a mean of 462 ppt. Production of TCDD-contaminated substances ended at Plant 1, when it closed down in 1969 and at Plant 2 by 1972, when the building was decontaminated (Table 2). Therefore, the serum TCDD levels reflect occupational exposures which occurred 15 to 37 years earlier. Figure 2 also shows that there is a high correlation between the logarithm of serum TCDD levels and the logarithm of years exposed to TCDD-contaminated processes ($r=.72$, $p<.0001$).

When the 253 serum TCDD levels were extrapolated to the dates when the individuals were last employed in TCDD-contaminated jobs, the mean level was 2000 ppt, with a range up to 32,000 ppt, assuming a 7.1 year half-life for TCDD elimination (Sweeney, 1990; Pirkle, 1989). A high correlation ($r=.70$, $p<.0001$) was found between logarithm of the half-life extrapolated serum TCDD levels and the logarithm of duration of exposure. Among the workers in the sample who had over 20 years of latency, the mean of the half-life extrapolated levels for the subgroup with less than one year of exposure was 640 ppt; for those with more than one year of exposure the mean was 3600 ppt.

Discussion:

Only a few populations have had sufficient exposure, long latency, and adequate size to provide an appropriate study population for assessing the relationship between exposure to TCDD-contaminated substances and long-term health effects. For these reasons, NIOSH researchers studied the mortality experience of essentially all U.S. production workers assigned to the manufacture of trichlorophenol and its derivatives, which are contaminated with TCDD.

TCDD has acquired the reputation of a potent carcinogen. This study, although limited in size to detect excesses of rare cancers, demonstrates little adverse effect from cancers associated with TCDD in prior human studies. The exception is the excess mortality from soft tissue sarcoma. The difficulties in evaluating soft tissue sarcoma in a cohort mortality study have been described (Fingerhut, 1984). These include variability in pathologic diagnosis and misclassification of cause of death on death certificates and in hospital records. Consequently, interpretation of the excess STS mortality in the cohort study is limited by the small number of deaths and by recognition that misclassification of cause of death has occurred on the death certificates of the workers (Table 7) and is also present in the U.S. comparison population (Percy, 1981). Continued surveillance of the cohort is needed to allow for the appearance of additional deaths, if an association is to be definitively established between soft tissue sarcoma and exposure to TCDD-contaminated substances.

It should be noted that an additional, previously unidentified STS death from Plant 8 occurred in a group of 139 individuals with chloracne, who were excluded from this cohort because they did not meet the entry criteria. The procedure for identification of the chloracne cases from medical records was described in O'Malley (1990). The death was identified as STS by review of the tissue specimen; however, STS was not coded as the underlying cause of death on the death certificate. The 139 workers will be included in a future mortality analysis, which will include about 700 additional workers with chloracne from this cohort.

Several case-control studies found statistically significant fourfold excesses of non-Hodgkin's lymphoma in persons reporting exposure to phenoxy herbicides (Hardell, 1981; Woods, 1987; Persson, 1989) (Table 1), although excesses were not found in other studies (Pearce, 1987; Wiklund, 1987). Based upon their longer duration of exposure, the production workers in the current study probably had greater exposure to TCDD-contaminated substances than the workers in the case control studies. The probable higher exposure in this cohort and the lower risk for NHL found in this cohort (SMR 137, 95% CI 66-254) (Table 5) do not provide evidence to support the fourfold elevated risks observed in the case control studies (Table 1).

Mortality in this cohort was not significantly elevated for several other cancers of a priori interest (liver, stomach, and Hodgkin's Disease). The results found in this cohort study do not provide evidence for increased mortality from these cancers, although the wide confidence intervals reflect the small numbers of deaths and the consequent limited statistical power of the study for these rare cancers (Table 5). An excess of liver cancer has been found in animals exposed to TCDD (Kociba, 1978; NTP, 1982), but a case control study of liver cancer did not find an association with phenoxy herbicides or chlorophenols (Hardell, 1984). Stomach cancer was of a priori interest based upon 3 deaths (SMR 470) in a German cohort (Theiss, 1982). No additional deaths from stomach cancer were reported in a recent update of the cohort (Zober, 1990), which found an SMR for stomach cancer of 297 (3 deaths, 90% CI 81-768). Elevated mortality was reported for Hodgkin's Disease in one case-control study (Hardell, 1983) but not in another (Persson, 1989). In the cohort study described here only one death due to Hodgkin's Disease occurred in the high exposure subcohort, precluding a meaningful interpretation.

Mortality from cancer of trachea, bronchus and lung was elevated nonsignificantly in the high exposure cohort (SMR 139, 95% CI 99-189). Respiratory cancer was significantly elevated in the high exposure cohort (SMR 142, 95% CI 103-192), but not in the subcohort with 20 years of latency but less than one year of exposure (SMR=103, 95% CI 62-161) (Table 5).

Lung cancer rates in blue-collar groups are known to be somewhat elevated compared to the general U.S. population due to increased cigarette smoking of blue-collar populations (Siemiatycki, 1988). However, the excess lung cancer in the high exposure subcohort is unlikely to be due to confounding by smoking, for several reasons. (1) Mortality from non-malignant respiratory disease (ICD 470-478, 490-519), which is often associated with smoking, was lower than expected (15 deaths, SMR 96, 95% CI 54-158) in the high exposure subcohort. (2) Among all exposed workers with 20 years of latency, who presumably shared similar smoking habits, the excess of respiratory cancer was confined to the high exposure subcohort (Table 5). (3) A limited adjustment

of the risk for lung cancer (Axelson, 1978; Steenland, 1984), based upon the smoking prevalence of surviving workers at two of the twelve plants in this study, did not substantially change the results in the high exposure subcohort. (4) Siemiatycki et al. (1988) have shown that confounding by smoking between a blue-collar population and the U.S. population usually does not account for an excess risk of greater than 10-20%, based on empirical evidence from other studies. Although confounding from smoking is unlikely to explain the respiratory cancer excess in the high exposure subcohort, it remains possible that the excess is due to confounding by occupational exposures other than TCDD. For example, there may have been a contribution to the lung cancer mortality in the cohort from asbestos, because there were two deaths due to mesotheliomas.

An unexpected finding was the statistically significant excess mortality for all cancers combined. The observed excess mortality from cancer is consistent with a carcinogenic effect of TCDD. This view is supported by the following observations: (1) Mortality was significantly elevated for all cancers combined in the entire cohort (SMR 115, 95% CI 102-130), was more pronounced in the high exposure subcohort (SMR 146, 95% CI 121-176), and was elevated at nine of 12 plants. (2) In an internal comparison of workers with more than one year of exposure to those with under one year of exposure, a significantly elevated SRR was observed for all cancers combined (SRR 127, 95% CI 100-160). (3) Excess mortality due to all cancers combined remains after excluding mortality due to smoking related cancers. With mortality from cancer of trachea, bronchus and lung excluded, the SMR for all remaining cancers combined was 117 (95% CI 101-136) in the overall cohort and 150 (95% CI 118-189) in the high exposure subcohort. Results were similar when mortality was removed due to other cancers sometimes associated with smoking (bladder, larynx, esophagus, kidney and pancreas). In the overall cohort the SMR was 113 (95% CI 95-134) and in the high exposure cohort the SMR was 150 (95% CI 113-194) This suggests that the elevated risk for all cancers combined is not explained by smoking or by excess mortality due to cancers associated with smoking. (4) Significantly elevated SMRs for all cancers combined are unusual in occupational studies of chemical workers. (5) The generation of tumors in multiple organs in animals exposed to TCDD (Kociba, 1978; NTP, 1982; Rao, 1988) and the demonstration that TCDD promoted tumors in two organs (Poland, 1982; Pitot, 1980) suggest that it is biologically plausible that TCDD might produce tumors in multiple sites in humans. (6) Similar results were observed in a recently updated study of German workers exposed to TCDD following a TCP reactor accident in 1953 (Zober, 1990). A subgroup with chloracne, which was used as a surrogate for exposure, and at least 20 years of latency had an SMR of 201 (90% CI 122-315) for all cancers combined, based on 14 deaths. In that subgroup, cancer of trachea, bronchus and lung (5 deaths, SMR 252, 90% CI 99-530) and cancer of colon and rectum (3 deaths, SMR 344, 90% CI 94-888) were nonsignificantly elevated. Excluding three previous studies of U.S. production cohorts exposed to TCDD, because those workers are included in the current study (Zack, 1980; Zack, 1983; Ott, 1987), the German cohort is the only other industrial cohort with substantial TCDD exposure and with long latency in which mortality has been examined (Zober, 1990; Theiss, 1982).

Several observations argue against an association between TCDD and an elevation of mortality due to "all cancers" combined: (1) A statistically significant linear trend of increasing mortality was not observed in the overall cohort with increasing duration of exposure to TCDD-contaminated

products (Table 9). However, this might be explained by misclassification of exposure of some workers by the use of duration as a surrogate for cumulative TCDD exposure. Additionally, a significant dose-response relationship with increasing exposure is generally viewed as fairly strong evidence for an association when present in a study, but as fairly weak evidence against an association when absent (Monson, 1990). (2) This study does not directly assess the effect of exposure solely to TCDD. Workers also had concurrent exposure to substances containing TCDD, e.g., chlorophenols and phenoxy herbicides. Additionally, workers were exposed to numerous other chemicals encountered while employed at the plants. (3) The significant excess in the overall cohort for all cancers combined could be due to chance, or to non-occupational factors, such as smoking or might be explained by major regional differences in cancer rates which were not accounted for in the use of national rates. However, these explanations are less plausible for the subcohort with long exposure and long latency, for which the SMR for all cancers combined is 146 (95% CI 121-176).

The study described here has several strengths: (1) The cohort is fairly large, consisting of 5172 male workers and 116,748 person-years of observation. (2) It includes essentially all U.S. production plants which made chemicals contaminated with TCDD. (3) Vital status was ascertained for 98% of the cohort. (4) Ninety seven percent of the cohort had work records documenting assignment to TCDD-contaminated processes and 3% had been identified as exposed in a previously published study, producing a cohort with clearly defined exposure. (5) Based upon a review of chemical processes, the measurement of serum TCDD levels in workers at two plants, and the presence of chloracne in medical records of 13% of the cohort, the population has had substantial TCDD exposure. (6) Exposure started sufficiently long ago that 60% of the cohort had at least 20 years of latency for the expression of cancers.

This study is limited in several ways: (1) The study, although relatively large, did not have adequate size to definitively evaluate several rare cancers of interest. Table 1 shows the relative risks which were detectable in the overall cohort with 80% power at an alpha level of 5% (Beaumont, 1981). Because all U.S. production workers with records of assignment to TCDD-contaminated processes have been included in this study, no improvement in power can be achieved at this time. With time, person years of observation will accrue and additional deaths will occur, and future studies of the cohort will be more powerful. Despite these limitations, the confidence intervals for some of the rare cancers indicate that the risks in this worker cohort are lower than might have been expected, based upon risks reported in previous studies. (2) The workers were exposed to phenoxy herbicides and chlorophenols contaminated with TCDD, and not to TCDD alone. A subsequent report will address the question of whether TCDD or the products themselves may be etiologically associated with the outcomes studied. Several studies have suggested that some risks may be associated with phenoxy herbicides which do not contain TCDD (Eriksson, 1981). (3) The members of the high exposure subcohort worked an average of 6.8 years in TCDD-contaminated processes and a longer time (mean 19.2 years) in total employment at the study plants. Additionally, some workers may have been also employed in other chemical plants. Consequently, other chemical exposures to which the workers were exposed may confound this analysis. For example, the occurrence of 2 cases of mesothelioma suggest some asbestos exposure. (4) There was limited

information about smoking status in 1965, which was obtained by interview in 1987 from surviving workers employed in only two plants, and which was applied by inference to the remaining ten plants. (5) In the exposure response analyses, an internal population with exposure less than one year was used as the base for comparison, rather than a non-exposed population. This could lead to a bias toward the null, and the risk ratios in the longer duration groups could be underestimated. (6) The high serum TCDD levels in living workers from two plants and the high correlation of this serum level with duration of exposure (Figure 2) are assumed to be similar in the overall cohort. (7) The exposure levels of some workers relative to others may have been misclassified, because the use of years worked in the TCDD-contaminated processes as a surrogate for cumulative TCDD exposure does not fully address differences between plants or even among the exposed jobs at a single plant. It assumes that a day of exposure to TCDD-contaminated substances is equivalent for all jobs at each of the 12 plants and for all years of production. Additionally, since some plants had longer production periods than others (Table 2), some plants may contribute more heavily to the longer exposure categories. An exposure matrix, based upon a review of job duties and process operations is being developed to estimate relative ratings of exposure to TCDD. The exposure response analyses for the cohort will be conducted using this matrix in a subsequent report.

The results of this occupational study have implications for other populations exposed to TCDD. Based upon measurements of serum TCDD levels, most other populations have experienced TCDD exposure that is substantially lower than that reported here (Patterson, 1989). Under the assumption that in humans TCDD has a 7.1 year half-life (Pirkle, 1989), the 253 exposed workers in the study with serum TCDD levels would have had a mean serum TCDD level of 1900 ppt, with levels as high as 32,000 ppt, on the dates when they left their TCDD-exposed jobs.

Recent analyses of a few stored blood specimens indicate that some residents of Seveso, Italy, had serum TCDD levels in the same high range of the workers in this cohort. The residents of Seveso were exposed in 1976 following a trichlorophenol reactor explosion which contaminated the surrounding residential areas. Several residents of Seveso had levels up to 27,000 ppt TCDD in blood drawn months after the incident (Mocarelli, 1988). A mortality study of the residents of Seveso, Italy has not demonstrated a cancer excess, although the follow-up interval in the study provided a latency period of only ten years (Bertazzi, 1989).

The U.S. Air Force Ranch Hand group, which carried out aerial sprays of Agent Orange in Vietnam, was reported to have a mean serum TCDD level of 49 ppt, with a range up to 423 ppt (Patterson, 1989; Wolfe, 1988). The individual with the serum TCDD level of 423 ppt would have had a level of 1530 ppt at the time of his last Agent Orange exposure (Patterson, 1989). A mortality study of this group has not demonstrated a cancer excess, although the study was of limited size and latency (Michalek, 1990). Two studies of other Vietnam veterans who handled Agent Orange also reported elevated TCDD levels. Kahn (1988) reported a mean serum TCDD level of 46 ppt in 10 veterans, with a range of 1-180 ppt, and Gross (1984) reported levels of 23 and 99 ppt in two veterans. Among Army ground troops, who were not known to have handled Agent Orange but were thought to have received exposure from aerial Agent Orange sprays, the Centers for Disease Control reported a mean serum TCDD level of 4 ppt and a range up to 45 ppt in 646 veterans (CDC, 1988).

Among individuals from the general populations residing in industrial countries, studies have usually found serum and adipose TCDD levels under 20 ppt, with a mean of 8 ppt (Patterson, 1989). It is assumed that the general population is exposed to TCDD primarily through the food chain, and also from incinerator fly ash, paper products, and other environmental situations (Amendola, 1989; Ryan 1989; Vainio, 1989).

CONCLUSION:

Mortality was evaluated in a large group of chemical workers with exposure to phenoxy herbicides and chlorophenols contaminated with TCDD and with sufficient latency for the expression of some occupationally related cancers. Because the exposure of this cohort was substantially higher than experienced by most non-occupational populations, the estimates of effect in this study may provide an upper level of risk to be anticipated in humans.

For several types of cancer previously associated with TCDD, excesses were not observed. An exception is soft tissue sarcoma, for which a nine-fold increase was seen among workers with more than one year of exposure and over 20 years of latency. However, interpretation of the elevated SMR is limited because of the small number of cases, and because of misclassification of this cause of death on the death certificates of the workers and of the national comparison population. Continued surveillance of the cohort may provide a more firm estimate of risk.

A 15% excess of all cancers combined was observed in the overall cohort. The subcohort with more than one year of exposure and over 20 years of latency had a 46% excess of all cancers combined and a 42% excess of cancers of the respiratory tract. Although the study could not completely exclude the possible contribution of other occupational carcinogens or smoking, the excess mortality, especially in the subcohort with more than one year of exposure, is consistent with TCDD being a carcinogen.

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Table 1. Statistically Significant (p<.05) Relative Risks Reported In Studies Used to Generate a Priori Hypotheses (Relative Risks Calculated as Detectable by the Current NIOSH Study with .80 Power, Alpha=.05 Are Provided for Reference).

Study Type	Reference	Exposure[a]	STS	HD	NHL	Stomach Cancer	Nasal Cancer	Liver Cancer
Case Control	Hardell, 1979	PH	5.3					
		CL	6.6					
Case Control	Eriksson, 1990	2,4,5-T	2.9					
		CL	3.9					
Case Control	Eriksson, 1981	PH	6.8					
		CL	3.3					
Case Control	Hardell, 1988	PH	2.4					
Case Control	Hardell, 1983	PH		5.0				
		CL		6.5				
Case Control	Hardell, 1981				4.8			
Case Control	Woods, 1987	PH[b]			4.8			
Case Control	Persson, 1989	PH			4.9			
Cohort	Axelson, 1980	PH				6.1		
Cohort	Theiss, 1982	TCP				4.7		
Case Control	Hardell, 1982	PH					2.1	
		CL					6.5	
Animal Studies	Kociba, 1978							d
	NTP, 1982							e
Relative Risks Detectable[c] in NIOSH Mortality Study with Power = .80, Alpha = .05.		TCP & PH	4.6	3.2	2.2	2.0	5.0	2.4

[a] PH, phenoxy herbicides; CL, chlorophenols; TCP, 2,4,5-trichlorophenol; 2,4,5-T, 2,4,5-trichlorophenoxy acetic acid; STS, soft tissue sarcoma; HD, Hodgkin's Disease; NHL, non-Hodgkin's lymphoma.

[b] Forest applicators

[c] Power calculation in Beaumont, 1981.

[d] Rats

[e] Mice, Rats

Table 2. Dates of Production and Distribution of Workers Exposed to TCDD-Contaminated Products at Twelve Plants.

Plant	Location	Years of Production	PYAR Start Date[b]	Type of Product[a]					Number of Exposed Workers			Years Exposed to TCDD-Contaminated Processes		Total Years Employed at Study Plants	
				TCP	2,4,5-T acid	2,4,5-T ester	PCP	HCP	TCDD Only	TCDD & HCDD	TOTAL	Mean	Median	Mean	Median
1	Newark, NJ	1951 - 1969	1951[c]	X	X	X			443	0	443	3.0	1.0	3.3	1.1
2	Verona, MO	1968 - 1972	1968	X		X		X	97	0	97	0.7	0.4	8.6	6.8
3	Jacksonville, AR	1958 - 1979	1961	X	X	X			695	0	695	1.6	0.4	2.3	0.4
4	Kansas City, KS	1957 - 1978	1957	X	X	X			360	0	360	2.0	0.5	5.2	1.4
5	Portland, OR	1961 - 1962	1961			X			114	0	114	0.7	0.5	6.8	2.2
6	St. Louis, MO	1949 - 1970	1957	X	X	X	X		93	44	137	2.9	1.0	3.2	1.2
7	Sauget, IL	1960 - 1969	1960			X	X		54	42	96	0.7	0.1	16.1	15.7
8	Nitro, WV	1948 - 1969	1948[d]	X	X				452	0	452	1.8	0.2	22.5	25.3
9	Midland, MI	1942 - 1982	1942	X	X	X	X		1411	681	2092	3.0	0.9	17.5	15.3
10	Niagara Falls, NY	1949 - 1973	1949	X					265	0	265	3.7	1.5	19.2	22.5
11	Clifton, NJ	1947 - 1984	1957					X	163	0	163	3.3	0.7	12.4	10.7
12	Ambler, PA	1949 - 1978	1953			X			258	0	258	6.2	2.9	10.2	5.5
Total									4405	767	5172	2.7	0.7	12.6	9.4

[a] Terms: TCP, 2,4,5-trichlorophenol and/or sodium 2,4,5-trichlorophenol; 2,4,5-T, Includes 2,4,5-trichlorophenoxyacetic acid and Silvex, Ronnel or Erbon and their formulations; PCP, pentachlorophenol and/or sodium pentachlorophenol; HCP, hexachlorophene; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; HCDD, hexa-, hepta- and octachlorinated dibenzo-p-dioxins.

[b] Year when person-years-at-risk (PYAR) started. At Plants 3, 6, 11 and 12, records did not permit identification of all TCDD exposed workers during earliest years of production.

[c] Job assignment records were first available in August, 1951, although exposure was coded from February, 1951 when the TCP process started.

[d] Excludes 202 workers missing duration of assignment to TCDD-contaminated processes on work records: 30 maintenance workers assigned PYAR start dates of 8-22-49 because they were identified as exposed in a company memo of that date, and 172 workers assigned PYAR start dates of 6-1-79 because they were identified as exposed for a medical study conducted on that date.

Table 3. Vital Status, Demographic and Employment Characteristics of the Study Population.

Variable	Persons Number	Percent
Vital Status[a]		
Alive	4043	78
Deceased	1052	20
Unknown	77	2
Total	5172	100
Deaths[a]		
White males	985	94
Nonwhite males	67	6
Total	1052	100
Death certificates obtained	1037	99
Race		
White Male	4590	89
Nonwhite Male	385	7
Unknown	197	4
Total	5172	100
Duration of Exposure[b]		
Under 1 year	2697	54
1 to <5	1427	29
5 to <15	639	13
15 years+	207	4
Total	4970	100
Duration of Employment[b]		
Under 5 years	2125	43
5 to <10	501	10
10 to <15	605	12
15 to <20	403	8
20 to <25	391	8
25 to <30	415	8
30+	530	11
Total	4970	100
Years Since First Exposure (Latency)[b]		
Under 10	271	6
10 to <20	1663	33
20+	3036	61
Total	4970	100
Years Since Last Exposure[b]		
Under 10	453	9
10 to <20	1789	36
20+	2728	55
Total	4970	100

[a] As of December 31, 1987.

[b] Excludes 202 workers missing duration of assignment to TCDD-contaminated processes on work records.

Table 4. Mortality From All Causes.

Cause	ICD Codes (9th Revision)	Obs[a]	SMR	95%CI
All deaths		1052	99	93-105
All cancers	140-208	265	115*	102-130
Benign and Unspec. Nature Neoplasms	210-239	2	61	7-223
Tuberculosis	010-018	1	22	1-123
Diabetes Mellitus	250	16	108	61-174
Blood and Blood Forming Diseases	280-289	2	72	9-262
Alcoholism and Mental Disorders	290-319	2	23*	3-87
Nervous System Diseases	320-337, 340-389	6	55	20-120
Diseases of the Heart	390-398, 402-404, 410-414, 420-429	393	96	87-106
Diseases of the Circulatory System	401, 403, 405, 415-417, 430-438, 440-459	67	77*	60-98
Respiratory System Diseases	460-466, 470-478 480-487, 490-519	59	94	72-122
Influenza	487	2	210	25-757
Pneumonia	480-486	14	67	36-112
Other Acute Infections	460-466	1	246	6-1367
Non-malignant Resp. Disease	470-478, 490-519	42	104	75-140
Emphysema	492	7	60	24-124
Asthma	493	1	58	1-323
Other Resp. Diseases	470-478, 490-491 494-519	34	139	96-195
Digestive System Diseases	520-537, 540-543, 550-553, 555-558, 560, 562-570, 572-579	38	70*	49-96

* p<.05, ** p<.01

[a] Obs, observed deaths; SMR, standardized mortality ratio; 95% CI, 95% confidence intervals.

Table 4. (Continued) Mortality From All Causes.

Cause	ICD Codes (9th Revision)	Obs[a]	SMR	95%CI
Genitourinary System Diseases	580-608, 610-611, 614-629	10	79	38-145
Musculoskeletal Diseases	710-739	1	53	1-295
Symptoms and Ill-defined Conditions	780-796, 798-799	6	44*	16-95
Accidents	E800-848, E850-888, E890-949	106	128*	104-154
Transportation	E800-848, E929.0-929.1	51	107	80-141
Poisoning	E850-869, E929.2	9	222*	101-421
Falls	E880-888, E929.3	4	53	14-135
Other Accidents	E890-928, E929.4-929.9	41	182**	131-248
Med. Complications	E870-879, E930-949	1	71	2-396
Suicide & Homicide	E950-E978	44	98	71-131
All other causes	Residual ICD Categories	19	119	72-185
Certificates Not Obtained		15		

* $p<.05$, ** $p<.01$

[a] Obs, observed deaths; SMR, standardized mortality ratio; 95% CI, 95% confidence intervals.

Table 5. Cancer Mortality In The Entire Cohort And In Workers With More Than 20 Years of Latency.

CAUSE	ICD[b] Codes (9th Revision)	Entire Cohort (N=5172) Mean Yrs. Exposed 2.7 Mean Yrs. Employed 12.6 Obs	Exp	SMR[c]	95%CI	Subcohorts with Over 20 Years Latency (N=3036)[a] Under 1 Year Exposure (N=1516; PY=12,299) Mean Yrs. Exposed 0.3 Mean Yrs. Employed 10.7 Obs	Exp	SMR	95%CI	Over 1 Year Exposure (N=1520; PY=15,136) Mean Yrs. Exposed 6.8 Mean Yrs. Employed 19.2 Obs	Exp	SMR	95%CI
All Cancers	140-208	265	229.9	115*	102-130	48	46.8	102	76-136	114	78.0	146*	121-176
Buccal and Pharynx	140-149	5	7.0	70	23-166	2	1.4	145	18-524	2	2.2	90	11-325
Pharynx	146-149	3	3.4	88	18-259	2	0.7	298	36-1080	0	1.2	0	--
Other Parts	142-145	2	1.9	105	13-379	0	0.4	0	--	2	0.6	329	40-1190
Digestive Organs	150-159	67	59.7	112	87-143	13	11.8	111	59-189	28	20.1	140	93-202
Esophagus	150	9	5.9	152	70-290	2	1.2	165	20-602	4	2.0	200	55-513
Stomach	151	10	9.7	103	50-190	3	1.7	178	37-521	4	2.9	138	38-353
Small Intestine & Colon	152-153	25	20.4	122	79-181	5	4.3	117	38-274	13	7.3	178	95-304
Rectum	154	5	5.6	89	29-209	1	1.0	100	03-557	2	1.7	115	14-415
Liver and Biliary	155, 156	6	5.2	116	42-252	1	1.0	100	03-557	1	1.7	59	01-327
Pancreas	157	10	11.9	84	40-155	1	2.4	41	01-232	4	4.0	100	27-253
Peritoneum and Unspec. digestive organs	158, 159	2	1.1	184	22-666	0	0.2	0	--	0	0.4	0	--
Respiratory System	160-165	96	84.5	113	92-139	19	18.4	103	62-161	43	30.2	142*	103-192
Larynx	161	7	3.3	211	84-434	2	0.7	297	36-1074	3	1.1	268	55-783
Trachea, Bronchus & Lung	162	89	80.1	111	89-137	17	17.5	96	56-155	40	28.8	139	99-189
Male Genital Organs	185-187	17	15.3	111	65-177	2	3.2	63	08-229	9	6.0	149	68-283
Prostate	185	17	13.9	122	71-195	2	3.0	67	08-237	9	5.9	152	70-290

* p<.05, ** p<.01

a Excludes 202 workers missing duration of assignment to TCDD-contaminated processes on work records.

b Abbreviations: ICD, International Classification of Disease; Obs, observed deaths; Exp, expected deaths; SMR, standardized mortality ratio; 95% CI, 95% confidence intervals; PY, person-years.

c SMR = Obs/Exp X 100. Slight differences in numbers are due to rounding.

Table 5. (Continued) Cancer Mortality In the Entire Cohort and in Workers With More Than 20 Years of Latency.

CAUSE	ICD[b] Codes (9th Revision)	Entire Cohort (N=5172) Mean Yrs. Exposed 2.7 Mean Yrs. Employed 12.6 Obs	Exp	SMR	95%CI	Subcohorts with Over 20 Years Latency (N=3036)[a] Under 1 Year Exposure (N=1516; PY=12,299) Mean Yrs. Exposed 0.3 Mean Yrs. Employed 10.7 Obs	Exp	SMR	95%CI	Over 1 Year Exposure (N=1520; PY=15,136) Mean Yrs. Exposed 6.8 Mean Yrs. Employed 19.2 Obs	Exp	SMR	95%CI
Urinary Organs	188-189	17	11.4	148	86-238	3	2.4	128	26-373	6	4.0	149	55-324
Kidney	189.0-189.2	8	5.7	140	60-275	3	1.2	253	52-742	2	1.9	106	13-384
Bladder & Other	188, 189.3-189.9	9	5.7	157	72-298	0	1.2	0	--	4	2.2	186	51-476
Lymphatic & Haematopoietic Tissue	200-208	24	22.1	109	70-162	4	3.9	102	28-260	8	6.4	125	54-247
Hodgkin's Disease	201	3	2.5	119	25-349	0	0.2	0	--	1	.4	276	07-1534
Non-Hodgkin's Lymphoma[d]	200,202	10	7.3	137	66-254	2	1.5	135	16-488	2	2.1	93	11-337
Lymphosarcoma & Reticulosarcoma[d]	200	5	3.5	142	46-332	0	0.6	0	--	1	0.9	107	3-594
Other Lymphatic[d]	202	5	3.7	133	43-313	2	0.9	215	26-779	1	1.4	71	2-385
Multiple Myeloma[d]	203	5	3.0	164	53-385	0	0.6	0	--	3	1.1	262	54-766
Leukemia and Aleukemia	204-208	6	8.9	67	24-146	2	1.6	126	15-457	2	2.6	77	09-277
Other Sites	170-173, 190-199	39	29.6	131	94-180	5	5.8	87	28-202	18	9.0	201*	118-316
Skin	172-173	4	4.9	82	22-211	0	0.9	0	--	2	1.3	155	19-559
Brain & Nervous System	191, 192	5	7.3	68	22-160	0	1.3	0	--	2	1.9	106	13-384
Bone	170	2	0.9	227	27-819	0	0.1	0	--	1	0.2	521	13-2903
Connective Tissue & Soft Tissue	171	4	1.2	338	92-865	0	0.2	0	--	3	0.3	922*	190-2695
Unspecified Sites	194-199	24	14.8	162*	104-241	5	3.1	159	52-372	10	5.1	196	94-361

* $p<.05$ **$p<.01$

a Excludes 202 workers missing duration of assignment to TCDD-contaminated processes on work records.

b ICD, International Classification of Disease; Obs, observed deaths; Exp, expected deaths; SMR, standardized mortality ratio; 95% CI, 95% confidence intervals; PY, person-years.

c SMR = Obs/Exp X 100. Slight differences in numbers are due to rounding.

d Person-years at risk and observed deaths are computed from 1960 for these categories. No deaths occurred before 1960.

Table 6. Observed Deaths and SMRs by Plant for Cancers of A Priori Interest, Lung Cancer, All Cancers Combined and "Other Accidents".

Plant	STS		Non-Hodgkin's Lymphoma		Hodgkin's Disease		Stomach		Liver		Lung		All Cancers		Other Accidents		Accidental Poisoning	
	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
1	0	0	1	120	1	368	0	0	1	156	7	72	32	115	4	164	2	507
2	0	0	0	0	0	0	0	0	0	0	1	155	2	111	2	747	0	0
3	0	0	0	0	0	0	0	0	1	384	4	107	10	87	4	193	1	182
4	0	0	1	323	0	0	0	0	0	0	3	101	7	75	4	305	0	0
5	0	0	0	0	0	0	0	0	0	0	3	166	7	141	1	202	0	0
6	0	0	1	556	0	0	0	0	0	0	2	104	7	129	2	320	0	0
7	0	0	0	0	0	0	0	0	0	0	3	238	3	86	0	0	0	0
8	2	1516*	0	0	0	0	0	0	1	151	15	144	35	118	3	160	1	377
9	2	384	7	217	2	171	7	160	1	44	28	78	105	102	16	162	1	59
10	0	0	0	0	0	0	2	297	1	277	13	214*	30	181**	3	206	3	1395**
11	0	0	0	0	0	0	0	0	1	791	5	239	11	193	0	0	0	0
12	0	0	0	0	0	0	1	193	0	0	5	125	16	141	2	173	1	476
TOTAL	4	338	10	137	3	119	10	103	6	116	89	111	265	115*	41	182**	9	222**

* p<.05 ** p<.01

[a] PYAR, person-years at risk; STS, soft tissue sarcoma; Obs, observed deaths; SMR, standardized mortality ratio.

Table 7. Description of Exposure, Mortality, and Histology for Soft Tissue Sarcoma Deaths Among Workers in the Cohort.

Case[a]	Plant	Years Employed	Exposure[b]	Year First Exposed[b]	Years Exposed[b]	Year of Death	Latency[b,d] (Years)	Death Certificate	Hospital Records	Tissue Review[e]
1	8	1946-1978	TCP,[c] 2,4,5-T	1950	8.8	1978	28	MFH[c]	MFH	MFH
2	8	1946-1972	TCP, 2,4,5-T	1948	7.1	1972	24	Liposarcoma	Liposarcoma	Carcinoma, poorly differentiated[f]
3	9	1950-1975	TCP	1963	1.2	1975	12	Fibrosarcoma	Fibrosarcoma	Renal Carcinoma[f]
4	9	1951-1982	TCP	1951	14.9	1983	32	MFH	MFH	MFH
5[g]	8	1943-1975	TCP or 2,4,5-T	Intermittent[b]	?	1980	?	Carcinomatosis[f]	Myxoid Neurogenic Sarcoma	Leiomyosarcoma
6[g]	8	1941-1964	TCP	1949	?	1965	16	Metastatic[f] Osteosarcoma	Fibrosarcoma	Not available

a Cases 1-5 correspond to those described earlier by Fingerhut et al, 1984. Other cases from that paper did not have records of exposure to TCDD and are not included in this cohort study.

b Information differs slightly from earlier report (Fingerhut, 1984) due to review of additional records. Few details about exposure were available for Cases 5 and 6. A company record indicated Case 5 had intermittent exposure, but no dates were recorded.

c Terms: TCP, 2,4,5-trichlorophenol; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; MFH, malignant fibrous histiocytoma.

d Time from first exposure to death.

e Conducted at the Armed Forces Institute of Pathology.

f Not a soft tissue sarcoma

g Death was not attributed to STS in the lifetable analysis.

Table 8. Mortality by Latency and Duration of Exposure to TCDD-Contaminated Processes for Cancers of a Priori Interest.[a]

Cause	Latency Period (Years)	Duration of TCDD Exposure (years) <1 Obs	<1 SMR	1-<5 Obs	1-<5 SMR	5-<15 Obs	5-<15 SMR	>15 Obs	>15 SMR	Overall Obs	Overall SMR
Stomach	0 - 10	0	0	0	0	1	363	0	0	1	59
	10 - 20	1	92	1	119	0	0	0	0	2	72
	Over 20	3	178	2	156	2	193	0	0	7	152
	Total	4	113	3	107	3	145	0	0	10	110
Non-Hodgkin's Lymphoma	0 - 10	1	188	0	0	0	0	0	0	1	106
	10 - 20	2	212	0	0	2	452	1	1488	5	241
	Over 20	2	135	2	183	0	0	0	0	4	105
	Total	5	169	2	98	2	152	1	188	10	146
Hodgkin's Disease	0 - 10	0	0	0	0	0	0	0	0	0	0
	10 - 20	0	0	1	410	0	0	1	3968	2	239
	Over 20	0	0	0	0	1	853	0	0	1	165
	Total	0	0	1	133	1	261	1	1035	3	122
STS	0 - 10	0	0	0	0	0	0	0	0	0	0
	10 - 20	0	0	1	962	0	0	0	0	1	284
	Over 20	0	0	0	0	3	2795**	0	0	3	548*
	Total	0	0	1	296	3	1520**	0	0	4	355
Liver and Biliary	0 - 10	1	287	0	0	0	0	0	0	1	134
	10 - 20	1	191	1	235	0	0	0	0	2	141
	Over 20	1	101	1	131	0	0	0	0	2	74
	Total	3	157	2	136	0	0	0	0	5	103

* $p<.05$ ** $p<.01$

[a] 202 workers were excluded, because their records lacked information with which to calculate duration of exposure to TCDD-contaminated processes. Therefore, the SMRs for each cause and the observed deaths for liver are slightly different from those on Table 5.

Table 9. Mortality from All Cancers Combined and from Cancer of Trachea, Bronchus and Lung by Latency and Duration of Exposure to TCDD-Contaminated Processes[a].

Cause	Latency Period (Years)	Duration of Exposure to TCDD-Contaminated Processes (Years)										Trend Test (p)
		<1		1-<5		5-<15		>15		Overall		
		Obs[b]	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	
All Cancers	0 - 10	10	68	8	71	3	71	0	0	21	70	
	10 - 20	28	109	16	87	18	122	7	340*	69	113	
	Over 20	48	102	59	165**	37	138	18	115	162	129**	
	Total (SMR)	86	98	83	127*	58	126	25	141	252	116*	
	(SRR)		100		127		123		129			(.3)
Trachea, Bronchus & Lung	0 - 10	3	77	3	95	1	79	0	0	7	84	
	10 - 20	6	69	5	79	9	180	1	137	21	101	
	Over 20	17	96	17	126	14	146	9	156	57	123	
	Total (SMR)	26	86	25	109	24	151	10	154	85	112	
	(SRR)		100		109		166		136			(.2)

* p<.05, ** p<.01

[a] Excludes 202 workers missing duration of assignment to TCDD-contaminated processes on work records. Therefore, the observed deaths and SMRs for lung and all cancers are slightly different from those on Table 5.

[b] Obs, observed deaths; SMR, standardized mortality ratio; SRR, standardized rate ratio.

Table 10. Mortality from All Cancers Combined and from Cancer of Trachea, Bronchus and Lung by Latency and Duration of Total Employment at the Study Plants[a].

Cause	Latency Period (Years)	Duration of Total Employment at Study Plants (Years)																Trend Test (p)
		<5		5-<10		10-<15		15-<20		20-<25		25-<30		30+		TOTAL		
		Obs[b]	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	
All Cancers	0 - 10	10	85	1	18	0	0	0	0	0	0	0	0	0	0	11	64	
	10 - 20	21	114	5	126	12	103	8	80	0	0	0	0	0	0	46	105	
	Over 20	40	138	15	140	6	70	15	98	34	134	31	116	54	135*	195	125**	
	Total (SMR)	71	120	21	104	18	89	23	91	34	134	31	116	54	135*	252	116	
	(SRR)		100		99		61		76		128		84		115			(.9)
Trachea	0 - 10	3	103	1	74	0	0	0	0	0	0	0	0	0	0	4	94	
Bronchus	10 - 20	5	82	0	0	5	139	4	122	0	0	0	0	0	0	14	98	
& Lung	Over 20	11	102	2	51	2	65	3	55	12	133	18	180*	19	126	67	117	
	Total (SMR)	19	96	3	46	7	105	7	81	12	133	18	180*	19	126	85	112	
	(SRR)		100		65		91		89		171		147		98			(.6)

* <.05 **<.01

[a] Excludes 202 workers missing duration of assignment to TCDD-contaminated processes on work records.

[b] Obs, observed deaths; SMR, standardized mortality ratio; SRR, standardized rate ratio.

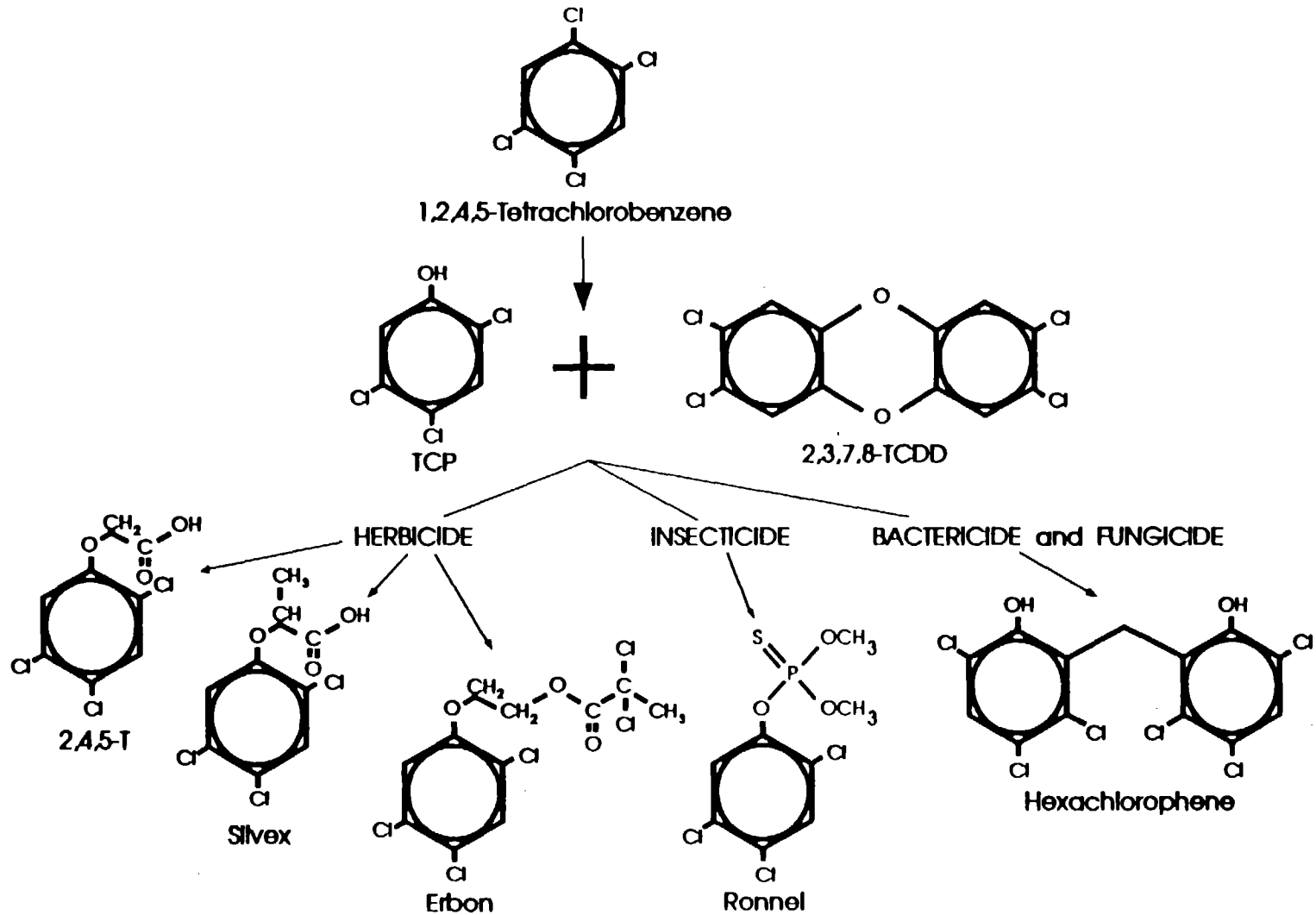

Figure 1. Chemical Derivatives of 2,4,5-Trichlorophenol Contaminated with 2,3,7,8-TCDD

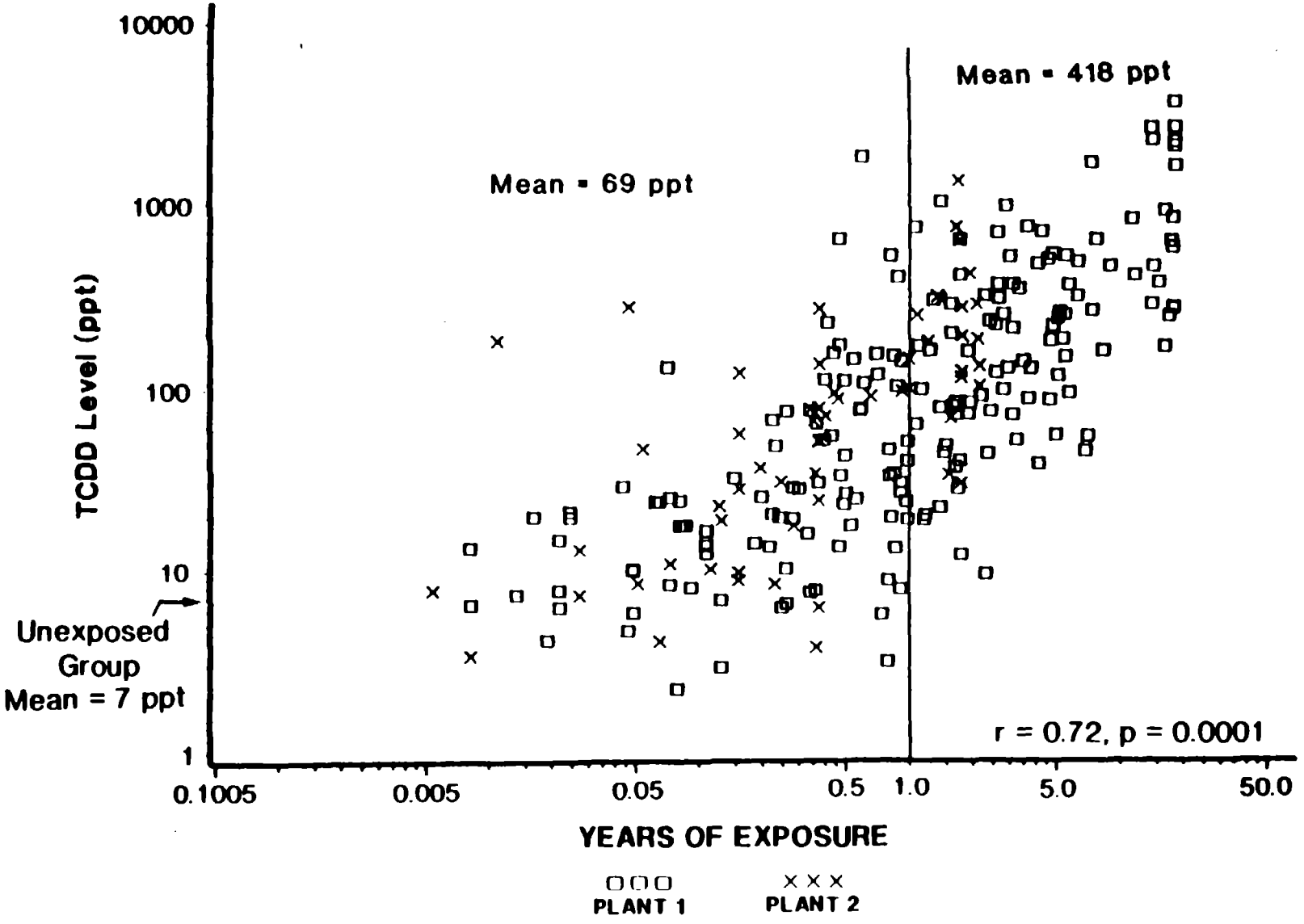

Figure 2. Lipid Adjusted Serum Levels of 2,3,7,8-TCDD (ppt) by Years of Exposure