SERDP
Strategic Environmental Research and Development Program
Improving Mission Readiness Through Environmental Research

Using Mode of Action to Assess Health Risks from Mixtures of Chemical/Physical Agents

Cleanup
CU-1073

RESEARCH CATEGORY: 6.2 Applied Research

LEAD AGENCY: U.S. Department of Energy

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OBJECTIVE: Mixtures of carcinogenic chemicals are a major problem in groundwater plumes and soils on Department of Defense (DoD) and Department of Energy (DOE) facilities. While there is frequently data available for interactions between chemicals to judge risks from short term exposures, data that describes how interactions influence the development of cancer are very rare. This is largely because of the high costs associated with conducting complex interaction studies over the lifetime of experimental animals. Therefore, it is important that the limited resources that are available for studying interactions be directed towards the development of general principles that can be applied to a wide variety of circumstances.

The specific technical objectives: 1) To provide a scientific basis for estimating the risk for liver cancer induction by mixtures of chlorinated hydrocarbon solvents in hazardous waste sites and contaminated groundwater, 2) Test the hypothesis that interactions between non-genotoxic modes of action can be meaningfully predicted from knowledge of the mode of action and the dose-response relationships found with the individual components of the mixture. To limit the cost of this initial effort, the test will be limited to tertiary mixtures in which the dose of only one compound will be varied dichloroacetate (DCA), 3) Based on these studies an experimental design will be developed to validate the approach using solvents that independently generate the metabolites responsible for liver cancer induction.

BENEFIT: Because of the high cost associated with conducting research to examine biological interactions, the study of every potential interaction of environmental concern is not feasible. This research is directed towards the development of general principles that can be applied to a wide variety of circumstances. The benefits to DOE and DoD from the work proposed are: 1) data bases that can be directly used to assess the risks from mixed exposures to DCA or TCA whether they arise as metabolites from a single solvent [e.g., Trichloroethylene (TCE)] or from a mixture of solvents, 2) the data necessary to see how these metabolites interact with a cytotoxic solvent (carbon tetrachloride), and 3) a test of the hypothesis that hazards associated with mixtures of carcinogenic chemicals can be addressed by simply identifying the mode of action and knowing the dose-response relationships for the individual chemicals.

TECHNICAL APPROACH & RISK: The hypothesis this project intends to test is whether classifying the modes of action represented in a mixture and knowledge about the dose-response characteristics involved in eliciting a particular mode of action will provide a simpler and more accurate means of predicting the hazards that the mixture poses over a range of exposure situations. Whereas the number of chemicals present in the mixture may be large, the number of modes of action responsible for these effects are small. Each mode of action may have dozens of mechanisms that might contribute to changes in cell birth/death processes, but establishing mechanisms for every chemical is very expensive.

The modes of action represented by the three chemicals proposed for study are general to chemical carcinogenesis. Thus, the approach that would result from proving our hypothesis should be broadly applicable to any mixtures of chemical and/or physical causes of cancer. The top seven chlorinated hydrocarbon solvents found on DOE facilities produce liver cancer by non-genotoxic mechanisms. Two others are clearly genotoxic. Therefore, all modes of action are represented among these compounds. The occurrence of the genotoxic compounds is much less frequent and generally at much lower concentrations than the first seven compounds. Their cleanup levels are less controversial because it is difficult to refute low dose linearity in response for such chemicals and their concentrations rarely exceed drinking water standards of the Environmental Protection Agency (EPA).

ACCOMPLISHMENTS: In FY98, embedding and sectioning of tissues were initiated and completed for all tissues collected to date (DCA/TCA and DCA/TCA mixture studies). Histological staining was initiated for these tissues. Summarization of the tumor yield and size data was initiated. As reported previously, the carbon tetrachloride interaction study (combinations of DCA, TCA, CC14) in initiated mice was terminated because the carbon tetrachloride dose was too high. This resulted in rapid liver tumor development and massive numbers of tumors in the mice. A protocol was developed for repeating the carbon tetrachloride interaction studies at lower doses of carbon tetrachloride. Pharmacokinetics studies were initiated. Seven solvents have been investigated for their ability to produce dichloroacetic acid and trichloroacetic acid as metabolites in mice. Trichoroethylene, tetrachloroethylene, 1,1,2-trichloroethane and 1,1,1,2-tetrachloroethane have been identified as producing either dichloroacetic acid, trichloroacetic acid or both. A protocol has been written and approved for research investigating metabolic profiles after exposure of mice to mixtures of carbon tetrachloride and these 4 solvents.

TRANSITION: The project has a transition plan that includes: 1) insuring utilization of the data through extensive interaction with EPA; 2) establishing the hypothesis that interactions between environmental carcinogens can be understood on the basis of their individual modes of action; and 3) expanding the concept to other important environmental mixtures.