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EDITORIAL

The Chronic Health Effects of Occupational Exposure to Dioxin: Unanswered Questions

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Concern about delayed toxic effects which may follow exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is widespread, since diverse groups have been exposed to this potent chemical toxin. TCDD is formed during the synthesis of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) from trichlorophenol (TCP) and is also generated when TCP is synthesized from tetrachlorobenzene. Workers have potential to be exposed to TCDD during these manufacturing processes, as well as in 2,4,5-T application [1, 2]. Soldiers and civilians in Vietnam during the 1960's had potential exposure, since TCDD-contaminated 2,4,5-T was a principal ingredient of the defoliant Agent Orange. Residents of communities have been exposed following industrial accidents–as in Seveso, Italy in 1976; through contact with soil–as in Times Beach, Missouri, where TCDD-contaminated waste oil was used for dust control; and from exposure to the TCDD-contaminated combustion products of electrical transformer fires.

Acute toxicologic testing led to the discovery that TCDD was lethal to some species in doses of less than one microgram/kilogram of body weight. That finding earned TCDD the sobriquet of "most toxic man-made chemical." Additional manifestations of acute animal toxicity include profound wasting, thymic atrophy, bone marrow suppression, hepatotoxicity, and microsomal enzyme induction [3-6]. In addition, TCDD has been found to be teratogenic and fetotoxic in pregnant female mice [7-9]. Finally, TCDD has been demonstrated to be carcinogenic in rats and mice [10,11]. Preliminary data collected by the National Institute for Occupational Safety and Health (NIOSH) suggest a possible association between occupational exposure to TCDD and an increased number of deaths from soft-tissue sarcoma [12]. Further investigation will be required, however, to confirm that association.

Work by American, British, German, and Czechoslovakian physicians suggests that there is a range of toxic effects associated with TCDD exposure in man, especially in heavily exposed workers. Chloracne, an atypically persistent form of

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acne which results from contact with the halogenated hydrocarbons, has been observed since 1949 in workers engaged in TCP production [1]. In the 1950's, TCDD was recognized as the probable chloracnegenic agent in these exposures, although initially the 2,3,6,7 isomer was thought to be the primary cause of the skin lesions [2]. Scattered reports also offer evidence of hepatotoxicity, including hepatic porphyria, metabolic and lipid abnormalities, neurotoxicity, and immunologic alterations in workers exposed to TCDD [13-19]. Except for chloracne, however, the persistence of each of these findings requires confirmation.

The study in this issue of the American Journal of Industrial Medicine by Moses et al of 226 workers actually or potentially exposed to TCDD between 1949 and 1969 is a welcome addition to the literature. The investigators administered questionnaires, physical examinations, and blood and urine tests to this group (or in the case of neurological exams, to a subset of these workers) in order to assess past medical and reproductive history, current or past symptoms, and current physical condition.

The authors report several medically significant findings: gamma glutamyl transpeptidase activity levels were elevated, sensitivity to pinprick in the lower extremities was diminished in workers with current or past chloracne, and triglyceride levels were elevated in those with a past history of chloracne. These findings corroborate and extend previously published observations. Moses et al found no increase in the age-adjusted prevalence of self-reported myocardial infarction or angina in the group with chloracne, no alterations in total cholesterol levels, and no adverse reproductive outcomes.

Although the data presented in this report are extremely valuable, several methodologic problems compromise somewhat the validity of the study. Among these are the cross-sectional nature of the study, the low participation rate, and the difficulties of assigning proper exposure status in the absence of industrial hygiene or other exposure data. The authors discuss several of these points.

Validity issues inherent in all cross-sectional surveys include the sampling of a "survivor" population, the difficulty of assessing causality when it is not possible to know with certainty whether or not exposure preceded illness, and the use of prevalence as a surrogate for incidence. As was noted, Moses et al found no increased prevalence of myocardial infarction in their workers after adjustment for age. Acknowledging that these are not data on incident, and that medical record confirmation was not sought, it is nevertheless unfortunate that the authors provide us with only a Mantel-Hanzel chi-square statistic and that they calculated no prevalence ratios or exposure odds ratios. When prevalence ratios for myocardial infarction are calculated for the age strata 40-59, 60-69, and 70+ years, the ratios are 3.0, 1.1, and 3.6. Although the age-specific pattern is difficult to interpret, the elevated ratios in two of these three strata are intriguing. Given these findings, one would like to know the prevalence of ever-having-had-a-myocardial-infarction in the entire cohort before concluding that there was, in the study by Moses et al, no association between TCDD exposure and heart disease.

A participation rate of 55% is discouraging and vulnerable to bias. Laudably, the authors sampled non-participants and ascertained their reasons for non-participation. They also determined the probable level of exposure of sampled non-participants to the 2,4,5-T process. The proportions with "none-minimal" and "moderate-heavy" exposure were almost identical in participants and non-participants. This information is encouraging since it indicates that participants and non-participants probably did not differ in their occupational exposures to the 2,4,5-T process.

Unfortunately, the authors were not able to use exposure status as defined from employee histories or company records as their indicator of exposure, and instead they had to rely upon past or present chloracne as a surrogate measure of exposure to TCDD. Although a positive correlation appears to exist between exposure classification and the presence of chloracne, we are given no quantitative estimate of this relationship, nor do we know what proportion of the dependent variable—chloracne—is predicted by the independent variable—exposure classification. In addition, the information that 36% of those workers reporting minimal exposure had a history of chloracne begs for further examination. A consequence of the uncertain relationship between chloracne and exposure is that there is no definitely unexposed comparison group in the study.

Future investigations of the toxicity of TCDD to man will build upon the work presented by Moses et al. The biologic significance of elevated triglyceride levels in workers exposed to TCDD needs to be explored further, and the possible relationship of this observation to vascular disease must be defined more precisely. Further investigation of the immunologic, hepatic, neurologic, and reproductive consequences of exposure to TCDD is also needed, and work along these lines is already underway at several centers in the United States and abroad. Finally, resolution of the question of the human carcinogenicity of TCDD is still urgently required.

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