FINAL REPORT

U.S. Department of Energy

BIOAVAILABILTY OF ORGANIC SOLVENTS IN SOILS: INPUT INTO BIOLOGICALLY BASED DOSE-RESPONSE MODELS FOR HUMAN RISK ASSESSMENTS

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Research Objective:

The purpose of this study is to determine the bioavailability of organic solvents following dermal exposures to contaminated soil and water. Breath analysis is being used to obtain real-time measurements of volatile organics in expired air following exposure in rats and humans. Rhesus monkeys were used as surrogates for humans in benzene exposures. The exhaled breath data was \analyzed using physiologically based pharmacokinetic (PBPK) models to determine the dermal bioavailability of organic solvents under realistic exposure conditions. The end product of this research will be a tested framework for the rapid screening of real and potential exposures while simultaneously developing PBPK models to comprehensively evaluate and compare exposures to organic compounds from either contaminated soil or water.

Research Progress and Implications:

This report summarizes activities 3 years into a 3-year project: Final Report

Numerous sites within the DOE Complex have significant levels of organic contaminants in soil, which are either slowly released or degraded, providing a potential long-term source for chemical exposures. Remediation clean-up costs vary dramatically with the level to which soil must be decontaminated. However, a difficulty in establishing soil cleanup levels stems, in part, from our lack of knowledge of the dermal bioavailability of chemicals following exposure to environmental mediums. Compared to dermal exposures with neat or aqueous compound, little is understood about the dermal bioavailability of solvents in soil, dust, sludge, or sediment matrices. Therefore, research in this project was designed to provide an understanding of the influence of various environmental factors on the kinetics and bioavailability of solvent-laden soils. To this end, a method was developed to determine dermal uptake of solvents under nonsteady state conditions using real-time breath analysis in rats, monkeys, and human

volunteers. The exhaled breath was analyzed using an ion trap mass spectrometer, which can continually quantitate chemicals in the exhaled breath stream in the 1-5 ppb range. The resulting exhaled breath data were evaluated using physiologically based pharmacokinetic (PBPK) models to estimate dermal permeability constants (K_p), under various exposure conditions. To date, exposures have been conducted comparing the impact of exposure matrix (soil versus water), occlusion versus non-occlusion, and species-differences on the percutaneous absorption of methyl chloroform, trichloroethylene, perchloroethylene and benzene. Thus far, studies have demonstrated that rat skin is roughly 40x more permeable than human skin, that bioavailability is decreased when exposures are in a soil versus aqueous matrix, and that under non-occluded exposure conditions the majority of the compound is lost to volatilization and unavailable for absorption. These results have clearly illustrated that the methodology was sufficiently sensitive to enable the conduct of animal and human dermal studies at low exposure concentrations over small body surface areas, for short periods of time. Ultimately, these data will impact human health risk assessments by replacing conservative default assumptions, reduce uncertainties in exposure/dose model paradigms, and may result in reduced cleanup costs for DOE. Furthermore, the deployment of this real-time technology linked with PBPK modeling could improve industrial hygiene practices by enabling on-site measurement of total human exposures to multiple chemicals and rapid evaluation of potential health risks.

Publication Information:

1. Thrall, K.D., Poet, T.S., and Corley, R.A. (1999). An innovative method to determine percutaneous absorption: Real-time breath analysis and physiologically based pharmacokinetic modeling. IN: *Percutaneous Absorption* (R. Bronaugh and H. Maibach, Eds.), Third Ed., Marcel Dekker, Inc., New York, Pp. 929-937.

2. Poet, T.S., Thrall, K.D., Corley, R.A., Hui, X., Maibach, H.I., and R.C. Wester. (2000). Utility of real time breath analysis and physiologically based pharmacokinetic modeling to determine the percutaneous absorption of methyl chloroform in rats and humans. *Toxicological Sciences* 54: 42-51.

3. Thrall, K.D., Poet, T.S., Corley, R.A., Tanojo, H., Edwards, J.A., Weitz, K.K., Hui, X., Maibach, H.I., and Wester, R.C. (2000). A real-time in-vivo method for studying the percutaneous absorption of volatile chemicals. *Int. J. Occup. Environ. Health* 6(2): 96-103.

4. Poet, T.S., Corley, R.A., Thrall, K.D., Edwards, J.A., Tanojo, H., Weitz, K.K., Hui, X., Maibach, H.I., and Wester, R.C. (2000). Assessment of the percutaneous absorption of trichloroethylene in rats and humans using MS/MS real time breath analysis and physiologically based pharmacokinetic modeling. *Toxicological Sciences* 56: 61-72.

5. Poet, T.S., Weitz, K.K., Gies, R.A., Edwards, J.A., Thrall, K.D., Corley, R.A., Tanojo, H, Hui, X., Maibach, H.I., and Wester, R.C. (2001). PBPK modeling of the percutaneous absorption of perchloroethylene from a soil matrix in rats and humans. *Toxicological Sciences* (Submitted).

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Presentations:

1. Poet, T.S., Thrall, K.D., Corley, R.A., Maibach, H.I., and Wester, R.C. (2001). Percutaneous PBPK model for the uptake of perchloroethylene (PCE) from soil exposures in rats and humans. *To be presented at the Annual Society of Toxicology Meeting, San Francisco, CA, March 25-29, 2001.*

2. Wester, R.C., Poet, T.S., Weitz, K.K., Edwards, J.A., Corley, R.A., Tanojo, H., Hui, X., Maibach, H.I., and K.D. Thrall. (2000). Human dermal absorption of trichloroethylene from soil and water. *Presented at the Annual Society of Toxicology Meeting, Philadelphia, PA, March 19-23, 2000.*

3. Poet, T.S., Corley, R.A., Thrall, K.D., Edwards, J.A., and Wester, R.C. (2000). Exhaled breath analysis and PBPK modeling of the dermal absorption of trichloroethylene in rats. *Presented at the Annual Society of Toxicology Meeting, Philadelphia, PA, March 19-23, 2000.*

4. Wester, R.C., Tanojo, H., Hui, X., Maibach, H.I., Poet, T.S., Weitz, K.K., Edwards, J.A., Corley, R.A., and Thrall, K.D. (2000). Bioavailability of organic solvents in soils: Input into biologically based dose-response models for human risk assessment. *Presented at the 2nd Environmental Management Science Program National Workshop, Atlanta, GA, April 24-27, 2000.*

5. Poet, T.S., Thrall, K.D., Corley, R.A., Weitz, K.K., Edwards, J.A., Tanojo, H., Hui, X., Maibach, H.I., and R.C. Wester. (2000). Determination of dermal uptake of solvents from soil and water in humans. *Presented at the Annual American Industrial Hygiene Conference and Exposition, Atlanta, GA, May 22, 2000.*

6. Poet, T.S., Corley, R.A., Thrall, K.D., and R.C. Wester. 1999. Assessing the dermal bioavailability of volatile organics in rats. *Presented at the Annual Society of Toxicology Meeting, New Orleans, LA, March 1999.*

7. Wester, R.C., Hui, X., Maibach, H.I., Poet, T.S., Weitz, K.K., Edwards, J.A., Corley, R.A., and K.D. Thrall. 1999. An innovative method to determine dermal uptake of solvents from soil and water *in vivo* in humans. *Presented at the Annual Society of Toxicology Meeting, New Orleans, LA, March 1999.*

8. Wester, R. C., Hui, X., Maibach, H. I., Poet, T. S., Corley, R. A., and K. D. Thrall. 1998. Bioavailability of Organic Solvents in Soils: Input into Biologically Based Dose-Response Models for Human Risk Assessment. *Presented at the Annual Department of Energy*

Environmental Management Science Program, Chicago, IL, August, 1998.

Award:

Risk Assessment Specialty Section of the Society of Toxicology 38th Annual Meeting, New Orleans, LA, 1999.