EMSP
Environmental Management Science Program
Project Summary Fact Sheet • April 2000

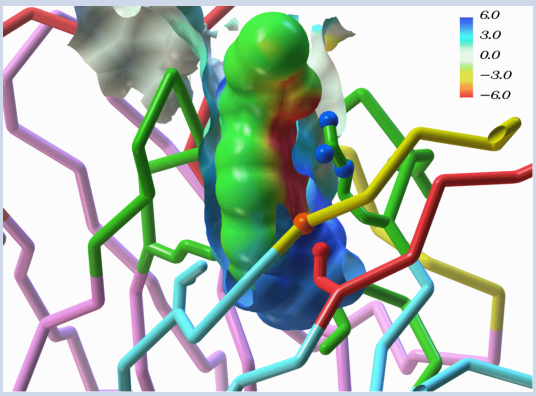
HEALTH SCIENCE

Research in the areas of health, ecology, and risk will impact remediation efforts at all major DOE sites

The central mission of the U.S. Department of Energy (DOE) Office of Environmental Management is to minimize risks to human health and to the environment from activities at DOE facilities. It is not possible to reduce the concentration of any contaminant to zero, but what are the appropriate end points for remediation efforts beyond which more extensive cleanup work is simply wasteful? How can the effects of long-term exposure to low doses of radiation or hazardous chemicals be determined without studies extending over many human lifetimes?

Specific questions being addressed by EMSP projects in this area include:

- What are the levels of risk associated with low concentrations of chlorinated hydrocarbons?
- Is the total concentration of a hazardous substance in a soil sample a reliable predictor of risk to health?
- How do some bacteria detoxify mercury at concentrations that would be harmful to higher organisms, and can understanding of this ability lead to practical techniques for remediation of mercury contamination?
- Can modern molecular biology techniques be used to identify early sensitization to contaminants before damage has occurred?
- Do some persons have variants of a particular gene that make them more susceptible to persistent DNA damage due to radiation or certain chemicals?
- What are the mechanisms by which exposure to radiation and/or certain chemicals induces leukemia, and can knowledge of the mechanisms lead to improved assessments of risks from long-term exposures to low levels of several contaminants?
- Can genetic engineering be used to improve antibodies that recognize hazardous chemicals such as polynuclear aromatic hydrocarbons for use in sensitive new multi-analyte analytical methods?



Antibodies for Monitoring Contaminants
A University of California project (54546) is using genetic engineering to improve detection of polynuclear aromatic hydrocarbons in the environment. This illustration shows submolecular charge distribution when benzo[a]pyrene(BaP; solid) is bound by antibody 4D5. Interaction of positively charged side chain of arginine H95 (blue) with p electrons on BaP (red) contributes to binding.

Problems/Solutions

- Clean-up standards that are too strict can result in the waste of millions of dollars for unnecessary remediation efforts, but standards that are too lax can also result in large long-term costs. EMSP studies of the mechanisms by which chlorinated hydrocarbons promote tumor growth may lead to improved risk-based standards for these substances.
- An important question for remediation standards is whether certain chemicals can interfere with endocrine systems and lead to detrimental reproductive or developmental effects. An EMSP project is developing methods to investigate this question for a class of common hydrocarbon contaminants.
- Sustainable and viable populations of non-human species are the most important factors for judging ecological relevance of low-level contaminants, but most risk analyses measure only cellular and molecular abnormalities. An EMSP project was designed to measure both chromosomal damage and metabolic rate in several species exposed to radiation and metal contaminants so that more reliable methods for risk analyses can be proposed.

Anticipated Impact

- Thousands of gallons of trichloroethylene and carbon tetrachloride were used at most major DOE sites, so accurate, risk-based standards are essential for determinations of the appropriate remediation goals at these sites.
- Numerous workers at DOE sites may have been exposed to excessive beryllium levels. An EMSP project is attempting to develop a biomarker that could detect beryllium sensitization well before reaching an exposure level that could lead to berylliosis.
- Workers at DOE sites may be exposed to low levels of radioactive or hazardous chemical species. One investigation is attempting to find genetic markers that would indicate whether an individual has a predisposition to suffering deleterious health effects from such exposures.

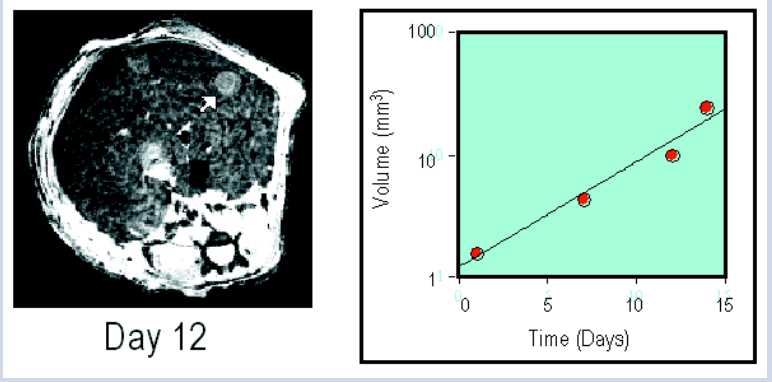
Antibodies for Monitoring Contaminants

Polynuclear aromatic hydrocarbons (PAHs) are found in coal tar and petroleum and as products of incomplete combustion. Some PAHs are toxic, and some are potent carcinogens, so reliable methods to detect them in the environment are needed. The University of California/Scripps Research Institute/University of Hawaii project (54546) involves a multidisciplinary team whose goal is to use genetic engineering to improve recombinant antibodies that detect PAHs, to explore the mechanisms by which the antibodies recognize individual PAHs, and to devise practical analytical methods to recover and measure PAHs in environmental samples. They recovered and characterized antibodies to specific PAHs from antibody gene "libraries" expressed in bacteria, and they found that selectivity and sensitivity of antibodies to PAHs can be altered considerably by changing the assay format. Computational studies revealed a novel mechanism of antibody-PAH binding based on electrostatic charge, and identified targets for in vitro mutagenesis of the antibodies.

Determination of Levels of Risk Due to Contaminants

The total concentration of a contaminant in a soil sample may not give a reliable estimate of exposure risk because bio-fluids may only extract a small percentage of the contaminant from ingested soil. Bioavailability can be ascertained by animal studies using addition of contaminated-soil samples to food with subsequent analysis of the uptake of the contaminant by the animal. However, use of animal models for testing the large number of DOE waste sites would be very costly, and the goal of the University of Medicine and Dentistry/Rutgers University project (54584) is to devise less expensive methods to determine the bioavailability of contaminants in soil samples. Their approach is to determine the ability of bio-fluids (saliva, gastric juices, intestinal fluids) to extract particular contaminants from a soil sample, and then to correlate these results with those obtained from the animal studies. They have identified some of the key compounds necessary for the simulated bio-fluids to extract hazardous metals, for example, in a manner that correlates with bioavailability.

The level of risk associated with low concentrations of a contaminant is often a complex and controversial subject. Trichloroethylene (TCE) is a common contaminant at DOE sites, and clean-up standards that are too strict could result in millions of dollars of useless remediation activities, but standards that are too lax could endanger persons in the vicinity of the sites. The objective of one PNNL project (54684) is to determine the mechanism involved in TCE-induced liver cancer in order to assist in developing appropriate risk-based standards. They have found that dichloroacetate and trichloroacetate, which are TCE metabolites, can completely account for liver tumor induction in mice by TCE. In addition, their results suggest that these metabolites cause growth of tumor cells that are initiated spontaneously rather than by direct involvement with DNA. These studies suggest that risk-per-unit-dose standards for TCE should be reduced by approximately ten-fold.



Determining Levels of Risk from Contaminants
A PNNL project (54684) is determining the mechanism involved in TCE-induced liver cancer. They have used magnetic resonance imaging to measure rates of tumor growth. The tumor shown above was produced by initiation with vinyl carbamate followed by administration of DCA at 2g/L for ~24 weeks. The tumor was imaged on successive days indicated in the above chart.

The purpose of the Lovelace Institute/PNNL project (54940) is to improve the scientific basis for assessing the cancer risk associated with exposure to carbon tetrachloride, CCl_4. They have found considerable differences in the effects of inhaled CCl_4 on certain enzyme activities in rats, mice, and hamsters, and hepatic cytotoxicity was also found to be greatest in hamsters and least in rats. Their early results suggested that minimal toxic effects occur in mice and rats at the current threshold limit value for CCl_4 of five parts per million. The in vivo metabolism by human, rat, mouse, and hamster liver microsomes as well as differences in the toxicokinetics of inhaled CCl_4 were being studied. The results of this study should provide the type of information needed to enable refined risk estimates for CCl_4.

The Savannah River Ecology Laboratory/Colorado State University project (55410) was initiated to determine the relevancy of less-than-lethal cellular damage for risk analysis. They have developed a chromosome-specific probe to measure cumulative damage in a common turtle species, and this probe was crucial to the goal of correlating cellular damage to factors such as age at maturity and longevity. An array of 50 tanks for turtles, fish, and amphibians has been constructed to enable studies of chromosome damage at various radiation exposures and metal contaminant concentrations, the relationships between cellular damage and metabolic rate, and the effects of the contaminants on growth and survival.

Controlled dose-response experiments using the irradiation facility are being done, and in vivo versus in vitro turtle lymphocyte responses to acute irradiation will be compared.

Mechanisms of Adverse Effects Due to Contaminants

Almost all heavy metal ions are toxic to biological organisms because they bind strongly to certain amino acids in proteins and thus interfere with the normal functions of the proteins. Some bacteria, however, have efficient mechanisms for the detoxification of these metals, and the goal of the University of Pennsylvania project (54856) is to determine the structures of proteins involved in the bacterial mercury detoxification system. They have used nuclear magnetic resonance techniques to explore the structural features of two mercury-binding proteins, one of which sequesters mercury in solution and the other transports mercury through cell membranes. The long-range goal is to use the basic structural knowledge to generate proteins with properties necessary to make biologically based devices for the detection and separation of mercury or other metals.

Compounds that can mimic hormones and thereby interfere with their normal functions are called endocrine disrupting substances. An important issue for environmental remediation standards is whether exposure to low levels of these substances can lead to harmful effects for humans or wildlife. The objective of the Tulane University project (55032) has been to determine if PAHs can act as "environmental hormones." Three biotechnology screening systems suggested that several PAHs could interact with hormone receptors of humans, amphibians, and shrimp. Animal screening studies were being done with two species of frogs as well as grass shrimp, and early results suggested that the endocrine neuroimmune systems of frogs could be adversely impacted.

Goals of the University of California – San Francisco project (55356) are to understand the mechanisms by which exposure to radiation and certain chemicals induce leukemia, to identify how combinations of chemicals may have a greater or lesser effect than individual species, and to optimize approaches for risk assessment. They have demonstrated that the persistence of genetically damaged blood cells may be greater for long-term, low-dose exposures than for high-dose exposures to substances that are toxic to blood cells, and this observation may have major implications for risk assessment. They have developed a technique to assay genetic damage to the stem cells that produce mature blood cells, and evaluations of damage caused by combinations of radiation, benzene, and/or trichloroethylene are underway.

Biomarkers for Exposure to Contaminants

The current occupational standard for worker exposure to beryllium (Be) is two micrograms per cubic meter of air over an eight-hour work shift. But even if Be levels in the air were monitored to ensure compliance with this standard, a sensitive biomarker for identifying early human sensitization to Be could perhaps prevent the occurrence of berylliosis from long-term exposures. The goal of the University of Vermont project (54931) was to develop a biomarker through identification of beryllium-reactive T-cells in peripheral blood. Results from Oak Ridge subjects were ambiguous because of uncertainty as to the Be sensitization status of the persons who were sampled, so ongoing work has concentrated on samples from Rocky Flats workers who had been unequivocally sensitized to Be. If beryllium-sensitized cells are not limited to the lungs, then it should be possible to develop this new biomarker.

Is it possible to identify a genetic variation that predicts a predisposition to the deleterious health effects that may result from exposure to radiation or to certain chemicals? The objective of the Columbia University project (55100) is to explore whether a particular gene, HRAD9, plays an important role in determining the biological consequences of DNA damage and to ascertain if alterations in this gene can be used as a marker for a reduced ability to cope with DNA damage. Early work indicated that HRAD9 participates in cellular responses to DNA damage, and detailed studies with mice were intended to clarify the biological impact of mutations in the corresponding mouse gene. Ongoing studies will establish the prevalence of variations in HRAD9 in the general population and resolve the key question as to whether a particular variant can be used to predict hypersensitivity to DNA-damaging agents.

Project Teams

Lead Principal Investigator (Award Number)

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  The Scripps Research Institute
  University of Hawaii
- University of Medicine & Dentistry of New Jersey
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  Rutgers University
- Pacific Northwest National Laboratory
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- University of Pennsylvania
  PI: Stanley J. Opella (54856)
- University of Vermont
  PI: Richard J. Albertini (54931)
- Lovelace Biomedical & Environmental Research Institute
  PI: Janet M. Benson (54940)
  Pacific Northwest National Laboratory
- Tulane University
  PI: John McLachlan (55032)
- Columbia University
  PI: Howard B. Lieberman (55100)
- University of California – San Francisco
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