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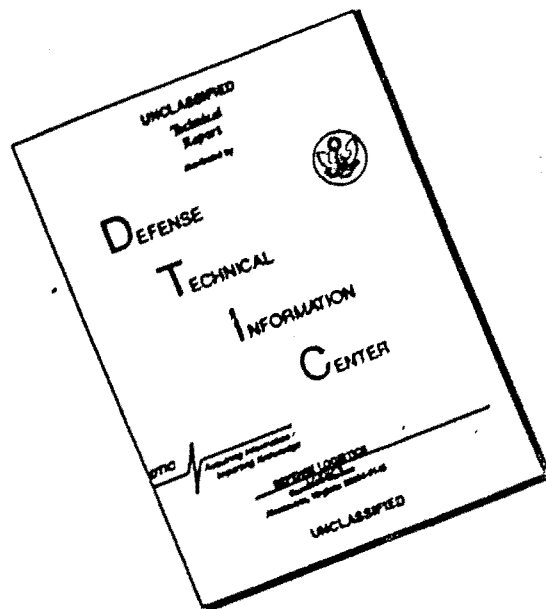
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History of Air Force Toxicology

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The U.S. Air Force Toxicology Program traces its beginning to the early 1950s with the hiring of Dr. Anthony A. Thomas. He assembled a staff consisting of a medical technologist, a pharmacologist, and a veterinary pathologist in the basement of the Wright-Patterson Air Force Base Area B hospital dispensary. Studies were initiated on the occupational toxicology of missile propellants and oxidizers. As the program grew in productivity and importance, it was moved to its present location in Building 79. There, four inhalation toxicology chambers with hypobaric, continuous exposure capability were constructed. They were named the "Thomas Domes" after the originator of the design. These original and four additional domes served as the "backbone" for inhalation studies on oxygen-enriched atmospheres, the hydrazine propellants, carbon monoxide, and a number of other compounds of interest to the Navy, Air Force, and the National Aeronautics and Space Administration during the 1960s and 1970s. This paper traces Air Force toxicology through the era of continuous inhalation exposure into inhalation carcinogenicity exposure and finally to the development of physiologically based, pharmacokinetic modeling.

The Beginning

The first documented reference to a toxicology effort in the Aero Medical Laboratory at Wright-Patterson Air Force Base (WPAFB) is found in *50 Years of Research on Man in Flight*.⁽¹⁾ Major Edward Westlake developed an industrial hygiene program for missile bases to ease military and civilian concern about the new rocket propellants' toxic properties. Surveys were conducted of potential hazards and handling procedures and preventive remedial measures were formulated.

It is generally accepted that the beginning of the Air Force research toxicology program as we know it today at WPAFB originated with the hiring of Dr. Anthony A. Thomas as a research toxicologist in 1956. He was assigned space in the basement of the WPAFB Dispensary in Area B. By 1960, he had assembled a staff consisting of Mildred Pinkerton, a medical technologist; Dr. James Prine, a veterinary pathologist; and Dr. Kenneth Back, a pharmacologist, who was later to become a Branch Chief and a major, long-term contributor to the program. They set about the complex task of defining the toxicology of Air Force missile propellants and related components to respond to some of the concerns raised by

Major Westlake's industrial hygiene surveys. From this relatively inauspicious beginning was to emerge an inhalation toxicology program and one-of-a-kind supporting facility that would gain national recognition for excellence within the next decade.

Growth and Maturity of the Program

The Aeromedical Laboratory became the Aerospace Medical Laboratory in 1959. It had been designated as the fundamental focal point of the new Air Force initiative entitled Man in Space in 1958. The design of ecological systems to support extended space travel required human exposure limits for a wide range of environmental contaminants present in space cabins. The only toxicologic data available were directed at the 8-hour/day, 40-hour/week occupational exposure. The need to extend this data bank to the 24-hours/day, 7 days/week continuous exposure for extended periods was obvious. The U.S. Navy was encountering similar requirements as it examined the prolonged submergence of Naval personnel in nuclear submarines. The Naval Medical Laboratory hosted a Symposium on Submarine and Space Medicine in 1958 as an initial thrust to address these problems.

Dr. Thomas recognized that a facility to perform continuous exposure toxicology studies was essential to meet these needs. Because no such facility existed to fulfill these needs, he set about the task of designing and constructing such a facility. In 1962, the toxicology program moved from its basement quarters in the dispensary to Building 79, its present location today. In 1964, four inhalation exposure chambers capable of continuous, uninterrupted exposure under hypobaric and oxygen-enriched atmospheres became operational. These chambers became known as the "Thomas Domes" named after the designer, Dr. Anthony A. Thomas. This facility, which was soon expanded to a total of eight chambers, served as the "backbone" of inhalation exposure studies on the toxicology of a number of atmospheric contaminants for two decades. The final recognition of the maturity of this program came with the establishment of the Toxic Hazards Division as one of the four major divisions of the 6570th Aerospace Medical Research Laboratories in 1965.

During this period of the 1960s, studies to further define the toxicology of the hydrazine missile propellants (hydrazine, monomethylhydrazine, and 1,2-dimethylhydrazine), borane fuels, inorganic fluorine oxidizing agents, and organic nitrogen fluorine-containing compounds were intensified. A number of 90-day, continuous inhalation studies were completed. In addition to the inhalation pathotoxicology of these compounds, studies on the biochemical mechanism of action and possible therapeutic intervention of toxic exposures were instituted. Studies on the cardiovascular and behavioral effects to crew members of halogenated fire extinguishing agents were undertaken because of their projected use in both aircraft and spacecraft cabins. Short-term inhalation exposure studies to develop Emergency Exposure Limits for Air Force personnel working in critical operational environments were performed. Improved analytical methods for detection of these compounds in the operational environment were developed.

The problem of long-term, continuous exposure to oxygen-enriched atmospheres was confronted. Inhalation studies at 100% oxygen at reduced atmospheric pressure corresponding to the early spacecraft cabin conditions were undertaken. Morphometric methodology to evaluate quantitatively the degree of pulmonary membrane thickening characteristic of oxygen toxicity was developed and utilized in these studies. The alteration of the toxic response of atmospheric contaminants in the presence of increased oxygen concentrations was evaluated. A critical evaluation of continuous exposure to the ever present, atmospheric contaminant carbon monoxide was completed. Included in these studies was a study to clarify the effect of carbon monoxide on normal sleep patterns. The renal toxicity from inhalation exposure to saturated concentrations of ethylene glycol was determined for the National Aeronautics and Space Administration (NASA). This was necessitated by the possibility of a leak of this coolant into the spacecraft cabin.

During this exciting time, another significant development occurred. The need for a forum to review progress critically and to exchange information in the rapidly expanding area of atmospheric contaminants in confined spaces became evident. In 1965, a Conference on Atmospheric Contamination in Confined Spaces, sponsored by the Air Force, was held in Dayton, Ohio. It is appropriate to quote from the "Introduction" to the Proceedings⁽²⁾ of this conference:

"As our research methods and techniques in toxicology progressed to the point where truly uninterrupted, long-term, continuous exposures became feasible, many new technical difficulties were discovered, and the costliness of this work became apparent. The need for a scientific meeting dedicated primarily to research problems in toxicology became increasingly urgent. Because the number of facilities available to conduct such work is limited in the free world, it has also

become critically important that researchers in these facilities should produce data that are directly comparable. This would prevent unnecessary or costly duplication of experiments and loss of valuable biological lead time. Although everyone abhors 'standardization' in research and finds it stifling of initiative, inevitably methodology must be standardized in the sense that only acceptable methods that can furnish reproducible and meaningful information should be used. Thus, the setting of a sort of minimum criteria for research methodology becomes, in fact, a sort of quality control procedure, a highly desirable situation in any research endeavor.

"Obviously, this meeting was not intended in any way to become a symposium. The issues at hand required a very practical approach to many matters of technical detail, and the guiding thought was one of trade-off between optimum experimental design and minimum requirements for comparability of data. To provide timely and useful toxicological information to the design engineers one must also compromise some of the goals which the ultimate perfectionist seeks. This compromise then is necessitated by two crucial and overriding factors, available time and money. Therefore, we felt that a conference which provided a workshop atmosphere was much more desirable than would be the highly academic approach of a formal symposium.

"We sincerely hope as experience grows and as research data accumulate that there will be a gradual tendency in this series of conferences toward the makings of a real symposium. Meanwhile, I must take the blame for arranging the technical program for this very first conference."

The hopes of the author of this introduction, Dr. Anthony A. Thomas, then the Director of the Toxic Hazards Division, were certainly fulfilled as seen by the successful annual conferences held thereafter.

The Response to Regulatory Pressure

With extended space flight a successful reality, the 1970s brought other pressures to bear on the Air Force Toxicology Program. The need for data to establish permissible exposure limits for chemicals in the workplace became pressing. The hazards associated with exposure to chemicals with carcinogenic potential became an overriding issue. The close structural relationship of the hydrazine propellants to the carcinogenic nitrosamines necessitated definitive data to determine the hazard associated with the continued use of these propellants. Six-month to one-year exposures of mice, rats, hamsters, and dogs to graded concentrations of hydrazine, unsymmetrical dimethylhydrazine, and monomethylhydrazine were conducted. The complete histological

work-up involved the evaluation of over 300,000 tissues according to a protocol designed by the National Cancer Institute. Both national and international corporations involved in the manufacture and use of these compounds provided support for these studies.

Legislative, mandated Environmental Impact Assessments and Statements focused on the need for data to determine the effect of Air Force operations on the environment. A major study on the effect of Space Shuttle exhaust products on the flora and fauna in the vicinity of Vandenberg Air Force Base was undertaken. Test batteries for determining the effect of chemicals on water quality were established. The program responded to the presence of women on the flight-line by adding the evaluation of chemicals on the unborn fetus to its capabilities.

The Navy Medical Research Institute established a toxicology detachment at WPAFB in 1976. Joint Navy/Air Force toxicology studies on jet fuels and hydraulic fluids were initiated. These included studies on proposed alternate fuels derived from such sources as oil shale.

Program Transition

The rapid growth of toxicology as a discipline during the 1960s and 1970s had produced extensive data on the toxicity of chemicals using animal models. There was growing concern among toxicologists about the methodology used to extrapolate animal data to human exposure limits. Under the direction of Dr. Melvin Andersen, the toxicology program initiated a major effort in physiologically based pharmacokinetic modeling. This methodology provides a more exact estimate of the relationship between external and internal dose allowing for species differences in metabolism and

distribution of chemical substances. The widespread acceptance of this methodology by the scientific community for use in hazard estimation and risk assessment once again focused the attention on the Toxic Hazards Division as a leader in innovative concepts for toxicologic research. The laboratory has also embarked on a program of developing and evaluating isolated cell systems for use in their research program. This is not, as some may perceive, a result of animal rights pressure but is part of an ongoing effort in the thirty or more years that this program has been in existence to provide the very best in scientific methodology to allow chemicals to be used with minimum adverse effects on employee, community, and environmental health.

With a contingent of the Army moving to Dayton to take part in the program, all three services are now active participants. I have heard Dr. Thomas and Dr. Back discuss many times the desirability of a "Purple Suit"* toxicology program that is Department of Defensewide, that would address the problems of all services because of their similar needs and requirements. One can only wonder if this may indeed become a reality.

*"Purple Suit" is a term coined to denote a military component composed of members of the U.S. Navy, Army, and Air Force but answering to no single service — a tri-service unit.

References

1. Dempsey, C.A.: 50 Years of Research on Man in Flight, pp. 68. Aerospace Medical Research Laboratory, Wright-Patterson AFB, OH (1985).
2. First Conference on Atmospheric Contamination in Confined Spaces — Proceedings of the Conference. AMRL-TR-65-230. Dayton, OH (1965).