

**Federal Assistance Program/Project Status Report and Technical Progress Report**

**Project EMSP-1**

**Title:**

DOE/AL/76406--T1

Improved Risk Estimates for Carbon Tetrachloride

**Principal Investigator:**

Janet M. Benson, Lovelace Respiratory Research Institute

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**Key Co-Investigators**

Kristen J. Nikula, Lovelace Respiratory Research Institute

Edward B. Barr, Lovelace Respiratory Research Institute

David L. Springer, Pacific Northwest National Laboratory

Karla D. Thrall, Pacific Northwest National Laboratory

**Progress May 1 - July 31, 1997**

**Task 1: Compare the rates of carbon tetrachloride metabolism by rats mice, and hamsters *in vivo*. Determine the rates of carbon tetrachloride metabolism *in vitro* using microsome preparations from livers of humans (available from tissue culture bank), F344 rats, B6C3F1 mice and Syrian hamsters.**

The materials needed for construction of the closed atmosphere exposure system for measurement of carbon tetrachloride uptake by the laboratory animals have been purchased, and construction of the system is underway. The system is expected to be operational by late summer.

**Task 2: Using hepatic microsome preparations, determine the role of specific cytochrome P450 isoforms in mediating carbon tetrachloride induced toxicity in laboratory animals. The effects of repeated inhalation and ingestion exposure to carbon tetrachloride on these isoforms will also be determined.**

A postdoctoral fellow, Dr. Richard Zangar, has been hired by Dr. David Springer to conduct the cytochrome 450 studies. He will begin work during August 1997. Dr. Zangar visited the Lovelace Respiratory Research Institute in June to review procedures for preparation and storage of microsomes for the work to be conducted at Pacific Northwest National Laboratories.

Inhalation exposures of rats, mice and hamsters to carbon tetrachloride began in June. Microsomal fractions from livers of all species exposed to 0, 5, 20 and 100 ppm carbon tetrachloride for 1 week have been prepared and are being stored frozen for future analysis.

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**Task 3: Evaluate the toxicokinetics of acutely inhaled and ingested carbon tetrachloride in rats, mice and Syrian hamsters as a function of exposure concentration in air or water. The effects of previous inhalation exposure to or ingestion of carbon tetrachloride on the toxicokinetics of subsequently inhaled or ingested carbon tetrachloride will also be determined.**

The toxicokinetic studies will be conducted early in FY98. Dr. Karla Thrall will participate in the conduct of these studies.

**Task 4: Revise the current PBPK model for Carbon Tetrachloride based on information obtained under Tasks 1, 2 and 3.**

This work will be conducted in FY98 when the needed information has become available.

**Task 5: Determine whether inhalation exposure conditions ultimately resulting in liver tumors in rats and mice produce hepatic cell injury, death, and regenerative proliferation under conditions of subchronic exposure. Determine whether repeated ingestion of carbon tetrachloride in drinking water at concentrations 100 and 1000 times the current drinking water standards results in hepatic cell injury, death, and regenerative proliferation.**

Inhalation exposures to address the goals of Task 5 began in June. The 1- and 4-week sacrifices of rats, mice and hamsters exposed to 0, 5, 20 and 100 ppm carbon tetrachloride have been completed. Final sacrifices of rats and mice will occur in September 1997. Because of unexpected high mortality among hamsters on study, we may be starting new groups on study to address the issues in Task 1 and 5.

Initial work on the drinking water study has begun. The protocol has been prepared and studies on palatability and consumption rate have begun. The drinking water study will be conducted in late September or October 1997.



Respiratory Research Institute

Lovelace Biomedical and  
Environmental Research Institute

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May 30, 1997

Michael G. Loera  
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Building 388  
Albuquerque, NM 87185

Dear Mr. Loera:

Enclosed are four copies each of the Technical Progress Report for FY1997 for the work we are conducting for the Environmental Management Science Program under Cooperative Agreement DE-FC04-96AL76406. If you have any questions on this material, please contact Chuck Hobbs (845-1045) or me (262-7938).

Sincerely,

Joe L. Mauderly  
President, LBERI

JLM:ah

xc: Joe Rudolph  
Chuck Hobbs  
Kathy Aragon

*Curing Respiratory Disease*

**TECHNICAL PROGRESS REPORT**

to the

**U.S. DEPARTMENT OF ENERGY**

for research conducted by

**THE LOVELACE RESPIRATORY RESEARCH INSTITUTE**

through its subsidiary

**LOVELACE BIOMEDICAL AND  
ENVIRONMENTAL RESEARCH INSTITUTE**

for the

**OFFICE OF ENVIRONMENTAL MANAGEMENT/SCIENCE PROGRAM**

under

**COOPERATIVE AGREEMENT**

**DE-FC04-96AL76406**

during

**October 1, 1996 - September 30, 1997**

**Submitted May 30, 1997**

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# TECHNICAL PROGRESS REPORT FOR OFFICE OF ENVIRONMENTAL MANAGEMENT/SCIENCE PROGRAM

## Project EMSP-1

### Title:

Improved Risk Estimated from Carbon Tetrachloride

### Principal Investigator:

Janet M. Benson

### Key Co-Investigators:

Kristen J. Nikula

Edward B. Barr

David L. Springer, Pacific Northwest National Laboratory

Karla D. Thrall, Pacific Northwest National Laboratory

### Abstract

Carbon tetrachloride ( $\text{CCl}_4$ ) has been used extensively within the Department of Energy (DOE) nuclear weapons facilities. Rocky Flats was formerly the largest volume user of  $\text{CCl}_4$  in the United States, with 5000 gallons used there in 1977 alone. At the Hanford site, several hundred thousand gallons of  $\text{CCl}_4$  were discharged between 1955 and 1973 into underground cribs for storage. Levels of  $\text{CCl}_4$  in groundwater at highly contaminated sites at the Hanford facility have exceeded the drinking water standard of 5 ppb by several orders of magnitude. High levels of  $\text{CCl}_4$  at these facilities represent a potential health hazard for workers conducting cleanup operations and for surrounding communities. The level of  $\text{CCl}_4$  cleanup required at these sites and associated costs are driven by current human health risk estimates which assume that  $\text{CCl}_4$  is a genotoxic carcinogen. The overall purpose of these studies is to improve the scientific basis for assessing the health risk associated with human exposure to  $\text{CCl}_4$ . Specifically, we will determine the toxicokinetics of inhaled and ingested  $\text{CCl}_4$  in F344/Crl rats, B6C3F<sub>1</sub> mice, and Syrian hamsters. We will also evaluate species differences in the metabolism of  $\text{CCl}_4$  by rats, mice, hamsters, and man. Dose-response relationships will be determined in all these studies. This information will be used to improve the physiologically based pharmacokinetic (PBPK) model for  $\text{CCl}_4$  originally developed by Paustenbach *et al.* (1988) and more recently revised by Thrall and Kenny (1996). We will also provide scientific evidence that  $\text{CCl}_4$ , like chloroform, is a hepatocarcinogen only when exposure results in cell damage, cell killing, and regenerative cell proliferation. In combination, the studies outlined in this proposal will provide the exact types of information needed to enable refined cancer risk estimates for  $\text{CCl}_4$  under the new guidelines for risk assessment proposed by the EPA in April 1996 (U.S. EPA, 1996).

### Recent Progress

This is a new project. Experimentation has just begun (May 1997).

## Future Direction and Expected Progress

- We will compare the rates of CCl<sub>4</sub> metabolism by rats, mice, and hamsters *in vivo*. Extrapolations to man will be based on parallel studies of the metabolism of CCl<sub>4</sub> by rat, mouse, hamster, and human liver slices *in vitro*.
- Using hepatic microsome preparations, we will determine the role of specific cytochrome P450 isoforms in CCl<sub>4</sub> mediated toxicity for laboratory animals and relate this to humans. The effects of repeated inhalation and ingestion exposure of CCl<sub>4</sub> on these isoforms will also be determined.
- We will evaluate the toxicokinetics of acutely inhaled and ingested CCl<sub>4</sub> in rats, mice, and Syrian hamsters as a function of exposure concentration of ingested dose. The effects of previous inhalation exposure to or ingestion of CCl<sub>4</sub> on the toxicokinetics of subsequently inhaled or ingested <sup>14</sup>CCl<sub>4</sub> will also be determined.
- We will revise the current PBPK model for CCl<sub>4</sub> based on information obtained from the above experiments.
- We will determine whether exposure conditions ultimately resulting in liver tumors in rats and mice produce hepatic cell injury, death, and regenerative proliferation under conditions of subchronic exposure. Conversely, we will determine whether exposure conditions that do not ultimately result in liver tumors in these species correspond to a no-observable-adverse-effects level (NOAEL) for these histopathologic and proliferative effects.
- We will determine whether repeated ingestion of CCl<sub>4</sub> in drinking water at concentrations 100 and 1000 times the current drinking water standards results in hepatic cell injury, death, and regenerative proliferation.

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