Epidemiologic Studies of Dioxin Exposed Populations: What Do They Tell Us?

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Epidemiologic studies have focused on the study of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a minor contaminant in a few phenoxy herbicides and chlorophenols, such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-trichlorophenol (TCP). In the first full decade of epidemiologic research, during the 1980's, studies examined cancer and other health effects in several populations with exposures to phenoxy herbicides or chlorophenols. The populations studied included herbicide applicators in Sweden, the community near Seveso, and Vietnam veterans; however, for all of these groups the characterization of the actual exposure of the individuals to TCDD was inadequate. Other studies involved chemical workers with clear exposure to TCDD, but the studies were of few workers, so that the statistical power of the studies was low. These studies have been reviewed.[1] The studies of the 1980's found that soft tissue sarcoma (STS) and malignant lymphoma were in excess in Swedish applicators exposed to phenoxy herbicides and chlorophenols, leading to the hypothesis that these excesses might be due to TCDD, a contaminant in some of these substances.[2-4]

A major breakthrough occurred during the 1980's in the laboratories of Rappe and Patterson,[5] permitting the measurement of TCDD in human serum. Using that technique, numerous studies have found that individuals in industrialized nations have mean serum TCDD levels of about 4-7 parts per trillion (range to 20 ppt), lipid adjusted.[6] In contrast, several groups have higher levels of exposure. The U.S. Air Force Ranch Hand group, which sprayed Agent Orange in Vietnam, had a median TCDD level of 13 ppt (range up to 600 ppt), when measured 15 years after exposure.[7] The U.S. National Institute for Occupational Safety and Health (NIOSH) found very high levels in U.S. chemical workers (mean 230 ppt; range up to 3400), when measured 15-37 years after their last occupational exposure. Based on a 7 year half-life assumption, the range was estimated to be as high as 30,000 ppt at last occupational exposure.[8] Similar measurements were found in German chemical workers.[9] Some people in Seveso, Italy had levels up to 50,000 ppt.[10]

Measurement of TCDD in serum has made it possible for certain epidemiologic studies to incorporate a quantitative measure of TCDD exposure. Three recent studies have provided evidence for the carcinogenicity of TCDD in chemical workers with heavy occupational TCDD exposure. A NIOSH study of over 5000 U.S. workers, found a 46% excess of total cancer in workers exposed over one year and who had their first exposure 20 years earlier.[8] Zober found about a two-fold excess of total cancer in 114 German workers had chloracne and were exposed following an accident 20 years earlier.[9] Manz reported a 24% excess of total cancer in a group of about 1500 German chemical workers.[11] The cancer excesses in these three studies were accounted for by cancers of various sites. The NIOSH study also found significant excesses of respiratory cancer and soft tissue sarcoma (based on 3 deaths) in the group with over one year of exposure to TCDD. None of the three studies reported statistically significant excesses of lymphoma. The three studies provide support for the carcinogenicity of TCDD in heavily exposed occupational populations; one provides some support for an association of TCDD with STS; none support an association of TCDD and malignant lymphoma.

A study of New Zealand applicators,[12] found that men who sprayed 2,4,5-T for 7 to 31 years had a mean serum TCDD level (53 ppt) ten times that in matched unexposed control subjects (5.6 ppt). Each 4 months of spraying resulted in a 1-ppt increase in the serum of the applicators, leading the authors to suggest that serum TCDD levels must have been low in the applicators in the Swedish studies,[2-4] since many men had exposures of less than one year. They concluded that it is unlikely that the Swedish soft tissue sarcoma and lymphoma excesses were due to TCDD. Thus, the question exists whether the excess STS and lymphoma found in the Swedish studies[2-4] might be due to phenoxy herbicides or chlorophenols or other unidentified factors, rather than to TCDD. In an IARC study[13] of over 18,000 applicators and production workers exposed to phenoxy herbicides and chlorophenols, most of which did not contain TCDD, no excess deaths from lymphoma were found. Based on 4 deaths, a statistically nonsignificant elevation of STS was found. Additional follow-up of the IARC and occupational cohorts, with particular attention to types of exposure may help to separate the effects of TCDD, phenoxy herbicides and chlorophenols.

OTHER HEALTH EFFECTS

Useful information is emerging from several ongoing studies of health effects in two populations for whom individual serum TCDD measurements provide a statistically powerful analysis. The study of 900 U.S. Air Force Ranch Hand veterans and 900 matched comparisons[7] has found statistically significant associations with increasing serum TCDD level for reduced HDL and for increased cholesterol, diabetes, fasting glucose level and percent body fat, suggesting effects on lipid metabolism. Although not considered physiologically meaningful, significant decreases were found in mean %T3 uptake and mean thyroid stimulating hormone, testosterone and testicular size with increasing serum level of TCDD. Alanine aminotransferase, gamma-glutamyl transpeptidase, erythrocyte sedimentation rate, platelet count, white cell count and

IgA were also associated with increasing TCDD levels. No association was found for liver disease, neurological, renal, dermatologic or cardiovascular outcomes.

The NIOSH medical study of TCDD-exposed U.S. chemical workers and unexposed referents included serum TCDD measurements for 273 workers and 79 referents. No association was found between TCDD level and liver disease,[14] lung disease[15] or peripheral neuropathy.[16] Among the measures of liver function, a statistically significant elevation of GGT was found with increasing serum TCDD levels, but only among heavy drinkers.[14] Assessment is underway of other organ systems. Comparison of the results of the Ranch Hand and NIOSH medical studies should provide useful insights into health effects in humans, especially if the results are consistent with those found in studies of animals dosed with TCDD.

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