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U.S. AIR FORCE BASIC RESEARCH IN BIOENVIRONMENTAL HAZARDS

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Air Force operations and maintenance, like many large industries, involve use of chemical and physical agents that are potentially harmful to personnel and the surrounding environmental ecosystems. An understanding of the fundamental interactions of potentially hazardous agents with biological systems and their actual mechanisms of action is essential to provide effective means of protecting man and the environment against hazards posed by such generated chemical and physical agents. These chemicals can include components of fuels, lubricants, pesticides, herbicides, solvents and aerospace materials. Data and methods to evaluate, measure and control these environmental hazards and reduce environmental contamination is explored.

Hazardous materials have many impacts upon our Air Force operational systems from early in their conception on the drawing boards through to retirement and disposal of a system. In the early planning stages for a new system every possibility of hazardous material presence must be determined, for they affect handling, storage, personnel protection, environmental control, medical monitoring, disposal and, perhaps most importantly, public relations.

The Bioenvironmental Hazards Program at the Air Force Office of Scientific Research in Washington, DC, is a very broad-based toxicology research effort with every aspect of toxicology being addressed. Specific areas of interest include health effects toxicology and environmental or eco-toxicology. Additionally, there is an Air Force laboratory component especially designed to research electromagnetic radiation (EMR) biological effects, another studying the effects of gravitational induced loss of consciousness, and another studying effects of heart loading on cardiovascular physiology.

Some of the major scientific issues addressed by these programs include the following questions. Do structurally similar compounds share common mechanisms of toxicity? What are the biological mechanisms for detoxification? Can they be enhanced? Are multiple sites of damage due to direct or sequential effects? What is the long-term relationship between early biochemical indications of toxicity and long-term damage? By what means do chemicals in the environment alter dynamic relationships within natural biological communities? Are there specific harmful bioeffects of EMR beyond thermal load? In response to these questions the research program is subdivided into categories of research which include mechanisms, biomembrane effects, molecular toxicity, ecotoxicology, and modelling.

There are several research efforts that fit within these categories and some that overlap boundaries and address two or more categories simultaneously. By directing attention to examples of some of the categories, perhaps an idea of the broad scope of this program will be gained.

Dr. Dickens, George Washington University Medical Center, Washington, DC, an investigator in mechanisms, has developed an exciting spin-trapping technique for determination of free radical mechanisms of toxicity. His early hypothesis proposed that free radical-induced injury participates in the pathogenic mechanism of chlorinated hydrocarbons in mammalian cells. His two most recent findings have provided strong evidence in support of this hypothesis. The first was that chlorinated hydrocarbons mixed *in vitro* with cumene hydroperoxide-in the complete absence of transition metals-was able to directly activate the hydroperoxide into an alkoxyl radical. And the second finding was the obtaining of direct spin trapping evidence for free radical production within cultured endothelial cells following exposure to selected Air Force chemicals (CCl_4, toluene, and trichloroethylene) (1). An interesting question has been posed by the finding that halogenated hydrocarbons are capable of interacting directly with lipid hydroperoxides. This raises an interesting medical question: Do halogenated drugs work the same way? Such a mechanism may explain the cytotoxicity associated with many chlorinated pharmaceutical agents.

Since there are more new chemicals produced annually than complete toxicity testing could possibly define, a method of risk assessment and extrapolation of information from lower species to man is essential to provide predictive capabilities. In this interest, physiologically-based pharmacokinetic (PBPK) modelling research and validation is being accomplished by Dr. Dallas at the University of Georgia Research Foundation, Athens, Georgia.

The pharmacokinetics of 1,1,1-trichloroethane (TRI) was studied in rats to characterize and quantify uptake and elimination by direct measurements of the inhaled and exhaled compound. Respiratory rates and volumes were continuously monitored during and following exposure and were used in conjunction with the pharmacokinetic data to characterize profiles of uptake and elimination. TRI was very rapidly absorbed from the lung as evident from high level in the first arterial blood samples at 2 minutes. Blood and exhaled breath concentrations of TRI increased rapidly following exposure, approaching, but not reaching, steady state during the 2 hour exposures, and were directly proportional to exposure concentrations. A PBRK model for TRI was used to predict blood and exhaled breath concentrations for comparison with observed values, and overall, model levels were in close agreement with actual measured values both during and following TRI inhalation (2) (see Fig. 1).

The Air Force Aerospace Medical Research Laboratory Toxic Hazards Division has produced significant contributions to the PBPK modelling effort. Models developed by the laboratory have aided in developing pregnancy and lactation guidance, resetting the underestimated level of methylene chloride, and providing a pragmatic risk assessment of a proposed replacement hydraulic fluid. Further discussion of this laboratory division will be addressed later.

A clear need for a specific environmetal toxicology program prompted the initiation of the ecotoxicology program. It was developed as a special toxicology subset to pro-

KINETICS OF INHALED TRICHLOROETHANE

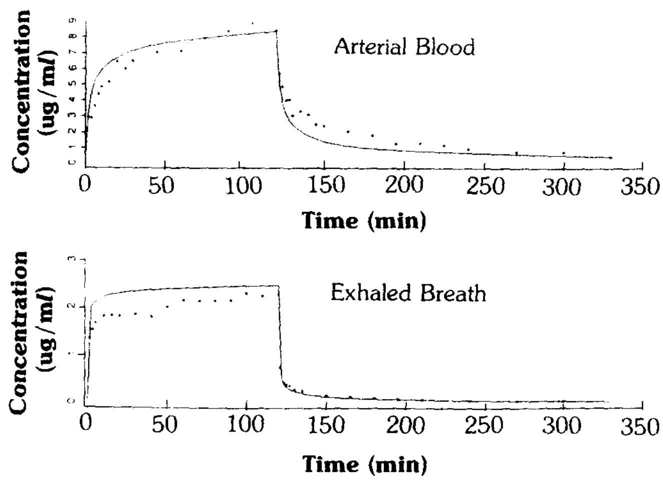

Fig. 1. Observed (·) and model-predicted(—) TRI concentrations in the blood (top graph) and exhaled breath(bottom graph) of rats during and following a 2-hr 500 ppm inhalation exposure. Each point represents the mean value for six rats.

vide basic experimental and theoretical research support of Air Force base clean-up efforts. Additionally, development of models for prediction of the future Air Force fuels, solvents and other aerospace materials of potential toxicity were included. This program has five major thrust areas. Degradation and detoxification addresses the relationships among chemical structure, natural and enhanced degradation by microbes and toxicity of metabolites. Fate and transport responds to the effects of chemical properties and environmental factors on transport and transformation of chemicals. Bioavailability determines routes of exposure and uptake of chemicals by plants and animals. Environmental behavior of complex mixtures zeroes in on the environmental fate of complex mixtures and their toxic effects, a very important issue given that most all fuels are highly complex mixtures. And, finally, interspecies extrapolation, the application of laboratory toxicity data to untested species to predict effects on populations, communities, ecosystems and -especially-humans.

Dr. Dickson, at the Institute of Applied Science, University of North Texas, is developing a method to measure cellular responses to stress that can be used to assess both levels and types of stressors in fish, as a water quality biomonitoring method. This study is evaluating the efficacy of using the phenotypic expression of the stress proteins, a cellular response that increases the organism's capacity to cope with high stress loads, as a means of determining the degree of stress caused by anthropogenic contaminants in the aquatic environment. Several categories of toxicants are being tested, i.e., heavy metals, pesticides and hydrocarbons. Results from muscle tissue indicate a definitively separate pattern of the phenotypic expression of the stress protein response to chromate and arsenic (Fig. 2). The pattern also applies for other tissue of the fish. The research is providing the basis for development of a water biomonitoring assay,

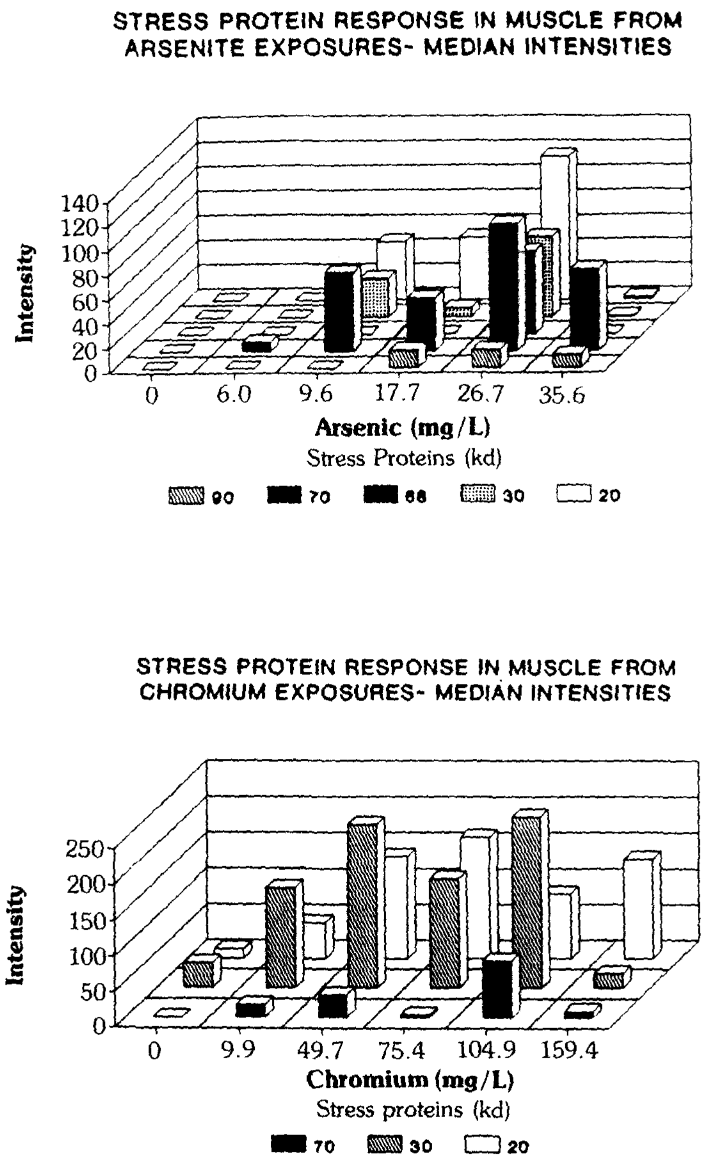

Fig. 2. Stress protein response in muscle.

which will likely be commercialized into an easy to perform kit.

The Air Force intramural toxicology effort is located in two geographical areas, one in Dayton, Ohio, responsible for defining potential hazards associated with Air Force system materials. In addition, they develop state-of-the-art methods for quantitative toxicology and risk assessment, which is used to determine safe human exposure criteria by extrapolating from laboratory animals to man. This laboratory has developed a cell culture toxicity screening method to rapidly screen potential toxicants from associated product research labs. The other intramural laboratory, the Air Force

Engineering Services Laboratory, is located in Tampa, Florida. This laboratory is mainly responsible for the environmental toxicology application of the Air Force. Scientists there are investigating biodegradation and biorestoration using a variety of biotechnology techniques, such as bacterial genetic engineering and selection. Bacteria which isolate a variety of halocarbon substituents of jet fuels have been isolated.

The Air Force is investing time and money in these two areas of toxicology with the intention of providing better prophylactic and therapeutic measures for dealing with the omnipresent bioenvironmental hazards in our operational and maintenance environment. In addition, another goal is esiablishment of realistic standards based on scientific criteria. And finally, the ultimate goal is enhanced protection of personnel and the environment.

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