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Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Ladies and Gentlemen:

Subject: Notice in Accordance with Section 8(e) -
Epidemiological Study of 2,3,7,8-TCDD

BASF Corporation is not a manufacturer, processor or distributor in commerce of 2,3,7,8-TCDD. Nevertheless, in order to accomodate EPA procedures, BASF Corporation is submitting a copy of a report on a retrospective cohort morbidity study of 2,3,7,8-TCDD exposed workers. These workers were exposed as a result of an accident in a BASF Aktiengesellschaft trichlorophenol production facility in Germany in the 1950s.

This study is based on diagnoses recorded on health insurance claims. The report indicates that several individual disease categories were elevated among TCDD exposed individuals. These included diseases of the skin and subcutaneous tissue (ICD: 680-709), infectious and parasitic diseases (ICD: 001-139), disorders of the peripheral nervous system and sense organs (ICD: 350-389, 781) and diseases of the thyroid (ICD: 240-246). Benign and unspecified neoplasms were marginally increased in the chloracne subgroup and in the high TCDD group. Chronic liver disease was also marginally increased in the high TCDD group.

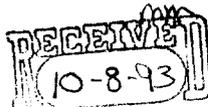
A copy of the full report is included with this submission. Please note that neither this letter nor the report includes any confidential business information.

Very truly yours,

BASF CORPORATION

Edward J. Kerfoot, Ph.D.
Director, Toxicology and
Product Regulations

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MORBIDITY FOLLOW-UP STUDY OF BASF EMPLOYEES EXPOSED TO
2,3,7,8-TCDD AFTER A 1953 CHEMICAL REACTOR INCIDENT

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ABSTRACT

Objective: To compare the long-term morbidity experience of individuals exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) with that of nonexposed referents.

Design: A retrospective cohort morbidity study.

Subjects and Setting: 158 men first exposed to TCDD between Nov. 17, 1953 and Nov. 16, 1954 subdivided according to chloracne status and back-calculated TCDD concentration, and 161 referents.

Main Outcome Measures: Cause-specific illness absence or hospitalization episodes between Nov. 17, 1953 and Dec. 31, 1989. Emphasis was placed on evaluation of skin, liver, kidney, endocrine, metabolic, gastrointestinal, peripheral nervous system (PNS), and immune system disorders.

Results: On an ever/never basis, Diseases of the Thyroid and Appendicitis were diagnosed more frequently in the TCDD-exposed group; these diseases were not differentially distributed by chloracne status, but occurred relatively more frequently among individuals with back-calculated TCDD concentrations above 1000 ppt (high TCDD group). It should be cautioned that Appendicitis had not been a hypothesized outcome of interest. An 18 percent increase in total illness episodes was seen ($p = 0.002$) with higher rates associated with both severity of chloracne and higher TCDD concentration within severity subgroup. Individual disease categories elevated among TCDD-exposed employees included Infectious and Parasitic Diseases [primarily ill-defined intestinal infections], Disorders of the PNS and Sense Organs, Upper Respiratory Tract Infections, Other Skin Diseases, Injury, and Poisonings by Nonmedicinals. Several of these elevations correlated with chloracne status and infectious disease episodes were associated with higher TCDD concentration within chloracne subgroup. Elevations in Mental Disorders were associated with severity of chloracne, but not with TCDD concentration. Benign and Unspecified Neoplasms were marginally increased in the severe chloracne subgroup and in the high TCDD group and Chronic Liver Disease was marginally increased in the high TCDD group. Findings relative to ulcer occurrence, chronic lung disease, and kidney and metabolic disorders including diabetes were largely unremarkable.

Conclusions: For a variety of conditions, illness episodes tracked over a 35 year period were seen to occur more frequently among TCDD-exposed workers compared to referents. Increased episodes for several illness categories were also associated with either or both chloracne severity and back-calculated TCDD concentration. Our results are derived from insurance data;

hence, it is possible that heightened awareness and personal health concerns led to increased utilization of medical services among exposed employees versus referents. The findings based on TCDD exposure response analyses should be less subject to this potential bias.

On 17 November 1953 within several months of its initial start-up, a BASF trichlorophenol manufacturing unit experienced an uncontrolled decomposition reaction. Fumes escaping from the affected autoclave, condensed on surfaces throughout the immediate work area of the enclosed facility. During initial clean-up efforts, workers were apparently exposed to surface condensates and many developed ~~acne~~ acne responses as well as other symptoms and signs of toxicity. The putative agent responsible for these toxic responses was not determined until 1957. In that year, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was chemically identified as a by-product of trichlorophenol production operations and was shown to be a potent inducer of chloracne.¹

Clinical accounts of the immediate health consequences of the autoclave accident were available as early as 1954.^{2 3} A series of follow-up studies has since been conducted to evaluate the clinical and mortality experience of all employees who were believed to have been exposed to TCDD-contaminated materials.^{4 5 6} The eventual study population included employees who assisted in demolition of the autoclave portion of the production unit in 1968-69 as well as employees assigned to prior assessment and clean-up activities. Although other materials were produced by the unit after the accident, trichlorophenol production was not resumed.

147 2.5.94. 700 11.10.94

Beginning in 1988, TCDD concentrations were determined in blood lipids for 138 surviving members of the accident cohort. Using these data and detailed descriptions of the circumstances of each employee's exposure, a regression model was developed to estimate the contribution of various exposure factors (time period, work activity, duration and location of work, and use of protective equipment) to overall TCDD burden. Cumulative TCDD concentrations, back-calculated to the time of exposure, have now been estimated for all cohort members based on the regression parameters and assuming a TCDD half-life of seven years.^{7 8} Concentrations of penta- through octa-chlorinated dioxins were not elevated in the accident cohort relative to external controls.⁷

Prior studies indicate that TCDD-exposed individuals may experience a wide range of symptoms during the days and weeks immediately following exposure. The frequency and severity of symptoms are generally reported to decline with time. Symptom histories and clinical evaluations indicate that the liver, kidneys, peripheral and central nervous systems, immune system and skin may all be targets of injury. Complaints have included headache, dizziness, nausea, severe muscle pain, fatigue, nervousness and irritability, dyspnea, decreased libido, and intolerance to cold.⁹ Other than a persistent acne, there has

been little evidence of lasting or progressive noncarcinogenic effects following exposure. Presently, there is limited evidence supporting a carcinogenic role for TCDD in humans. Since TCDD is eliminated very slowly, there may be target tissue exposure long after the initial contact with TCDD and, consequently, reason to follow the long-term morbidity experience of even workers with short-term TCDD exposure.

New health legislation enacted in Germany during 1990 has enabled insurers to share anonymous medical diagnosis data with occupational medical departments provided that these data cannot be linked back to specific individuals. Use of this data resource offers several advantages from an epidemiologic perspective. First, it can provide morbidity information over a very long observation period - even back to the 1950s. Secondly, the medical diagnoses are generally the result of independent evaluations and are arrived at without knowledge as to the degree of exposure, thus minimizing the potential for observation bias. There are inherent disadvantages as well. Because of confidentiality considerations, it is not possible to confirm diagnoses through an independent validation process. Secondly, the availability of data is restricted to individuals insured through the company health insurance fund, the Betriebskrankenkasse (BKK). Data are accessible for retirees, but not for contract workers or individuals who have left the

company for other jobs. For example, information was not initially available for some exposed contract workers. Fortunately, most of these men later became company employees and BKK members. Diagnoses are provided for illness absences from work and for all hospitalizations, but may not be required for less debilitating conditions such as headaches, dizziness and sleep disturbances. However, the experience of this cohort relative to such conditions has already been presented as case reports by Goldmann in 1972.⁴ Finally, again because of confidentiality considerations, potential confounding factors such as age can only be addressed through prior selection of comparable referents.

The current study objectives were to describe the long-term morbidity experience of TCDD-exposed individuals and to determine if exposed workers had experienced and are continuing to experience higher rates of morbidity than comparable nonexposed workers. A corollary objective was to evaluate the usefulness of medical insurance data as a means of assessing possible work-related health effects. The observation period was from November 17, 1953 through December 31, 1989 and the indices of morbidity were the coded diagnoses and conditions reported in the medical insurance claims of workers.

POPULATION AND METHODS

Study Group

The study population was selected as a subgroup of the 247 TCDD-exposed individuals reported in the latest cohort mortality study⁶ and seven additional employees subsequently identified as having been exposed to TCDD⁷. To permit analysis of morbidity trends by interval since exposure and, at the same time, protect participant anonymity, it was decided to restrict the study population to the 175 cohort members whose first TCDD contact occurred within one year of the accident (target population). This decision was also made because the highest potential for TCDD exposure undoubtedly occurred during the early time period after the accident. The remaining individuals had experienced potential exposures to residual TCDD at some time between late 1954 and early 1969.

A detailed exposure assessment completed after initiation of this study confirmed the likelihood of higher exposures among members of the target population.⁷ In the total cohort there were 79 individuals with a model-based TCDD blood lipid concentration exceeding 1,000+ parts-per-trillion (ppt) back-calculated to the time of exposure. Of these, 74 were exposed to TCDD within one year of the accident, and hence, belonged to the target population. The final study group consisted of 158 men after exclusion of four women employees because of anonymity

considerations and 13 male employees who were never BKK members. Most of these excluded employees held managerial or professional positions and were from the no chloracne subgroup. Only one of these 17 individuals had a back-calculated TCDD level above 1,000 ppt, thus leaving 73 men in the final study group with TCDD concentrations above 1,000 ppt.

$$52 + 45 = 97$$

The study group was divided into three subgroups based on chloracne status as determined from a prior review of occupational medical records.⁶ Subgroup I consisted of 52 individuals whose chloracne was classified as extensive or severe. Subgroup II consisted of 61 individuals, 50 with moderate chloracne and 11 with a diagnosis of "erythema" at the time of exposure but no chloracne. Finally, subgroup III comprised 45 men with no evidence of chloracne or "erythema". These groups were similar in size and large enough to protect the anonymity of individuals. The numbers of individuals with back-calculated TCDD values above 1,000 ppt in each subgroup were 33, 29 and 11, respectively.

Referents

The referent group was selected from a computerized data base, which included all persons who worked at this manufacturing complex at any time after 1970 as well as retirees from before

1970. In 1989, the complex employed more than 50,000 individuals. These individuals were presumed not to have experienced above background TCDD exposures. Very limited sampling of six non-exposed individuals at the site revealed TCDD blood lipid concentrations averaging 3.3 ppt consistent with background TCDD concentrations in Germany.⁷ In addition, 42 samples of long-term employees not included in this study, but who were assigned duties in and around the affected building between 1960 and 1968, averaged only 5.1 ppt. Initial identification of potential referents was made using a master computer file sorted by birth date. The referent pool was also restricted to persons with German or German-French surnames since this was true for all study group members. Finally, employees from managerial or professional ranks were excluded, since less than 10% of the exposed employees came from these positions and because BKK membership is less common among members of high income groups who can hold private insurance. BKK membership is over 95% percent among hourly workers.

Initially two potential referents were selected per exposed individual based on closest birth date among men with a company hire date prior to November, 1953. The final referent selection process was carried out by computer using random selection without replacement based on birth year distribution frequencies and was performed separately for each of the three exposure

subgroups. This process leads to referents that are frequency but not individually matched on age. Referents who were determined to be non-BKK members were replaced using the same selection procedure. Three individuals in the study group were determined not to have been BKK members after referent selection had been completed. Hence, in the "no chloracne" subgroup, there were three more referents than study group members.

Several notable factors could not be controlled through the selection procedure described above. First, there were 43 study group members who left active employment prior to 1970 including 13 individuals who died before 1970. The corresponding referent group included only 27 persons who left employment prior to 1970, all presumably due to retirement. Six of these men had died before 1970. Secondly, a number of employees in the study group were contract workers in 1953 and only later became company employees. Thus, these individuals would not have been members of the BKK until 1954 or later, whereas, all referents were company employees as of November, 1953.

Data Provided through Insurance Records

Separate lists containing the names, employee ID numbers and birth dates were provided to insurance personnel for each of the six study and referent subgroups. Insurance folders were then

reviewed and the following information was provided to the Medical Department on separate sheets for each person: (1) a unique personal identifier number assigned by the Insurance Department, (2) for each reported illness absence or hospitalization, from one to five diagnoses abstracted from the physician's report and provided in both ICD code format (International Classification of Diseases, 9th Revision) and in text form for quality assurance purposes, and (3) an indication of retirement status and time period in which the illness episode occurred. Five distinct time periods were later collapsed to three: 17 November, 1953 - 31 December, 1959; 1 January, 1960 - 31 December, 1969; and 1 January, 1970 - 31 December, 1989.

The BKK separately provided an annual frequency tabulation of the number of BKK members within each study and referent subgroup and also provided an annual tabulation of the number of retirees in each group. This information was used for calculation of person years of observation by group and time period. Since retiree episodes were limited to hospitalizations, it was expected that fewer episodes would be reported following retirement.

Statistical Approach

A complication of the health outcome data is that repeat visits for the same condition may have a different meaning depending on

the condition being observed. For example, repeat claims for a malignant neoplasm most likely represent continued treatment of the same disease. The condition has occurred once and there is no additional information to be gained from counting the number of recurrent claims per individual. On the contrary, multiple claims related to upper respiratory tract infection may provide new information pertinent to assessing overall respiratory health status of the employee. In general, the outcome measure for examining acute and non-specific conditions was the number of illness episodes per time period per employee, whereas chronic disease conditions were classified on an ever/never basis. When multiple diagnoses were reported, each was associated with the specific episode in the analyses. The selection of ICD categories was made a priori and was based largely on disease entities postulated to be related to TCDD exposure in the literature. The disease category, Appendicitis, is an exception, in that this category was included on the basis of ICD frequency tabulations suggesting an unusual distribution with respect to exposure status. A second exception was made for the category, Poisonings by Nonmedicinals. Based on review of the diagnosis text and the time period of the episodes, it was realized that most of these episodes related to the immediate consequences of TCDD overexposure following the accident.

Comparisons of disease conditions coded on an ever/never basis were made using Fisher's exact test. An approximate statistical test for identifying differences in illness rates between the exposed and referent groups was based on a comparison of directly standardized rates. Rates were standardized by time period but not by employment status since the percentage of person years among retirees was relatively constant across employee subgroups. This is not surprising in view of the frequency matching by birth year. For this study, the standard population was chosen to be the combined study and referent groups.

For a given employee subgroup, the standardized illness episode rate can be expressed as: $\sum_i (P_i (\sum_j n_{ij}) / py_i)$ where P_i represents the proportion of total person years assigned to the i^{th} stratum within the standard population and where n_{ij} and py_i represent the number of episodes reported for the j^{th} individual in the i^{th} stratum and the observed person years in the i^{th} stratum, respectively. The variance of n_{ij} is estimated as the variance of episode counts among individuals within the i^{th} stratum. The statistical comparison of two rates was based on normal distribution assumptions using a z-score statistic formed as the difference in rates over the square root of the sum of the rate variances.

Secondary Analyses Based on TCDD Concentration

The results of regression modeling of past TCDD concentrations were not available during the basic data collection and analysis phases of this study. However, because of later questions about possible differences in illness patterns in chloracne versus high TCDD concentration subgroups, we identified the individuals within each chloracne subgroup who had back-calculated TCDD concentrations above 1,000 ppt and provided this information to the BKK. The 73 individuals were distributed as follows: 33 men in the severe chloracne subgroup, 29 men in the moderate chloracne subgroup, and 11 men in the no chloracne subgroup. On a group basis, the BKK provided lists of identifier numbers so that separate analysis of the each employee subgroup could be performed.

53 29 11
Severe moderate no chloracne

RESULTS

Selected characteristics of the chloracne subgroups and their referents are shown in Table 1. The mean age in 1954 of individuals in the six exposure and referent subgroups ranged from 32.0 to 33.9 years and the mean duration of insurance coverage ranged from 25.2 to 31.8 years. The lower average duration of coverage among exposed compared to referent subgroups was in part due to greater membership of referents in the BKK as of late 1953 and partly due to fewer individuals in the exposed group remaining covered near the end of the observation period.

This was particularly the case for the moderate chloracne subgroup where twelve fewer exposed than referent individuals were BKK members in 1989. The percent hourly paid was lowest among exposed men in the no chloracne subgroup (41%) and was highest among men with moderate chloracne (72%).

Geometric mean TCDD blood lipid concentrations back-calculated to date of exposure were lowest for the no chloracne group (148 parts-per-trillion (ppt)) and highest for the severe chloracne group (1,118 ppt). Nevertheless, the broad range in the 20th to 80th percentile concentrations demonstrates considerable overlap in TCDD exposures between the no chloracne and severe chloracne subgroups. The geometric mean TCDD concentration among the 96 persons in the total cohort, who were excluded from the present morbidity study, was 7.3 ppt. This mean concentration is considerably less than that of even the no chloracne subgroup potentially exposed to TCDD within one year of the accident.

Analyses by exposure and chloracne status

The percent of TCDD and referent group members ever diagnosed with selected conditions between November 1953 and December 1989

is shown in Table 2. In the total group comparisons, a significantly increased percent of individuals with Diseases of the Thyroid (ICD: 240-246) and Appendicitis (ICD: 540-543) were seen in the TCDD group. The percentage differences between exposed men and referents were similar in magnitude across all exposure subgroups. Only one condition, Diabetes Mellitus (ICD: 250), was observed significantly less frequently in the TCDD than in the referent group. This finding was largely due to a low percent of exposed individuals with diabetic conditions in the no chloracne and moderate chloracne subgroups. A significantly lower frequency of Ulcers (ICD: 531-534) was reported in the no chloracne subgroup compared to referents and a marginally lower frequency of ulcers was reported in the severe chloracne subgroup. For the severe chloracne subgroup, there was a significantly higher likelihood of disability due to Diseases of the Sebaceous Glands (ICD: 706). This was expected based on the severity of the chloracne described in the occupational medical records of these men. It is also not surprising that no illness absences due to acne or other disorders of sebaceous glands were seen in the no chloracne subgroup. Benign and Unspecified Neoplasms (ICD: 210-229, 235-239) were marginally increased in the severe chloracne subgroup with a positive diagnosis made for 25% of all men in the subgroup.

Illness episodes per 100 person years of observation are summarized by exposure subgroup, time period and employment status (active versus retired) in Table 3. There was a total of 10,335 illness absences or hospitalizations among the 319 men studied. Illness rates are much lower among retired employees since only hospitalizations and not disability episodes are reflected in the numbers. Less than 13% of the person years of observation occurred among retirees. During active employment, illness rates declined over time in both the study and referent groups. A single diagnosis entry was provided for 78.0% of the referent and 81.2% of the TCDD group episodes and three or more diagnoses were provided for 3.7% of the referent and 2.9% of the TCDD group episodes. Multiple diagnoses per episode were more likely to be reported in both groups in later years of the study.

Illness rates were highest in the severe chloracne subgroup for each time period and following retirement as well. The differences in illness rates between exposed individuals and referents were rather constant across time periods for both the total exposed group and the severe chloracne subgroup. An inconsistent pattern was observed for the no chloracne and moderate chloracne subgroups.

Cause-specific illness rates are examined in Table 4 for disease categories in which the recurrence of episodes may be etiologically important. The directly standardized illness rates

were 18 percent higher in the TCDD group compared to referents for total episodes ($p = 0.002$) and for the following specific disease categories: Disorders of Peripheral Nervous System and Sense Organs ($p = 0.018$), Upper Respiratory Tract Infections ($p = 0.003$), Other Skin Diseases ($p = 0.001$), Injury ($p = 0.008$) and Poisonings by Nonmedicinals ($p = 0.003$). The illness rate was also marginally elevated for Infectious and Parasitic Diseases ($p = 0.067$).

Subgroup comparisons are summarized in Table 5. Only disease categories for which one or more statistically significant findings were observed among the subgroups are presented. Other than a significant increase in illness rates due to Other Skin Diseases seen in the moderate chloracne subgroup, all statistical findings pertain to the severe chloracne subgroup. Overall illness rates are 46 percent higher in this group compared to referents with greater than two-fold increases seen for all disease categories in Table 5 except for Total Respiratory Disease, which was increased by 35 percent.

Analyses by back-calculated TCDD concentration

As previously mentioned, secondary analyses were performed examining the possible effects of high TCDD concentration (1,000+ ppt) on illness rates based on comparisons to both the low TCDD

subgroup and referents. Frequency matching by age was not possible in these analyses and there were age differences among the groups. In contrast to a mean age of 33.1 years among all referents in 1954, the average age of the high TCDD group was 35.5 years and that of the low TCDD group was 30.8 years. The highest mean age (37.4 years) was observed for the 29 men in the subgroup with moderate chloracne and high TCDD concentrations. These age differences indirectly reflect our prior observation that chloracne occurrence and severity is greater among younger individuals after controlling for TCDD concentration.⁷ Bond et al (1989) had previously observed that chloracne risk appeared to be highest among men under age 25.¹⁰

Among comparisons based on ever/never disease status, a higher percentage of Diseases of the Thyroid was observed in the high TCDD group, 8.2% (6 cases), versus 5.9% in the low TCDD group and 1.2% among referents. A single case of thyroid adenoma also occurred in a person with high TCDD exposure and severe chloracne. There were also 14 cases of Appendicitis observed in the high TCDD group (19.2%) versus 12 cases in the low TCDD group (14.1%) and 9 cases among all referents (5.6%). The percentages of Diabetes were: 11.0% in the high TCDD group, 2.4% in the low TCDD group, and 14.3% among referents. The corresponding percentages of Benign and Unspecified Neoplasms were: 24.7%, 15.3%, and 16.8%, respectively. Chronic Liver Disease was

marginally higher in the high TCDD group: 31.5% versus 21.2% in the low TCDD group and 23.0% among referents. Ischemic Heart Disease percentages were unrelated to TCDD concentration.

Illness rates are summarized in Table 6 according to TCDD concentration across and within each chloracne subgroup. Total episodes per 100 person years are increased with higher TCDD concentration overall and are increased similarly within each of the chloracne subgroups. A similar pattern is observed for Infectious and Parasitic Diseases, Disorders of the Stomach and Duodenum, and several other categories, but not for the respiratory disease categories and Mental Disorders. These latter categories were elevated in association with chloracne status but not consistently with high TCDD concentration.

DISCUSSION

In this study, morbidity was examined both on the basis of conditions that were ever diagnosed during the 35+ year follow-up period and on the basis of illness rates expressed as episodes per 100 person years of observation. Overall illness rates were positively correlated with prior chloracne status and were increased with higher TCDD concentration within chloracne subgroup. Elevated illness rates were observed throughout the

observation period and not just in the early years following exposure. Illness rates were notably increased in the severe chloracne group, where statistically elevated rates were seen for Infectious and Parasitic Diseases, several respiratory disease categories, Disorders of PNS and Sense Organs, Mental Disorders and for Other Skin Diseases. Consistency was observed for some disease categories but not for others when the data were subcategorized by back-calculated TCDD concentration. For example, Mental Disorders were associated with chloracne status but not high TCDD concentration.

From a potential organ toxicity perspective, positive findings were seen in regard to skin, thyroid, immune system, and the central as well as peripheral nervous systems. The dermatological findings observed in this study are consistent with the known chloracne status of this population. Increased morbidity due to dermatological conditions occurred mainly in the severe chloracne subgroup. This was true both when both Diseases of the Sebaceous Glands (ICD 706) and other dermatological conditions were used as the diagnostic endpoint. These findings probably also reflect a lack of specificity in the diagnostic information provided to the insurance carrier. The absence of any insurance diagnoses attributable to Diseases of the Sebaceous Glands in the no chloracne group indicates that either this subgroup was resistant to acne or that any existing acne among

exposed individuals had been classified as chloracne in the occupational medical records.

A total of eleven individuals were diagnosed with thyroid disease in the TCDD cohort versus only two individuals in the referent group. Unspecific goiter was reported in four exposed and the two referent cases. Four cases of thyrotoxicosis, two cases of hypothyroidism, and one case of another thyroid disorder were observed among TCDD-exposed individuals. These cases were evenly distributed across the three chloracne subgroups, but were somewhat more likely to occur in the high TCDD concentration group. Both cases of hypothyroidism occurred among individuals with a high TCDD concentration and moderate to severe chloracne. A single case of thyroid adenoma was also reported in the severe chloracne, high TCDD, subgroup. Concerns about possible TCDD effects on thyroid function have been raised based on mechanistic arguments and experimental studies.^{11 12 13} A clear understanding of the mechanisms through which TCDD could influence the complex thyroid regulatory system and how these effects might be expressed as human disease presently is lacking. McKinney and Pedersen have modeled the effect of TCDD-like materials competing for thyroid hormone binding sites and have suggested that this could lead to varying degrees of hypothyroidism.¹⁴ Thyroid hormone economy could also be disrupted by increased metabolism due to hepatic microsomal enzyme induction.¹⁵ Capen also

discussed how loss of thyroid hormone economy could lead to chronic hypersecretion of thyroid stimulating hormone (TSH) and an increased incidence of follicular cell tumors.¹⁵ The Ah-receptor mediated toxicity of TCDD could also play a role, for instance, through induction of Thyroxin Binding Globulin (TBG) synthesis in the liver. We have observed TBG to be positively associated with internal TCDD dose in this same population.¹⁶ No clear changes in serum T4 were observed. However, among older individuals, marginal increases in both TSH and serum T4 were observed among individuals with higher back-calculated TCDD levels.

Our findings of increased morbidity due to Infectious and Parasitic Diseases in the severe chloracne subgroup and in the high TCDD group are consistent with reduced host resistance, but also may reflect differences in insurance utilization. There were no specific diagnoses of Disorders involving the Immune Mechanism (ICD 279) among either exposed employees or referents. Within the severe chloracne subgroup, much of the overall difference was accounted for by one disease subcategory, ill-defined intestinal infections. Within this subcategory there were 37 episodes among 15 different individuals in the severe chloracne subgroup and only 13 episodes among 10 different individuals in the referent group. More episodes involving mycoses, particularly tinea pedis "Athlete's foot", were also

reported among TCDD-exposed individuals. For most other infectious diseases there were no notable differences in the frequency of diagnosis. However, there were 5 individuals in the high TCDD group diagnosed with tuberculosis or late effects of tuberculosis compared to no cases among employees in the low TCDD group and 3 cases among all referents.

Regarding upper respiratory tract infections (URI), there was nearly a two-fold differential in rates between employees with severe chloracne and their referents. The relative rate differential held throughout the observation period, although absolute rates in both groups declined steadily over time. However, URI rates were not consistently elevated in the high TCDD subgroups. Again there is a possibility that differences in medical care utilization rates between the exposed and referent groups could bias the findings. For example, individuals in the exposed group and, in particular, in the severe chloracne subgroup, may have been more prone than referents to seek medical attention either because of their concerns about long-term sequelae from exposure or because of medical counseling.

In contrast to the findings for the two categories above, the percent of individuals ever diagnosed with appendicitis was elevated across all chloracne subgroups. The 26 cases were nearly equally distributed by subgroup, but tended to occur in

the earlier time periods. There were 23 exposed versus 5 referent cases prior to 1970 and 3 exposed versus 4 referent cases after that date. Within each chloracne subgroup, cases were more likely among men with estimated TCDD concentrations above 1,000 ppt. The relevance of these findings to TCDD exposure is unclear. Generally, the diagnosis of appendicitis should be verified histologically and this was not possible in the present study. The intestine does play a role both in metabolizing xenobiotics and in immunological protection of the host. Because the residency of feces possibly containing lipid soluble compounds may be much longer in the appendix than in the intestinal lumen and the concentration of immunocompetent tissue, Peyer's patches, is very high in the appendix, these unanticipated findings would be plausible if TCDD were specifically toxic to this tissue.

In all exposure subgroups and among the referents, there was no indication of interaction between the occurrence of appendicitis and that of either upper respiratory tract infections or other infectious diseases. In other words, the occurrence of upper respiratory tract infection was independent of whether or not the same person had been diagnosed with appendicitis. There were also no differences in influenza rates among the exposure subgroups. A somewhat higher pneumonia rate based on 17 exposed cases was observed in the severe chloracne group compared to

referents: 1.1 versus 0.6 episodes per 100 person years of observation. The corresponding rate for the high TCDD group was 1.0 episodes per 100 person years.

Although there have been several clinical investigations of immune system parameters (e.g., lymphocyte subset populations, immunoglobulins, and delayed hypersensitivity tests), we are unaware of human studies that have specifically examined infectious disease rates in exposed populations. There have been some reports correlating respiratory symptoms and the concentration of PCBs in blood.^{17 18} It is generally difficult to demonstrate immunotoxic effects of xenobiotics on infectious disease occurrence because of a remarkable functional reserve capacity in immune response.¹⁹ Although our findings are not consistent across a spectrum of infectious diseases, it is also difficult to attribute all the positive findings to confounding or observation bias.

Regarding mental and peripheral nervous system diseases (ICD: 290-317, 350-389, 781), increased illness episodes for the total exposed cohort were seen only for the category: Disorders of Peripheral Nervous System and Sense Organs. Review of diagnoses by subject revealed that 13 percent of the exposed group episodes in this latter category represented repeat occurrences of trigeminal nerve disorder in one individual from the severe

chloracne subgroup. Eye and ear disorders accounted for about half of the total episodes in the category. There was only one diagnosis of peripheral neuropathy (ICD: 356) in the severe chloracne subgroup and this individual was also diagnosed as diabetic. Our findings are thus consistent with the results of cross-sectional studies of TCDD exposed workers in the U.S. which found no evidence of increased peripheral neuropathy in exposed workers.^{20 21}

Within the severe chloracne subgroup there was a statistical increase in episodes due to Mental Disorders. More than 50 percent of the episodes related to ICD 306, a category including physiological malfunction arising from mental factors but not secondary to psychiatric disorders. The individual episodes were spread across individuals rather than being concentrated in only a few persons. A number of the individuals with severe chloracne have been subject to both persistent and disfiguring lesions. This could explain the association with chloracne severity but not with high TCDD concentration per se.

Taken as a whole, the pattern of mental and peripheral nervous system disorders seen in this study provide no concrete evidence linking specific pathological entities to TCDD exposure but suggest more frequent episodes of a broad spectrum of mental

and/or nervous system disorders may be linked to high TCDD exposure.

Among other disease categories the only noteworthy findings were a marginal increase in Benign and Unspecified Neoplasms within the severe chloracne subgroup and a general increase in illness rates due to Injury (ICD: 800-959) and Poisoning by Nonmedicinals (ICD: 980-989) in the total cohort. Review of the written diagnoses in the latter category revealed statements consistent with effects of chemical exposure following the 1953 accident. In general injury statements on the insurance forms pertained to nature of injury rather than external cause. Since there was no differential distribution of Injury diagnoses (ICD: 800-959) by exposure subgroup, these findings are uninterpretable at this time.

The 13 cases of benign and unspecified neoplasms in the severe chloracne subgroup included one adenoma of the thyroid, one angioma, four neoplasms of the digestive system (three benign and one of uncertain behavior), and seven neoplasms of unspecified sites (one benign and six of unspecified nature). Only one of these 13 individuals was later diagnosed with a malignant neoplasm (a leukemia). There was no significant increase in the number of malignant neoplasms in the total population or in any of the subgroups. In an earlier mortality study of the total

cohort, an increase of malignancy-related deaths was seen among individuals with chloracne allowing for a 20 year latency.⁶

Questions have been raised relative to TCDD causing liver disease, ulcer, ischemic heart disease and disorders of lipid metabolism as well as diabetes. In this study we examined the frequency of disease occurrence within each of these categories. For ulcer and diabetes there was no increased frequency of occurrence within the total exposed population, no increasing frequency with chloracne severity and the high TCDD group was not elevated relative to controls. For ischemic heart disease there were again no differences observed based on exposure status, chloracne severity or TCDD concentration. Three of the five cases of Disorders of Lipid Metabolism (e.g., hypercholesterolemia) that were observed in the combined study and referent groups did occur among men in the high TCDD group. For chronic liver disease there were marginal increases in the percent of cases in the total exposed group, in the moderate and severe chloracne subgroups, and in the high TCDD group. However, it is not possible to draw firm conclusions from these limited observations.

A proper interpretation of the findings of this study can only be made in the light of findings from the mortality study, which is currently being updated, and clinical laboratory studies, which

are also being completed among surviving members of the study population.

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TABLES

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Table 1: Selected characteristics of TCDD-exposed groups and referents.

Group	Mean duration of insurance coverage per person between 1953 and 1989 (years)		Hourly Paid (%)	TCDD concentration back-calculated to exposure date (ppt)	
	AM ± SD	AM		GM	Percentile 20 - 80
Total Cohort					
TCDD (N = 158)	33.0 ± 10.9	27.8	61	434	79 - 1,777
Referents (N = 161)	33.1 ± 11.0	30.7	58	---	---
No Chloracne					
TCDD (N = 45)	32.0 ± 10.3	29.3	41	148	20 - 1,279
Referents (N = 48)	33.1 ± 11.0	31.8	52	---	---
Moderate Chloracne					
TCDD (N = 61)	33.9 ± 10.5	25.2	72	429	81 - 1,484
Referents (N = 61)	33.6 ± 10.5	29.5	59	---	---
Severe Chloracne					
TCDD (N = 52)	32.7 ± 11.8	29.5	66	1,118	493 - 2,955
Referents (N = 52)	32.7 ± 11.9	31.1	62	---	---

AM = Arithmetic mean SD = Standard deviation GM = Geometric mean

Table 2: Percent of TCDD and referent group members ever with selected morbidity diagnoses by chloracene status of TCDD group (1953 - 1989)

Disease Category	PERCENT OF PERSONS EVER WITH DIAGNOSIS															
	Total Group		No Chloracene		Moderate Chloracene		Severe Chloracene									
	TCDD	Referent	TCDD	Referent	TCDD	Referent	TCDD	Referent	TCDD	Referent						
Malignant Neoplasms (140-209)	14.6	11.2	8.9	8.3	19.7	13.1	13.5	11.5	N = 158	N = 161	N = 45	N = 48	N = 61	N = 61	N = 52	N = 52
Benign and Unspecified Neoplasms (210-229, 235-239)	19.6	16.8	15.6	18.8	18.0	19.7	25.0	11.5								
Diseases of the Thyroid (240-246)	7.0 *	1.2	6.7	0.0	8.2	1.6	5.8	1.9								
Diabetes Mellitus (250)	6.3	14.3 *	2.2	18.8 *	4.9	11.5	11.5	13.5								
Disorders of Lipid Metabolism (272)	2.5	0.6	0.0	0.0	1.6	1.6	5.8	0.0								
Ischemic Heart Disease (410-414)	43.0	41.0	51.1	60.4	39.3	29.5	40.4	36.5								
Ulcer (531-534)	15.8	23.0	2.2	18.8 *	26.2	21.3	15.4	28.9								
Appendicitis (540-543)	16.5 **	5.6	20.0	6.3	14.8	4.9	15.4	5.8								
Chronic Liver Disease (570-573)	26.0	23.0	15.6	20.8	29.5	24.6	30.8	23.1								
Nephritis and Nephrosis (580-589)	5.1	5.0	4.4	8.3	6.6	3.3	3.9	3.9								
Calculus of Kidney and Ureter (592)	11.4	9.9	11.1	6.3	4.9	11.5	19.2	11.5								
Diseases of the Sebaceous Glands (706)	10.1	8.7	0.0	8.3	6.6	13.1	23.1 **	3.9								

* (0.01 <= p < 0.05) by two-sided Fisher's exact test

** (p < 0.01) by two-sided Fisher's exact test

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Table 3: Illness Episodes per 100 person years by employment status, time period, and exposure group.

Exposure Group	Active Employment										Retired	
	Total Period		1953 - 1959		1960 - 1969		1970 - 1989		Total			
	Rate	(TE)	Rate	(TE)	Rate	(TE)	Rate	(TE)	Rate	(TE)	Rate	(TE)
Total Cohort												
TCDD (N = 158)	132.9	(5,057)	156.2	(1,338)	145.1	(1,827)	111.9	(1,892)	42.1	(244)		
Referents (N = 161)	111.7	(4,848)	133.5	(1,258)	112.1	(1,634)	100.8	(1,956)	30.8	(186)		
No Chloracene												
TCDD (N = 45)	104.5	(1,206)	120.9	(286)	115.1	(405)	91.0	(515)	19.1	(31)		
Referents (N = 48)	109.6	(1,455)	102.9	(300)	105.9	(483)	115.8	(672)	19.0	(38)		
Moderate Chloracene												
TCDD (N = 61)	138.1	(1,756)	155.7	(520)	151.6	(705)	112.3	(531)	40.8	(108)		
Referents (N = 61)	120.0	(1,873)	163.1	(552)	128.5	(674)	92.8	(647)	34.2	(81)		
Severe Chloracene												
TCDD (N = 52)	151.9	(2,095)	186.0	(532)	162.2	(717)	129.9	(846)	68.9	(105)		
Referents (N = 52)	104.8	(1,520)	130.1	(406)	100.1	(477)	96.2	(637)	39.9	(67)		

TE = Total Episodes

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Table 4: Illness episodes per 100 person years for selected disease categories (1953 - 1989).

Disease Category ¹	Episodes per 100 person years ²		
	TCDD (N = 158)	Referents (N = 161)	p-Value
Total Episodes	120.7	101.9	0.002
Infectious & Parasitic Diseases (000 - 139)	3.0	2.2	0.067
Mental Disorders (290 - 317)	2.6	2.4	0.704
Disorders of the CNS (320 - 349)	0.6	0.5	0.912
Disorders of PNS and Sense Organs (350 - 389, 781)	3.2	1.8	0.018
Disorders of Circulatory System except Ischemic Heart Disease (392 - 404, 415 - 459)	10.3	9.4	0.488
Total Respiratory Disease (460 - 519)	33.7	31.0	0.215
Upper Respiratory Tract Infections (460 - 478)	12.0	9.0	0.003
Pneumonia and Influenza (480 - 487)	17.4	18.8	0.078
Chronic Obstructive Pulmonary Disease (490 - 496)	8.0	7.5	0.306
Disorders of Stomach and Duodenum (535 - 537)	5.5	4.8	0.395
Diseases of Intestine & Peritoneum (555 - 569)	3.8	3.1	0.202
Other Skin Diseases (680 - 705, 707 - 709, 782)	6.7	3.7	0.001
Arthropathies (710 - 719)	4.7	3.6	0.180
Disorders of Soft Tissue (728 - 729)	2.1	1.9	0.608
Symptoms & Ill-defined Conditions (780 - 799)	5.8	5.5	0.624
Injury (800 - 959)	19.5	15.7	0.008
Poisonings by Nonmedicinals (980 - 989)	0.8	0.3	0.003

¹ When multiple diagnoses are reported for an episode, each represented disease category is counted for the episode.

² Rates directly standardized to the overall distribution of person years by time period.

Table 5: Illness episodes per 100 person years by exposure subgroup for disease categories with one or more statistical findings ($p < 0.05$).

Disease Category ¹	Episodes per 100 person years ²					
	No Chloracne		Moderate Chloracne		Severe Chloracne	
	TCDD	Referent	TCDD	Referent	TCDD	Referent
Total Episodes	95.5	97.7	118.4	109.4	143.7**	98.0
Infectious and Parasitic Diseases (001-139)	2.0	2.8	2.8	2.2	4.1**	1.7
Mental Disorders (290-317)	1.6	2.6	2.8	2.9	3.2*	1.5
Disorders of PNS and Sense Organs (350-389, 781)	1.9	2.1	3.0	1.8	4.4*	1.6
Total Respiratory Disease (460-519)	28.8	32.4	30.5	30.7	40.8*	30.2
Upper Respiratory Tract Infections (460-478)	8.4	9.1	11.1	9.5	15.8**	8.2
Chronic Obstructive Pulmonary Disease (490-496)	6.7	9.1	6.5	6.9	10.8*	6.7
Other Skin Disease (680-705, 707-709, 782)	4.5	4.1	4.6**	2.5	10.5**	4.7
Poisonings by nonmedicinals (980-989)	0.4	0.1	0.8	0.4	1.3**	0.2

¹ When multiple diagnoses are reported for an episode, each represented disease category is counted for the episode.

² Rates directly standardized to the overall distribution of person years by time period.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table 6: Illness episodes per 100 person years for selected disease categories (1953 - 1989).

Disease Category ¹	Episodes per 100 person years ²					
	Back-calculated TCDD		Referents		Chloracne	
	1,000 + ppt (N = 73)	< 1,000 ppt (N = 85)	1,000 + ppt (N = 161)	Severe Chloracne < 1,000 ppt (N = 19)	Moderate Chloracne 1,000 + ppt (N = 29)	No Chloracne 1,000 + ppt (N = 11)
Total Episodes	134.8	108.6	101.9	134.8	125.9	108.3
Infectious & Parasitic Diseases (000 - 139)	4.2	2.0	2.2	3.0	3.5	3.9
Mental Disorders (290 - 317)	2.2	2.9	2.4	4.3	2.7	0.3
Disorders of PNS and Sense Organs (350 - 389, 781)	3.3	3.0	1.8	3.6	1.6	2.3
Disorders of Circulatory System except Ischemic Heart Disease (392 - 404, 415 - 459)	10.4	10.2	9.4	9.8	10.9	6.7
Total Respiratory Disease (460 - 519)	35.9	31.7	31.0	45.2	34.9	29.2
Upper Respiratory Tract Infections (460 - 478)	13.3	10.8	9.0	18.8	13.8	9.2
Pneumonia and Influenza (480 - 487)	18.0	16.9	18.8	18.6	17.2	15.7
Chronic Obstructive Pulmonary Disease (490 - 496)	8.5	7.6	7.5	12.5	6.3	9.4
Disorders of Stomach and Duodenum (535 - 537)	7.8	3.6	4.8	7.0	7.9	7.3
Diseases of Intestine & Peritoneum (555 - 569)	4.3	3.4	3.1	4.6	5.1	5.4
Other Skin Diseases (680 - 705, 707 - 709, 782)	7.9	5.6	3.7	9.6	4.7	5.5
Arthropathies (710 - 719)	6.2	3.4	3.6	3.2	3.9	8.4
Disorders of Soft Tissue (728 - 729)	2.3	1.9	1.9	2.5	1.3	2.5
Symptoms & Ill-defined Conditions (780 - 799)	8.0	3.9	5.5	6.3	8.6	4.8
Injury (800 - 959)	19.2	19.8	15.7	18.7	23.3	14.1
Poisonings by Nonmedicinals (980 - 989)	1.0	0.6	0.3	1.1	1.0	0.0

¹ When multiple diagnoses are reported for an episode, each represented disease category is counted for the episode.

² Rates directly standardized to the overall distribution of person years by time period (no age standardization was possible).



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EQMS Ratings on 8 (E) NonCAP Submissions--Set 15--Sept. 8, 1995

8E Number and Chemical Name	Rank	Reason or Brief Description
-12440A TCDD, Dioxin	High	<p>A German chemical manufacturer had an incident in 1953 where dioxin contaminated the works. The existence of dioxin as a contaminant and its various adverse health effects were unknown at that time, and over 200 workers were exposed during the clean-up and subsequent work in the plant. The 1992-submitted study is a long-term historical prospective cohort study of the workers' morbidity experience covering the period through the end of 1989. 158 workers, representing a survivor population, constitute the cohort. The cohort was sub-divided into three groups based on the severity of their chloracne, as well as through modelled total TCDD-body-burden. A considerable number of findings were generated in the study, typical of dioxin exposure scenarios, where a broad spectrum of adverse health effects with imprecise symptomology is often reported. The "severe chloracne" group had significantly increased incidence of episodes of illness as well as higher rates for several nonneoplastic disease endpoints.</p>