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How to assess possible health effects of PCE exposure

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Background:

- **Epidemiological studies consistently show increased risk for cancer among dry-cleaning workers.**
- **Over 90% of an estimated 50,000 U.S. drycleaning shops currently use tetrachloroethylene (perchloroethylene, PCE) as their primary dry cleaning solvent.**
- **PCE is a recognized animal carcinogen classified by the International Agency for Research on Cancer (IARC) as a probable human carcinogen.**
- **Increased risk for some cancers in dry cleaners has been attributed to life-style or medical access risk factors, or possibly to other solvents, in previous epidemiological studies of cancer in solvent-exposed workers.**



On-going epidemiological studies

- **An update on mortality in The National Cancer Institute dry-cleaning cohort (in press 2002)**
- **A study of cancer incidence among dry cleaners in Scandinavia, funded by the Halogenated Solvent Alliance**





Why study dry cleaners?

- 50% women workers
- 50% minority workers
- 90% use perchloroethylene (PCE), a "probable carcinogen"
- For most, PCE is the only solvent exposure (no mixed exposures)



Problem:

How can we ascertain whether there is a connection between exposure to PCE and health effects, such as cancer?





Our response:

This question was investigated in a NIOSH pilot project designed to explore the feasibility of and refine the methods to be used in a full-scale study. The experimental design is presented here. In the pilot project 18 women working in dry cleaning were compared with 20 women working in industrial laundries, matched by age, race, and smoking status.



Measures of external exposure to perchloroethylene

**Personal breathing zone air monitoring of PCE
Area monitoring of PCE**





Biomarkers of internal exposure to PCE and metabolites

- PCE in exhaled breath
- PCE in blood
- Trichloroacetic acid in blood and urine
- Dichloroacetic acid in urine
- S-Trichlorovinyl-L- cysteine in urine
- N-Acetyl-S-(trichlorovinyl)-L-cysteine in urine
- N-Acetyl-S-(trichlorovinyl)-L-cysteine in cervical mucus



Biomarkers of biologically effective dose

- DNA adducts in cervical cells
- DNA strand breaks in lymphocytes (Comet Assay)
- Protein adducts in plasma
- Protein adducts in lymphocytes
- 8-Hydroxy-2-deoxyguanosine in lymphocyte DNA (oxidative damage)
- 8-Hydroxy-2-deoxyguanosine in urine (repair of oxidative DNA damage)
- 8-Epi-prostaglandin F_{2α} in urine (oxidative damage to cell membranes)





Biomarkers of early biologic effect

- Chromosome aberrations in lymphocyte DNA
- Somatic mutations in lymphocyte DNA



Biomarkers of altered structure/function

- **Early indicators of:**
 - renal proximal tubule damage (glutathione-S-transferase α in urine)
 - renal distal tubule damage (GST π in urine)
 - hepatocyte damage (GST α in plasma)
 - glomerular damage (albumin in urine)
 - damage to tubular reabsorption capability (retinol-binding protein in urine)
 - direct release of tubular tissue into urine (N-acetyl- β -D-glucosaminidase, alanine aminopeptidase in urine)
 - renal damage (brush border antigen in urine)
- **Cervical cell cytology abnormalities**





Biomarkers of susceptibility

- **Polymorphisms in genes encoding enzymes that catalyze metabolism of PCE and PCE metabolites**
 - **GSTM1**
 - **GSTT1**
 - **GSTP1**
 - **CYP2E1**
 - **NAT2**



Physiologically based pharmacokinetic modeling

- **incorporating:**
 - **Measures of exposure**
 - **Polymorphisms in metabolic genes**
 - **Measures of metabolites**
 - **Participant's body size and metabolic rate**
 - **Biomarkers of effective biological exposure**





Results:

- The NIOSH pilot study succeeded in collecting environmental samples & biological specimens & in processing and distributing samples & specimens to laboratories.
- We collected 97% of scheduled blood specimens, 95% of gynecological specimens, 100% of four core urine specimens requested from each participant and 86% of urine specimens requested from exposed participants to analyze variability over a three-week exposure period, & sent aliquots to 15 laboratories across the United States.
- Over thirty biomarkers of exposure, effect, and susceptibility were analyzed. Some analyses have been completed; others are on-going.



Conclusion:

- It was not expected with a group this size to find significant health status differences between dry-cleaning and laundry workers. However, there have been some results suggestive of an effect of PCE on health.
- These results, as well as the findings of multiple lifestyle risk factors, warrant a full-scale study, for which changes in study design have been suggested. A similar study design could be used to investigate a group exposed to another solvent.





Extramural PCE biomarker studies

- **PCE metabolism / physiologically based pharmacokinetic modeling**
- **Reproductive effects**
- **Environmental effects**



PCE metabolism

- **Birner, Dekant, et al., University of Wurzburg, Germany first found the metabolites of the GST pathway (S-Trichlorovinyl-L- cysteine and N-Acetyl-S-(trichlorovinyl)-L-cysteine) in humans exposed to PCE**
- **A group at the University of Mississippi is studying the effects of PCE and other peroxisome proliferating agents on metabolic pathways in catfish**





Assessment of PCE exposure

- Oregon Health and Science University is assessing human exposure to PCE and other VOCs near Superfund sites
- Schriber et al. at the New York State Department of Health investigated PCE metabolism and possible effects of exposure in apartment dwellers who lived above dry-cleaning shops (Environmental Health Perspectives, July 2002)



Reproductive effects

- The U. Mississippi group is also studying possible endocrine disruption by chemical contaminants
- Aschengrau et al at Boston University are investigating PCE contaminated drinking water & disorders of reproduction & development
- U. California Davis is exploring the relationship between metabolism and testicular toxicity caused by environmental chemicals, including PCE which has been reported to cause sperm motility changes in dry cleaners





Environmental effects

- The University of Washington is exploring whether plants can be used to remediate toxic spills of PCE and other contaminants.



Does PCE cause cancer?

- Will any of the current epidemiological studies provide the “definitive answer”?
- Will any of the current biomarker studies provide the “definitive answer”?
- What types of studies need to be done to answer this question?

