IMPLICATIONS FOR VETERANS OF LIVER FINDINGS IN HUMANS AND ANIMALS EXPOSED TO HIGH LEVELS OF TCDD

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Introduction

Among the first recognized toxic manifestations from administration of acute, subchronic and chronic doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) to rats, mice and other experimental animals were effects on the liver. Despite concern years ago that humans would be affected similarly, it has become apparent that hepatic effects in animals given TCDD are variable among species and depend on the age, sex, and strain, and species. In light of this variability, scientists have struggled to understand the relevance to humans of the various animal studies.

Methods

To understand the relevance to humans, animal and human studies of potential liver effects from TCDD were evaluated critically. Focus was given to studies of individuals with the highest doses of TCDD, and the liver findings were evaluated according to accepted causation criteria (e.g., Hill's criteria of consistency, strength, dose-response, coherence, specificity, etc.). Populations in which TCDD dose levels are highly elevated (thousands of times higher than those in typical background populations1 or in Ground troops in Vietnam2) include occupational cohorts in the United States,[3] Germany,[4,5] the accident cohort in Seveso, Italy,[6] and the Ranch Hand veterans.[7, 32]

Results

Enlarged Liver. The striking variability in changes in liver structure and function (e.g., hyperplasia and hypertrophy) in TCDD treated animals have been summarized.[8-10] Clinical investigation of humans at doses of TCDD sufficient to induce chloracne has disclosed only a few reports of enlarged livers among industrial cohorts[11-14] and among the Seveso cohort.[15] In controlled epidemiological studies, no evidence for liver enlargement or other lesions was reported.[16]

Enzyme Induction. In animals, enzyme induction is a notable effect of administration of TCDD on an acute, subchronic or chronic basis, although with considerable interspecies variation. In humans, direct evidence for enzyme induction is lacking. Elevated *gamma*-glutamyl transpeptidase (γ-GTP) has been reported in Seveso children with chloracne,[17, 18] in British workers,[19] in one sample of Monsanto workers[20] (but not another),[21] and among Ranch Hand veterans when examined as a continuous variable.[7] However, the non-specificity of γ-GTP precludes any conclusion that this change is indicative of effects on the liver at all let alone induction of liver microsomal enzymes or specific liver damage.[22] Significant elevations in D-glucaric acid excretion (an indirect indicator of enzyme induction) have been reported in adults in the intermediate exposure zone at Seveso and the children in the high exposure zone,[23] in industrial workers in Great Britain[24] but not in U.S. workers.[16]

AST/ALT. In animals, elevated serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been observed in conjunction with severe liver damage, particularly in rats.[8-10] In highly exposed humans, transient elevations in AST or ALT have been reported following initial exposures at Seveso[17, 18] and in some exposed industrial workers,[14, 25] but not in studies conducted ten or more years after exposure.[16, 19, 20, 21] In Ranch Hand veterans ALT, AST, and γ-GTP but not overt liver disease showed a statistical association with TCDD levels.[7]

Porphyria. TCDD increased urinary excretion of porphyrins in mice and rats.[8-10] However, any association between exposure to TCDD in humans and porphyrin changes, particularly the acquired porphyria cutanea tarda, which can be induced by hexachlorobenzene,[26] is questionable. Although there were three reports indicative of increased urinary porphyrins in persons highly exposed to dioxin[14, 28, 29, 30] Careful follow-up in U.S. workers disclosed no evidence for porphyrin abnormalities.[27]

Liver Cancer. Finally, the concern generated by the observation of elevated liver cancers in female rats[31] has not been reflected in humans. A consistent finding in cancer epidemiological studies of groups highly exposed to dioxin has been an absence of increased hepatoma. While several studies do report an increase in "all cancers," the interpretation of this finding is ambiguous because of potential confounding exposures to other chemicals.[3] Moreover, this observation directly conflicts with the data in animals treated with TCDD at the maximally tolerated dose for a lifetime that total cancers at all sites are decreased.

Discussion and Conclusion

Analysis of the major published clinical studies by the use of accepted causation criteria fails to establish that a cause and effect relationship between TCDD and liver toxicity has been demonstrated. For example, liver injury was not observed in the remarkably thorough and extensive prospective investigations by the Air Force of Ranch Hand veterans. Review of studies that report "positive" liver effects leads to the conclusion that the findings are inconsistent, transient, confounded by such common liver toxins as alcohol or viral infections, or are not specific to the liver. Despite animal data, the lack of consistent, affirmative human findings in studies of high dosed populations for many years should offer reassurance to veterans of the Vietnam war that the low levels of TCDD in Agent Orange to which they may have been exposed do not constitute a threat to their health from damage to the liver.

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