CANCER IN HUMANS RELATED TO EXPOSURE TO CHEMICALS CONTAMINATED WITH 2,3,7,8-TCDD: THE NIOSH STUDIES

Marie Haring Sweeney, Marilyn A. Fingerhut, Laurie Piacitelli, Kyle Steenland

National Institute for Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH USA

Introduction

Over the past 20 years, epidemiologic studies of human exposure to chemicals contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) have examined both cancer and noncancer endpoints in populations throughout the world. This paper describes the results of the NIOSH mortality studies of a cohort of U.S. chemical workers exposed to TCDD during the production of TCDD-contaminated chemicals. Serum TCDD concentrations measured in a sample of living cohort members served to confirm that these workers had high exposures to TCDD and to evaluate the relationship of occupational TCDD exposure to cancer mortality.

Methods and Materials

The NIOSH cohort consisted of 5,172 men who handled TCDD-contaminated wastes while working at 12 U.S. plants in the production of TCP, 2,4,5-T, or hexachlorophene, or in the formulation of Agent Orange. Production or formulation of these chemicals occurred for various periods spanning 2 to 35 years between 1942 and 1984. The concentrations of TCDD in TCP and derivatives depended on process operating parameters such as temperature, pressure and reaction time, and level of purification.

Cancer mortality of the cohort was examined in a series of epidemiologic studies. The studies include a baseline mortality study published in 1991[1] and an update of the study, which added 6 years of followup[2] and analyses based on a cumulative exposure score and serum TCDD concentrations.[3] During 1987–1988, a cross-sectional morbidity study was conducted among living workers from 2 of the 12 plants (located in New Jersey and Missouri) and matched nonexposed referents or controls.[4] The study focused on outcomes other than cancer, including reproductive outcomes. Lipid-adjusted serum concentrations of dibenzodioxins (PCDDs), including TCDD, and selected dibenzofurans (PCDFs) were measured in the 273 participating workers and a sample of 79 referents.[5]

The baseline study—1991

In the baseline study, the vital status of the 5,172 workers was followed through 1978. To assess potential TCDD exposure for workers at each plant, a comprehensive review was conducted of job duties, final and intermediate products, production processes and waste streams, and environmental measurements (air, surface, and product samples). This assessment revealed considerable similarities in starting products, operations, and job tasks across many of the plants. Standard life table analyses were conducted for the entire cohort of 5,172 using the U.S. population for comparison.[6]

The 1999 update study

In the update study, vital status of the cohort was continued through 1993.[2] The overall analysis included 5,132 workers; 40 workers previously included in the baseline study were eliminated because they were female, had never worked in a TCDD-contaminated production process, or were missing a date of birth. Also defined was an “exposure subcohort” of 3,538 workers who had sufficiently detailed

personnel or exposure records to estimate the TCDD exposure concentration by job and who worked only in TCDD-contaminated processes with no known confounding exposure to pentachlorophenol or PCBs. In addition to considering duration of exposure and latency as surrogates of cumulative exposure, the updated study estimated relative TCDD exposure concentration using a job exposure matrix for the 3,538 workers in the exposure subcohort.[3] Briefly, the matrix was developed by assigning each worker a TCDD exposure score based on (1) concentration of TCDD (μg/g) in process materials, (2) a qualitative factor to account for contact with TCDD-contaminated dust via inhalation or dermal routes, and (3) the fraction of the day the subject worked in TCDD-contaminated processes. This qualitative score allows the worker to be ranked across all plants and jobs.

The analyses in this study followed several strategies. Life table analyses, using the U.S. population for comparison, were conducted for the cohort of 5,132 workers and for the exposure subcohort of 3,538 workers—taking into account the cumulative exposure scores as an estimate of exposure likelihood. For analyses, cumulative exposure scores were categorized into septiles. Finally, Cox regression analyses were conducted for all cancers and specific cancers using various exposure metrics such as cumulative exposure score, logarithm of the cumulative exposure score, average cumulative exposure score, and categorized exposure score. Rate ratios and tests for trends were calculated for each septile.

Results and Discussion

Serum TCDD concentrations

Serum TCDD concentrations were measured in 273 workers and 79 unexposed, matched referents who were included in the cross-sectional medical study.[5] For workers, the mean lipid-adjusted serum concentration was 220 pg/g (range =2–3,400 pg/g), and the median was 70 pg/g. For referents, the mean was 7 pg/g (range 2–20 pg/g), and the median was 6 pg/g. In this population, the total TEQs are dominated by the 2,3,7,8-TCDD isomer. Serum concentrations for 2,3,7,8-TCDD, 2,3,4,7,8-dibenzofuran(F), and 1,2,3,4,7,8F were significantly different between the exposed workers and the referent population. The elevated dibenzofuran concentration was attributed to one study participant.

Mortality studies

In the baseline study, mortality from all cancers was statistically significantly elevated for the cohort of 5,172 workers (N=265 deaths; SMR=1.15; 95 % CI=1.02–1.30) and for workers with more than 1 year of employment and 20 years of latency (N=114 deaths; SMR=1.46; 95 % CI=1.21–1.76).[1] Although the SMRs for a majority of specific cancers were increased, they were not statistically significantly elevated.

In the update study (as in the baseline study) mortality from all cancers combined for the entire cohort (N=5,132) was significantly elevated (N=377 deaths; SMR=1.13; 95 % CI=1.02–1.25).[2] Mortality from all cancers was not statistically significantly higher than that expected except for cancers of the larynx (N=10 deaths; SMR=2.22; 95 % CI=1.06–4.08) and bladder (N=16 deaths; SMR=1.99; 95 % CI=1.13–3.23). The excess bladder cancer is most likely a result of exposure to 4-aminobiphenyl at one plant. In the chloracne subcohort of 393 workers with exposure scores, overall cancer mortality was generally increased (SMR=1.36; 95 % CI =0.98–1.84) and statistically significantly increased in the two highest cumulative-exposure septile categories (SMR=1.68; 95 % CI=1.19–2.30). For the cohort of 3,538 workers with cumulative exposure scores, mortality from all cancers combined and from lung cancer significantly increased with increasing cumulative exposure score (trend test for all cancers, P=0.02; and for lung cancer, P=0.05) using life table analyses. The significant positive trends were also observed between mortality from all cancers or lung cancer and cumulative exposure scores when using an internal comparison. The association was stronger using the

log cumulative exposure score after a 15-year lag period. This pattern was repeated when using an internal referent group, log-cumulative exposure score with a 15-year lag. In the two highest cumulative exposure septiles, the rate ratios (RRs) for all cancers were significantly increased (exposure score=6,140–15,800, RR=1.88, 95% CI=1.22–2.91; exposure score ≥15,800, RR=1.76, 95 % CI=1.14–2.72) (trend test, *P*=<0.001). The trend test for lung cancers was also statistically significant using log cumulative exposure score and a 15-year lag.

Conclusions

Many workers in this cohort were exposed to TCDD-contaminated chemicals on a daily basis for as many as 20 years. In this cohort, serum TCDD concentrations at the time of last occupational exposure to TCDD are estimated to be three to five orders of magnitude higher than concentrations in the general population of the United States. The overall results of the mortality studies indicate that in this highly exposed occupational population, a general, dose-related increase in mortality exists from all cancers and does not appear to be related to an excess in any single type of cancer. Furthermore, the highest rate of cancer was most evident in workers at the highest exposure categories using either an estimated cumulative exposure score or a cumulative serum concentration of TCDD. Taken together, these results suggest that in this cohort of chemical workers, overall cancer mortality was influenced by high, long-term TCDD exposure.

References

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