Environmental Management Science Program

Project ID Number 54684

Mechanism Involved in Trichloroethylene-Induced Liver Cancer: Importance to Environmental Cleanup

Richard J. Bull
Pacific Northwest National Laboratory
MS P7-56
P.O. Box 999
Richland, Washington 99352
Phone: 509-373-6218
E-mail: dick.bull@ccmail.pnl.gov

Brian D. Thrall, Co.-P.I.
Pacific Northwest National Laboratory
P7-56
P.O. Box 999
Richland, Washington 99352
Phone: 509-376-3809
E-mail: Brian.thrall@pnl.gov

Lyle B. Sasser
Pacific Northwest National Laboratory
P7-56
P.O. Box 999
Richland, Washington 99352
Phone: 509-376-2560
E-mail: Lyle.sasser@pnl.gov

John H. Miller
Pacific Northwest National Laboratory
P7-56
P.O. Box 999
Richland, Washington 99352
Phone: 509-376-5803
E-mail: John.h.miller@pnl.gov

Irvin R. Schultz
Pacific Northwest National Laboratory
P7-56
P.O. Box 999
Richland, Washington 99352
Phone: 509-376-5031
E-mail: Irvin.schultz@pnl.gov

June 1, 1998

54684

Mechanism Involved in Trichloroethylene-Induced Liver Cancer: Importance to Environmental Cleanup

Richard J. Bull, Pacific Northwest National Laboratory

Brian D. Thrall, Co.-P.I., Pacific Northwest National Laboratory
Lyle B. Sasser, Pacific Northwest National Laboratory
John H. Miller, Pacific Northwest National Laboratory
Irvin R. Schultz, Pacific Northwest National Laboratory

Research Objective

The objective of this project is to develop critical data for changing risk-based clean-up standards for trichloroethylene (TCE). The project is organized around two interrelated tasks:

Task 1 addresses the tumorigenic and dosimetry issues for the metabolites of TCE that produce liver cancer in mice, dichloroacetate (DCA) and trichloroacetate (TCA). Early work had suggested that TCA was primarily responsible for TCE-induced liver tumors, but several, more mechanistic observations suggest that DCA may play a prominent role. This task is aimed at determining the basis for the selection hypothesis and seeks to prove that this mode of action is responsible for TCE-induced tumors. This project will supply the basic dose-response data from which low-dose extrapolations would be made.

Task 2 seeks specific evidence that TCA and DCA are capable of promoting the growth of spontaneously initiated cells from mouse liver, in vitro. The data provide the clearest evidence that both metabolites act by a mechanism of selection rather than mutation. These data are necessary to select between a linear (i.e. no threshold) and non-linear low-dose extrapolation model.

Research Progress and Implications

As of May of 1998, this research has identified two plausible modes of action by which TCE produces liver tumors in mice. These modes of action do not require the compounds to be mutagenic. The bulk of the experimental evidence suggests that neither TCE nor the two hepatocarcinogenic metabolites of TCE are mutagenic. The results from our colony formation assay clearly establish that both of these metabolites cause colony growth from initiated cells that occur spontaneously in the liver of $B_6C_3F_1$ mice, although the phenotypes of the colonies differ in the same manner as tumors differ, in vivo. In the case of DCA, a second mechanism may occur at a lower dose involving the release of insulin. This observation is timely as it was recently reported that occupational exposures to trichloroethylene results in 2 to 4-fold elevations in serum insulin concentrations, as well. The increases in insulin have not been shown responsible for the induction of liver tumors. Therefore, this problem is a subject of a proposal to the Office of Biological and Environmental Research Low-Dose Initiative. However, even if this is demonstrated to be the most sensitive mechanism for liver tumor induction, it is unlikely to contribute to induction of cancer at lower doses, since this involves modification of normal endocrine function. As doses are decreased to levels that do not induce increase in serum insulin level, there should be no risk from this metabolite either. Therefore, there is clearly a rational basis for considering a margin of exposure for low dose extrapolation of liver cancer risks for TCE.

Planned Activities

There are technical questions that still arise from whether TCA or DCA is primarily responsible for the induction of liver cancer. If TCA could be shown solely responsible for the tumors, it would simplify the argument for low dose extrapolation. Our current pharmacokinetic data does not allow us to conclude that effective concentrations DCA are not formed from TCE because the effective

carcinogenic concentrations in blood at the limit of detection. We will pursue this further during the final phases of this project. Nevertheless, the demonstration that DCA is also acting by a tumor promoting mechanism will still provide a basis for using a threshold or margin of exposure approach for estimating cancer risk.

Beyond completing current experiments and analysis of data that has already been generated in the project, our research over the remaining period of the project is to obtain good dose-response data on insulin- releasing properties of DCA and make certain that TCA does not also produce the same effect. If these data prove that the effect is specific for DCA, we will evaluate serum insulin concentrations in animals being chronically administered TCE. If serum insulin is increased in these animals, we should be able to use serum insulin levels as a surrogate for effective doses of DCA derived from TCE. In addition, we are pursuing further the possibility that the key step in TCA-induced carcinogenicity may be attributed to the induction of phosphotidylinositol-3-kinase activity.

A member of our research team (RJB) is preparing the final draft on the mode of action paper being used by the Environmental Protection Agency as a test case for their new Proposed Cancer Risk Assessment Guidelines. The arguments put forward above have been generally accepted by the Agency and will form the basis for their decision. Since kidney tumors in rats are also produced with TCE, the impact of this work will be to change the potency estimate from that derived on liver tumor induction in the mouse to kidney tumor induction in mice. This should decrease the estimated risk per unit dose by approximately 10-fold. Informal discussions have been conducted with the Office of Water of the EPA to determine if that office is going to be responsive to any new recommendations from the National Center for Environmental Assessment related to low-dose estimates of cancer risk associated with trichloroethylene. If the new guidelines are determined appropriate for liver tumor induction by TCE, they do intend to determine whether the drinking water MCL should be revised.

Other Access To Information

Publications

Stauber, A.J., Bull, R.J. and Thrall, B.D. (1998) Dichloroacetate and trichloroacetate promote clonal expansion of anchorage-independent hepatocytes, in vivo and in vitro. Toxicol. Appl. Pharmacol. In press.

Kato-Weinstein, J., Thrall, B.D. and Bull, R.J. (1998) The effect of haloacetates on carbohydrate metabolism in $B_6C_3F_1$ mice. Society of Toxicology, 37th Annual Meeting #308

Mounho, B.J., Stauber, A.J., Bull, R.J. and Thrall, B.D. (1998) Peroxisome proliferator-induced activation of extracellular signal-regulated kinase (Erk) pathway contributes to hepatocellular clonal expansion. Carcinogenesis. Submitted

Merdink, J.L., Gonzalez-Leon, A., Bull, R.J. and Schultz, I.R. (1998) The extent of dichloroacetate formation from trichloroethylene, chloral hydrate, trichloroacetate, and trichloroethanol in B6C3F1 mice. Toxicological Sciences. In press

Orner, G.A., Malone, J.A., Stillwell, L.C., Cheng, R.S., Stauber, A.J., Sasser, L, Thrall, B.D. and Bull, R.J. (1998) Factors that affect H-ras mutation frequency and spectra of chemically-induced liver tumors in B6C3F1 mice. Toxicol. Appl. Pharmacol. In preparation

Presentations

Mounho, B.J. and Thrall, B.D. (1998) Tumor promotion by peroxisome proliferators may involve the activation of mitogenic activated protein kinases (ERK1/ERK2). Society of Toxicology, 37th Annual Meeting, #51

Orner, G.A., Stillwell, L.C., Cheng, R.S., Sasser, L.B., Bull, R.J. and Thrall, B.D. (1998) Effects of trichloroacetate (TCA) and dichloroacetate (DCA) on H-ras in male B6C3F1 mice. Society of Toxicology, 37th Annual Meeting, #60

Lingohr, M.K., Thrall, B.D. and Bull, R.J. (1998) Dichloroacetate (DCA) affects proteins involved in insulin signaling in mouse liver cells. Society of Toxicology, 37th Annual Meeting #61

Stauber, A.J., Bull, R.J. and Thrall, B.D. (1998) Dichloroacetate and trichloroacetate promote clonal expansion of anchorage-independent hepatocytes. Society of Toxicology, 37th Annual Meeting #62

Kato-Weinstein, J., Thrall, B.D. and Bull, R.J. (1998) The effect of haloacetates on carbohydrate metabolism in B6C3F1 mice. Society of Toxicology, 37th Annual Meeting #308

Gonzalez-Leon, A., Merdink, J.L., Schultz, I.R. and Bull, R.J. (1998) Dichloroacetate auto-inhibits its degradation in the cytosol. Society of Toxicology, 37th Annual Meeting #426

Schultz, I.R., Gonzalez-Leon, A., Merdink, J.L. and Bull, R.J. (1998) Comparative toxicokinetics and metabolism of haloacetic acids in F344 rats. Society of Toxicology, 37th Annual Meeting #1045

Merdink, J.L., Schultz, I.R. and Bull, R.J (1998) Formation of dichloroacetic acid in B6C3F1 mice from trichloroethylene or its metabolites. Society of Toxicology, 37th Annual Meeting #1621