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Operational Toxicology Research

Darol E. Dodd
MaryAnn Angell

Alion Science and Technology
Wright-Patterson AFB, OH 45433-5707

David R. Mattie

AFRL/HEPB
2729 R. Street, Bldg 837
Wright-Patterson AFB OH 45433-5707

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Final Report for March 2001 to March 2006

Air Force Research Laboratory
Human Effectiveness Directorate
Biosciences and Protection Division
Applied Biotechnology Branch
Wright-Patterson AFB OH 45433-5707

NOTICE

TECHNICAL REVIEW AND APPROVAL

AFRL-HE-WP-TR-2006-0082

THIS TECHNICAL REPORT HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION

FOR THE DIRECTOR

//SIGNED//

MARK M. HOFFMAN
Deputy Chief, Biosciences and Protection Division
Air Force Research Laboratory

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14. ABSTRACT

This is a final report for the Operational Toxicology Research (OTR) Contract F33615-00-C-6060 initiated in March, 2001 to support the Air Force Research Laboratory Applied Biotechnology Branch (AFRL/HEPB) at Wright-Patterson Air Force Base (WPAFB), OH. The purpose of the OTR contract was to acquire descriptive, mechanistic, and predictive toxicology research and technical research support to complement a variety of project teams supporting Tri-Service Toxicology Research Programs (Air Force, Navy, and Army) at WPAFB and Aberdeen Proving Ground, Edgewood, MD. The first section describes the Study Requests tasked by the government to initiate the toxicological and biotechnical investigations to be performed by the Alion SAIC JV research team. Section 2 of this report highlights the research accomplishments and technical products associated with the ten largest Study Request efforts performed by the Alion SAIC JV team. Section 3 lists the major subcontracts that were initiated and completed under the JV contract. The final section lists the scientists, technicians, and management/administrative personnel..

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PREFACE

The Operational Toxicology Research contract (F33615-00-C-6060) was performed by Alion Science and Technology, Corp. (acquired ManTech Environmental Technology, Inc.) and Scientific Applications International Corporation (acquired GEO-CENTERS, Inc.) through a Joint Venture (JV) agreement. The OTR contract was under the direction of Dr. Darol E. Dodd, JV Program Manager, and Dr. David R. Mattie, Air Force Research Laboratory/Applied Biotechnology Branch (AFRL/HEPB) Program Manager. The period of performance for the contract was 16 March 2001 through 15 March 2006. This report is a final deliverable under the OTR contract (CDRL Data Item No. A001).

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LIST OF ACRONYMS

ACS	American Chemical Society
AFB	Air Force Base
AF/IERA	Air Force/Institute for Environment, Safety, and Occupational Health Risk Analysis
AFOSR	Air Force Office of Scientific Research
AFRL	Air Force Research Laboratory
AFRL/HED	Air Force Research Laboratory/Human Effectiveness Directed Energy Division
AFRL/HEPB	Air Force Research Laboratory/Human Effectiveness Protection and Biosciences Division Applied Biotechnology Branch
AFRL/HEPC	Air Force Research Laboratory/ Human Effectiveness Protection and Biosciences Division Counterproliferation Branch
AFRL/HEST	Air Force Research Laboratory/Human Effectiveness Deployment and Sustainment Division Operational Toxicology Branch
Alion	Alion Science and Technology Corporation
ALS	Amyotrophic lateral sclerosis
ANIT	α-Naphthylisothiocyanate
ARDEC	Armament Research, Development and Engineering Center
ATSDR	Agency for Toxic Substances and Disease Registry
BBK	Biologically-based kinetic
BIN	Biological Interactions of Nanomaterials
BRL	Buffalo rat liver
BSP	Bromosulfophthalein
CDRL	Contract data requirements list
COATS	Cream/Ointment Augmentation of Topical Skin
CW	Chemical Warfare
CWA	Chemical Warfare Agent
2-D	Two dimensional
DHHA	Department of Health and Human Administration
DNA	Deoxyribonucleic acid
DoD	Department of Defense
DTRA	Defense Threat Reduction Agency
EPA	Environmental Protection Agency
ERA	Environmental Restoration Account
GB	Sarin (O-Isopropyl methylphosphonofluoridate)
GshA	Glutathione A
GshB	Glutathione B
HE	Human Effectiveness
IEEE	Institute of Electrical and Electronics Engineers
IPRL	Isolated perfused rat liver
ITAS	Integrated Toxicity Assessment System
JANNAF	Joint Army Navy NASA Air Force
JP-4	Jet fuel-4
JP-8	Jet fuel-8
JV	Joint Venture
LC-MS	Liquid chromatography-mass spectrometry
MEHN	Monoethyl hydrazine nitrate
MILCON	Military construction
Mn	Manganese
MRLs	Minimal risk levels
mRNA	Messenger RNA

MURI	Multidisciplinary university research initiatives
NHRC/EHEL	Navy Health Research Center/Environmental Health Effects Laboratory
NHRC/TD	Navy Health Research Center/Toxicology Detachment
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
Nm	Nanometer
NMR	Nuclear magnetic resonance
NORA	National Occupational Research Agenda
NRC	National Research Council
OP	Organophosphate
OTR	Operational Toxicology Research
OVALS	Ohio Valley Affiliates for Life Sciences
OVSOT	Ohio Valley Society of Toxicology
PBPK	Physiologically-based pharmacokinetic
PD	Pharmacodynamic
Ppb	parts per billion
Ppm	parts per million
QSAR	Quantitative structure activity relationship
RfD	Reference dose
RNA	Ribonucleic acid
RT-PCR	Reverse transcription – polymerase chain reaction
SD	Sprague Dawley
SAIC	Scientific Applications International Corporation
SBDD	Serum Biomarkers for Degenerative Disease
SETAC	The Society of Environmental Toxicology and Chemistry
SOP	Standard operating procedure
SOW	Statement of work
T	Thymic
TARA	Technical area review and assessment
TCE	Trichloroethylene
US	United States
USAF	United States Air Force
USAFSAM/FEH	United States Air Force School of Aerospace Medicine/Department of Force Enhancement, Hyperbaric Medicine Division
WPAFB	Wright-Patterson Air Force Base

OPERATIONAL TOXICOLOGY RESEARCH CONTRACT

F33615-00-C-6060

INTRODUCTION

This is a final report for the Operational Toxicology Research (OTR) Contract F33615-00-C-6060 initiated in March, 2001 to support the Air Force Research Laboratory Applied Biotechnology Branch (AFRL/HEPB) at Wright-Patterson Air Force Base (WPAFB), OH. Alion Science and Technology (Alion; acquired ManTech Environmental Technology, Inc.) and Science Applications International Corporation (SAIC; acquired GEO-CENTERS, Inc.) were the companies that managed the OTR contract under a joint venture (JV) relationship. The purpose of the OTR contract was to acquire descriptive, mechanistic, and predictive toxicology research and technical research support to complement a variety of project teams supporting Tri-Service Toxicology Research Programs (Air Force, Navy, and Army) at WPAFB and Aberdeen Proving Ground, Edgewood, MD. The report is divided into three sections. The first section describes the Study Requests tasked by the government to initiate the toxicological and biotechnical investigations to be performed by the Alion SAIC JV research team. Section 2 of this report highlights the research accomplishments and technical products associated with the ten largest Study Request efforts performed by the Alion SAIC JV team. Section 3 lists the major subcontracts that were initiated and completed under the JV contract. The final section lists the scientists, technicians, and management/administrative personnel who were assigned to the Alion SAIC JV team to conduct the Study Request efforts. An appendix of additional products of the Alion SAIC JV staff is also provided.

SECTION 1 – STUDY REQUESTS

Table 1

Alion SAIC Joint Venture Study Requests 2001-2006

Work Unit #	Study Req #	Study Request Title	Active Years & Final Disposition	Study Request Scope (Brief General Description)
		AFRL/HEPB Initiated Study Requests		
2312A210/ 1710D425	120	In Vitro Laboratory Support	2001-2003 Completed	Design and conduct appropriate experiments to establish biochemical assays for toxicological research. Establish and maintain appropriate cell culture systems for toxicological research projects.
2312A208	121	Development of Quantitative Structure - Activity Relationships (QSARs)	2001-2003 Completed	Design and conduct experiments for *in vitro* toxicity assessments of Air Force chemicals. Assay samples collected for biochemical and molecular endpoints and calculate chemical descriptors using computational chemistry software. Collaborate with AFRL and academic scientists for development of QSAR models.
2312A206	122	Predictive Toxicokinetics	2001-2004 Completed	Conduct experimental studies to investigate chemical kinetics in the isolated perfused rat liver. Confirm predictions with conduct of *in vivo* studies and develop biologically-based kinetic models from *in vitro* and *in vivo* kinetics.

2312A206/ 2312A209	123	In Vitro/In Vivo Extrapolation Using Biologically Based Kinetic/Dynamic Modeling	2001-2005 Completed	Develop innovative toxicity testing methodologies to accurately predict human health risks of new Air Force systems, materials, and technologies. Develop and apply molecular biology techniques to measure *in vitro* mRNA induction kinetics, protein-DNA interactions, and to synthesize oligonucleotide probes. Develop biologically-based kinetic/dynamic models.
2312A207	124	Genomics & Proteomics for Toxicity Risk Assessment	2001-2006 On-going (transitioned)	Develop experimental protocols to evaluate patterns of gene expression in various cell types following exposure to test chemicals. Studies will focus on use of Affymetrix gene expression system and investigate biomarkers of toxic response.
2312A204	125	Mechanisms and Modeling of JP-8 Dermal Toxicity	2001-2003 Completed	Conduct research to gain a quantifiable, mechanistic understanding of the time course of skin response to contact with JP-8 fuel so that assessments can be made about safe exposure scenarios.
2312A205	126	Toxicity of High Energy Chemicals	2001-2006 Completed	Conduct *in vitro* toxicity experiments using primary cultures of rat hepatocytes to evaluate the toxicity of high energy chemicals (e.g., hydrazine derivatives) using multiple end points (e.g., oxidative stress and apoptosis).
1710D406/ 1710D432	127	Exposure Standards for Halon Replacement	2001-2006 On-going (transitioned)	Determine and evaluate health hazards associated with use of halon replacement candidates, such as perfluoro-n-butyl iodide. Conduct risk assessment approaches (e.g., physiologically based pharmacokinetic modeling) and recommend human exposure levels in occupied or unoccupied spaces.

1710D410	128/ 301	Toxicity of JP-8 Based Fuels	2001-2005 Completed	Develop and conduct dermal (*in vitro* and *in* vivo) and inhalation studies to predict human toxicity following repeated exposures of JP-8 based fuels via skin or inhalation administration.
1710D414	129	Modeling of Chemical Warfare Agent Exposure	2001-2006 On-going (transitioned)	Use experimentally derived data to evaluate, modify, and validate a miniature pig model that will describe the relationship between chemical warfare agent exposures (dermal and inhalation) and biological endpoints.
1710D415	130	Dermal Irritation Based on Exposure Duration	2001-2004 Completed	Develop and demonstrate a mathematical approach that can be used by health professionals to predict hazards of irritant contact dermatitis from various durations of dermal exposures to solvents.
1710D418	131	Development of a Reference Dose (RfD) for Ammonium Perchlorate	2001-2006 Completed	Propose and conduct toxicity studies that will permit the determination of a science-based RfD. Studies should include kinetic and dynamic model development in naïve female rats, pregnant and lactating dams, and nursing pups. Develop analytical techniques for perchlorate in water, groundwater, soil and biological matrices such as blood, urine, milk, thyroid and other tissues required for development of kinetic and dynamic models.
N/A	132	ATSDR Dermal MRLs	2001-2002 Completed	Conduct library research and provide scientific analysis to determine the best approach for determining Minimum Risk Levels for dermal exposures of chemicals.
1710D410	133	JP-8 Additives for Cold Flow Program	2001-2006 Terminated	Provide an approach for evaluation and prediction of toxicity of potential JP-8 fuel additives without having to completely retest new JP-8 formulations that are being considered for use by the Air Force Fuels Lab.

1710D425/ 1710D431	134	Development of Biotechnology Solutions for Toxicity Assessment Integrated Toxicity Assessment System (ITAS)	2001-2006 Terminated	Provide biotechnology approaches (e.g., functional genomics) to assist in the design of an integrated software system that will be used to predict toxicity of newly designed Air Force chemicals or chemicals from deployed locations
2312A211	135	Intrinsic Cellular Toxicity	2001-2006 Completed	Develop a profile for toxicity screening or a toxicity report card based on biochemical assays and cell models using benchmark chemicals, such as hydrazine as positive controls.
1710D433/ 7184D405	136	Genomic Assessment of Chemicals for Deployment Toxicology	2002-2006 On-going (transitioned)	Use molecular biology methods to measure gene expression (*in vivo* or *in vitro)* induced by chemicals (e.g., hydrocarbons, fuel mixtures) and compile profile databases to study dose-response relationships. Use bioinformatics tools for analysis and pattern recognition.
1710D432	137	Research to Develop Pharmacokinetic Information for Risk Assessment	2002-2006 Completed	Research tasks include measurement of partitioning of a select group of volatile organic chemicals into tissues of laboratory animals at varying life stages and human organ donors; quantification of rates of chemical metabolism; and development/application of biologically based models.
2312A212	138	Designing Tools for Biomolecular Network Modeling	2002-2006 Completed	Develop a research program plan for creating tools for modeling including selection of a prototypical biomolecular network model in a biologically relevant system; performing genomic/proteomic experiments to develop biomolecular profiles; creating computational tools to integrate data; and develop mathematical models of biomolecular network.

1710D434	139	In Vitro Assessment of Chemical Irritants/ Assessment of Barrier Creams and Ointments to Lower JP-8 Liquid Dermal Adsorption and Penetration	2002-2006 Completed	Use an *in vitro* co-culture cell system to assess time and dose-dependent release of pro-inflammatory mediators from keratinocytes. Quantify biochemical response, including proteomic changes. Obtain over-the-counter barrier creams and lotions to assess the barrier formulation qualities using static penetration cells (rat and pig skin preparations). Test results of best barrier products *in vivo* using rats or rabbits to determine JP-8 adsorption and irritancy.
1710D435	140	Chemical Mixtures Toxicology	2002-2006 Completed	Use mathematical modeling techniques to describe pharmacokinetic and pharmacodynamic behavior of complex mixtures and potential interacting components; test and validate models; and provide approach on use of models for health risk assessments and for insights into mechanisms.
1710D436/ 1710D701/ 7184D405	141	Metabonomic Characterization of Toxicological Response in Urine Using NMR and Metabolic Pattern Recognition Technologies	2002-2006 On-going (transitioned)	Conduct *in vivo* laboratory animal experiments with a variety of known target organ toxicants, collect urine, and use NMR, clinical chemistry, and mathematical modeling techniques to determine if NMR and pattern recognition technologies can be used to rapidly screen for toxicity.
1710D442	142	Physiological Parameters and PBPK Modeling for the Perinatal Period	2003-2006 Completed	Analyze existing literature of physiological parameters and PBPK modeling for the perinatal period, then identify and prioritize data gaps. Ascertain if new models and data can provide a framework for improvement in perinatal risk assessment of chemicals.

1710D432	143	State-of-the-Science Panel Review for Independent Calculation of Trichloroethylene Toxicity Potency Factors	2003-2006 Completed	Assemble an expert panel of scientists to develop consensus on outstanding scientific issues (e.g., sensitive endpoints, use of PBPK models) related to the derivation of safe exposure concentrations for trichloroethylene.
1710D432, Task 5	144	Genomic collaboration	2003-2006 Completed	Use GeneChip™ Technology to determine gene expression changes in cells from studies conducted by laboratories collaborating with AFRL/HEPB. Studies include exposure of millimeter wave radiation and environmental chemicals.
1710D440	145	Biomolecular Network Modeling	2003-2006 On-going (transitioned)	Develop a research program plan for creating tools for modeling including selection of a prototypical biomolecular network model in a biologically relevant system; performing genomic/proteomic experiments to develop biomolecular profiles; conducting analyses of relevant experimental endpoints; creating computational tools to integrate data; and develop mathematical models of biomolecular network.
1710D443/ 7184D405	146	Proteomic Profile and Biomarker Assessment Techniques for Organ-Specific Toxicity	2004-2006 On-going (transitioned)	Utilize proteomic technique of liquid chromatography-mass spectrometry (LC-MS) to identify protein changes following organ specific insults induced by low level toxic exposures. Compare data set with 2D gel separation MS methods and parallel metabonomic and genomic research data efforts.
2312A215	147	JP-8 Collaborations	2004-2006 Completed	In cooperation with the Naval Medical Research Initiative and the American Petroleum Institute, run JP-8 fuel analytical tests to develop study methods and procedures; search for methods to determine toxicity limits for JP-8 exposures; and support JP-8 inhalation studies on animals.

1710D444	148	Barrier to Chemical Irritants Cream/Ointment Augmentation of Topical Skin (COATS)	2004-2006 Completed	Apply penetration methods to test skin creams on silastic vs. skin; test skin creams for dermal irritation; select the best cream for JP-8 fuel protection; and test cream for protection against other hazards, such as fuels, greases, oils, engine cleaners, and hydraulic fluids.
2312A214	149	Biological Interactions of Nanoparticles (BIN)	2004-2006 On-going (transitioned)	Conduct studies using *in vitro* cell models such as cellular responses elicited by human T cells and rat/human macrophages after exposure to different sizes of nano-materials composed of diverse compounds, such as nano metals. Provide initial insight on cellular mechanisms.
2312A215, Task 2	150	JP-8 Collaborations: Modeling of complex mixtures: JP-8 Toxicokinetics	2004-2006 On-going (transitioned)	Use mathematical modeling techniques to develop models of individual hydrocarbons or fractions to address pharmacokinetic and pharmacodynamic behavior of complex mixtures. Both *in vivo* and *in vitro* studies may be needed for model development and validation.
1710D445	151	Serum Biomarkers for Degenerative Disease (SBDD)	2005-2006 On-going (transitioned)	Focus is to identify serum biomarkers for degenerative disease and determine if identified phenotypic patterns can be validated for predictive use. Collaborate with Genome Research Institute-University of Cincinnati. Samples obtained from ALS patients culled from historical DoD serum samples will be used.
CAP	152	Collaborations with AFRL/HED	2005-2006 On-going (transitioned)	Determine and evaluate the reaction of a protein compound following capsaicin exposure of the rabbit eye. Gather time-dependent and concentration-dependent data and results. Address effectiveness of single vs. multiple applications.

1710D425	201	2001 Toxicology and Risk Assessment Conference	2001-2002 Completed	Provide conference coordination support for the 2001 Toxicology and Risk Assessment Conference. Duties include role of Conference Coordinator, handling invitation and registration procedures, publication of proceedings, providing continuing education credits, and maintenance of records. Expanded assignment, when applicable, is support of the Marketing Coordinator for AFRL/HEPB.
1710D425	202	2002 Toxicology and Risk Assessment Conference	2001-2004 Completed	Provide conference coordination support for the 2002 Toxicology and Risk Assessment Conference. Duties include role of Conference Coordinator, handling invitation and registration procedures, publication of proceedings, providing continuing education credits, and maintenance of records. Expanded assignment, when applicable, is support of the Marketing Coordinator for AFRL/HEPB.
1710D425	203	2003 Toxicology and Risk Assessment Conference	2002-2006 Completed	Provide conference coordination support for the 2003 Toxicology and Risk Assessment Conference. Duties include role of Conference Coordinator, handling invitation and registration procedures, publication of proceedings, providing continuing education credits, and maintenance of records. Expanded assignment, when applicable, is support of the Marketing Coordinator for AFRL/HEPB.
1710D425	204	2004 Toxicology and Risk Assessment Conference	2003-2006 Completed	Provide conference coordination support for the 2004 Toxicology and Risk Assessment Conference. Duties include role of Conference Coordinator, handling invitation and registration procedures, publication of proceedings, providing continuing education credits, and maintenance of records. Expanded assignment, when applicable, is support of the Marketing

				Coordinator for AFRL/HEPB.
1710D425	205	2005 Toxicology and Risk Assessment Conference	2004-2006 Completed	Provide conference coordination support for the 2005 Toxicology and Risk Assessment Conference. Duties include role of Conference Coordinator, handling invitation and registration procedures, publication of proceedings, providing continuing education credits, and maintenance of records. Expanded assignment, when applicable, is support of the Marketing Coordinator for AFRL/HEPB.
1710D425	206	2006 Toxicology and Risk Assessment Conference	2005-2006 On-going (transitioned)	Provide conference coordination support for the 2006 Toxicology and Risk Assessment Conference. Duties include role of Conference Coordinator, handling invitation and registration procedures, publication of proceedings, providing continuing education credits, and maintenance of records. Expanded assignment, when applicable, is support of the Marketing Coordinator for AFRL/HEPB.
1710D425	302/ 601	Vivarium Support for Medical Center	2001-2006 On-going (transitioned)	Provide full range of clinical training and research vivarium support as required by AFRL/HEPB and WPAFB Medical Center personnel. Duties include animal husbandry, veterinary support, assisting at training sessions, cleanup and the disposal of biological waste.
N/A	303	Environmental Restoration Account (ERA)	2002-2006 Completed	Work with AF/IERA to support the Interagency Perchlorate Steering Committee in extrapolating rat pregnancy and lactation PBPK models to human females for assessing risk. Assist in the risk assessment for jet fuel fractions and evaluate hazard data for cadmium from databases.

1710D418	401	Development of Reference Dose (RfD) for Ammonium Perchlorate	2004-2006 On-going (transitioned)	Interpret perchlorate data for DoD's Perchlorate Working Group; continue interaction with industry and regulators; provide conference support; and provide technical support for perchlorate projects (e.g., human urine study).
1710D418	501	Development of a Reference Dose (RfD) for Ammonium Perchlorate	2002-2006 Completed	Interpret perchlorate data for DoD's Perchlorate Working Group; assess human health toxicity data; complete analysis of kinetic models; continue interaction with industry and regulators; provide conference support, including preparation of briefing material, attending critical scientific conferences; and provide comments on documents from EPA and state regulators.
1710D413	901	Toxicity of Propellants	2001-2003 Completed	Depending on funding availability, determine acute toxicity, probable mode of action, tissue distribution and disposition for select propellants, such as hydrazine, hydrazine derivatives (MEHN), bicyclopropylidene, quadricyclane, and composition B replacement – 12. Develop analytical methods and use PBPK models, if necessary.
		AFRL/HEPC Initiated Study Requests		
1710D425	115	The Effects of Hyperbaric Oxygen on Mechanisms of Wound Healing Resulting from Acute Traumatic and Directed Energy Forces	2001-2004 Completed	Provide technical support to current research program at Hyperbaric Medicine Division, USAFSAM/FEH, Brooks AFB, Texas to understand how hyperbaric oxygen modulates tissue repair and immune system function in human, animal, and *in vitro* models.

N/A	116	Support for Development of Technology for Detection of Microorganisms in Water	2001-2003 On-going (transitioned)	Research effort involves development of technology for devising a portable instrument that recovers microorganisms from drinking water and processes the recovered organisms to allow effective identification on the basis of DNA.
N/A	117	Support for Development of Technology for Decontamination of Microorganisms	2001-2003 Completed	Conduct research to determine efficacy of metallic oxide nanoparticles amended to an air filter for inactivating *Bacillus anthracis* spores collected on the filter during filter operation.
N/A	118	Support for Evaluation and Development of a Colorimetric Biosensor System for Detection of Microorganisms	2005-2006 On-going (transitioned)	Research effort involves evaluating a variety of technologies that will be employed for development of a complete detection system of microorganisms and biological agents. Determine strengths and weaknesses of available technologies and development for more reliable and more rapid detection of biological materials.
		NHRC/EHEL Initiated Study Requests		
N/A	175	Neurobehavioral Research Support for NHRC/TD Studies	2001-2003 Completed	Support the development of techniques for measuring electrical potentials in multiple brain areas and neural systems using microelectrode array technology. Focus on neuro-pharmacological characterization of effects of relevant neuroactive compounds.
N/A	176	Inhalation Toxicology Operations Support for NHRC/TD Studies	2001-2006 On-going (transitioned)	Support the conduct of inhalation toxicology studies and related studies in the specialized facilities dedicated to the evaluation of combustion and neurobehavioral toxicology for both aerosolized and gaseous materials.

N/A	177	Analytical Chemistry Operations Support for NHRC/TD Studies	2001-2003 Completed	Support chemical analysis associated with the conduct of inhalation toxicology studies and related studies in the specialized facilities dedicated to the evaluation of combustion and neurobehavioral toxicology for both aerosolized and gaseous materials.
		Non-Technical Study Requests		
1710D425	101	Nontechnical Administration	2001-2006 Completed	Provide financial, administrative, human resources, secretarial and data automation support per contract SOW 4.5.5 and related CDRL requirements. Expanded to include marketing coordination for the branch. Includes addressing MILCON issues and move from Bldg. 79 to Bldg. 837/838.
1710D425	103	Computer Support	2001-2006 Completed	Provide computer systems management and operations for existing Local area Network in coordination with branch computer support elements per contract SOW 4.4.1.
1710D425	104	Pathology and Vivarium Support	2001-2006 Completed	Provide complete necropsy and tissue preparation for histopathologic evaluations from assigned research studies, and provide daily husbandry of laboratory animals per contract SOW 3.1.10, 3.2, 4.3, 4.3.4, and 4.4.2.
1710D425	105	Statistics Support	2001-2006 Completed	Perform mathematical and biostatistical procedures to assure valid experimental design, data analyses, model development, and risk assessment to support assigned research studies per contract SOW 4.3 and 4.4.3.
1710D425	106	Safety/Environmental/Security	2001-2006 Completed	Comply with Air Force Occupational and Safety Program, WPAFB environmental compliance program, and WPAFB security procedures as defined in contract

1710D425	107	Quality Assurance	2001-2006 Completed	Comply with requirements necessary to meet good laboratory practice standards as defined in contract
1710D425	108	Research Planning	2001-2006 Completed	Plan descriptive, mechanistic and predictive toxicological research and research support to complement Tri-Service project teams at Wright-Patterson AFB, Ohio and Aberdeen Proving Ground – Edgewood Area, Maryland per contract SOW 2.0, 2.2, 2.3, 2.4, and 4.6. Expanded to include proposal writing support for intramural government proposal efforts.
1710D425	109	Research Management	2001-2006 Completed	Exercise administrative, financial and logistics support management functions, including subcontract management, program planning, and status reporting per contract SOW 4.0, 4.1, 4.1.1, 4.1.2, 4.2, 4.3, 4.4, 4.5, 4.6, 5.0 and related CDRL requirements.
1710D437	110	Research Support for Predictive Toxicology Product Line	2002-2003 Terminated	Track research support costs of research planning and management activities for Predictive Toxicology Product Line.
1710D438	111	Research Support for Deployment Toxicology Product Line	2002-2003 Terminated	Track research support costs of research planning and management activities for Deployment Toxicology Product Line.
1710D439	112	Research Support for Cellular Dynamics and Engineering Product Line	2002-2003 Terminated	Track research support costs of research planning and management activities for Cellular Dynamics and Engineering Product Line.
1710D432	113	Research Support for Science-Based Toxicity Standards Product Line	2002-2003 Terminated	Track research support costs of research planning and management activities for Science-Based Toxicity Standards Product Line.

SECTION 2 - ACCOMPLISHMENTS AND PRODUCTS OF SELECT STUDY REQUESTS

Study Request 122 – Predictive Toxicokinetics

BACKGROUND: A major component of quantitative risk assessment is to estimate the target dosimetry of a chemical or its metabolites at the site of action. Biologically based kinetic (BBK) models are used to estimate target dosimetry. The focus of this project is to develop *in vitro* techniques to experimentally determine chemical specific kinetic parameters and to develop appropriate mathematical models to utilize these parameters to predict *in vivo* kinetics.

QUESTION: (1) Can the isolated perfused rat liver (IPRL) serve as a model system to evaluate, both qualitatively and quantitatively, the transport and metabolism of water soluble chemicals? (2) Can kinetic parameters determined *in vitro* model systems be scaled to the *in vivo* situation? (3) Can BBK models be developed to simulate the kinetics of chemicals in the IPRL and *in vivo*?

SCOPE: Experimental studies will include the investigation of chemical kinetics in the isolated perfused rat liver. *In vivo* kinetic studies will be required to confirm predictions. BBK modeling of *in vitro* and *in vivo* kinetics will be required. Successful completion of this project will require scientific oversight, training of new personnel, designing of experimental studies, developing SOPs for major activities and writing of peer reviewed manuscripts and technical reports. Work to be conducted will involve laboratory studies.

ABSTRACTS, PRESENTATIONS, TECHNICAL REPORTS, AND JOURNAL PUBLICATIONS (listed chronologically):

Soto A., Foy B. and Frazier J. M. 2001. Effect of Cadmium on Bromosulfophthalein Kinetics in the Isolated Perfused Rat Liver (IPRL) System. *The Toxicologist* 60(1): 352. AFRL-HEST-WP-PO-2001-0001 and AFRL-HEST-WP-PO-2001-0027.

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Foy B. D., Gearhart J., Soto A. and Frazier J. M. 2002. In-Vitro to Ex-Vivo Extrapolation of Intracellular BSP Metabolism Parameters in Rat Liver. *The Toxicologist* 66(1-S): 231-232. AFRL-HEST-WP-AB-2002-0013 and AFRL-HEST-WP-PO-2002-0007.

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Study Request 124 – Genomics and Proteomics for Toxicity Risk Assessment

BACKGROUND: Most of traditional toxicological testing assays use whole animal to test potential toxicity of chemicals. These assays are inherently expensive and take a long time to complete, and usually provide less accurate and characteristic data for risk assessment particular on the early low dose effects as well as effects on gene expression of cells. The most recent developed gene chip provides us a unique tool that allows for the monitoring of the expression levels of thousands of genes simultaneously. DNA chip can be used as rapid and highly sensitive detectors for toxicity evaluation and prediction. In addition, they can be used to characterize mechanisms and pathways underlying toxicity for a specific chemical. Our proposed study is to (1) establish a reproducible experimental "baseline" for rat primary hepatocyte cultures using the Affymetrix RatTox Expression Array Chip, (2) determine how chemicals, such as cadmium and hydrazine, affect gene expression profiles in rat primary cultured hepatocytes, (3) investigate the effect of pre-treatment with modulators of toxicity on the response of hepatocytes to test chemicals, and (4) compare rat and mouse hepatocytes to investigate species extrapolation issues. These studies will develop new tools that will significantly enhance our ability to investigate chemical toxicity in cells in culture.

QUESTION: (1) Can gene array technologies be used to evaluate the toxicity of chemicals? (2) Can changes in gene expression be used as a biomarker of toxicity? (3) How different is the pattern of gene expression between different cell types?

SCOPE: Develop experimental protocols to evaluate the patterns of gene expression in various cell types. Studies will focus on, but not be limited to, using the Affymetrix gene expression system. Changes in patterns of gene expression will be determined for exposure to test chemicals. Biomarkers of toxic response will be investigated. Successful completion of this project will require scientific oversight, training of new personnel, designing experimental studies, developing SOPs for major activities and writing of peer reviewed manuscripts and technical reports. Work to be conducted will include both laboratory studies and bioinformatics activities.

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Harker, B.W., Rudnicki, D.C., Utendorf, K.A., Hussain, S.M., Frazier, J.M., and Wang, C. 2002. Application of Gene Array Technology to Transcriptional Fingerprints of Primary Rat Hepatocytes Exposed to Cadmium Acetate. *The Toxicologist* 66 (1-S): 115. AFRL-HEST-WP-PO-2002-0004 and AFRL-HEST-WP-AB-2002-0011.

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Study Request 125 – Mechanisms and Modeling of JP-8 Dermal Toxicity

BACKGROUND: JP-8 has been the Air Force's primary jet fuel since 1996. JP-8 is a kerosene based petroleum distillate which is produced to meet performance specifications and for that reason the composition of JP-8 varies from batch to batch. It contains literally hundreds of hydrocarbon components. Petroleum distillates have been associated with renal, hepatic, neurologic, immunologic and pulmonary toxicity when they are inhaled or ingested and they are irritating to the skin and mucus membranes (Committee on Toxicology, 1996). When compared to JP-4, JP-8 has higher viscosity and lower volatility, which can result in aerosol exposures to ground crews, particularly in cold climates. These changes result in increased potential for dermal exposures and soaking of clothing, decreased evaporation, and therefore the potential for longer exposures. There is currently a great deal of concern in the Air Force community about the potential for dermal and systemic toxicity with JP-8. Funding for this project is by a grant from the Air Force Office of Scientific Research.

QUESTION: (1) What are the cellular and histologic responses of rat skin to JP-8 over 24 hours? (2) How are JP-8 surrogate chemicals distributed in rat skin? (3) What is the relationship between internal skin concentration and cellular response and can this information be used to predict damage from different exposure paradigms? (4) Can the mechanistic rat model be adjusted to predict human responses to JP-8?

SCOPE: This research addresses a very relevant, timely and important problem for the Air Force, namely dermal toxicity from current jet fuel, JP-8. The goal of this research is to gain a quantifiable, mechanistic understanding of the time course of the skin's response to contact with the fuel, so that assessments can be made about safe exposure scenarios. We hypothesize that the duration and amount of chemical on the skin determines the amount of chemical in the skin. We also hypothesize that the amount of chemical in the skin directly determines the cellular response. We believe that these relationships can be quantified and understood well enough to develop a predictive model of dermal damage based on exposure. We propose to develop pharmacokinetic and pharmacodynamic models for predicting the immediate dynamic events that occur with the presence of JP-8 in the skin.

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Study Request 129 – Modeling of Chemical Warfare Agent Exposure

BACKGROUND: The link between low level chemical warfare agent exposure and biological effects can be quantified using mathematical modeling approaches and appropriately designed kinetic studies. Considerable utility could be made of a reliable kinetic/dynamic model in planning activities related to operations in chemical warfare environments. A preliminary model for the pig based on literature data has been developed (Vinegar, AFRL-HE-WP-TR-1999-0236).

QUESTION: (1) Can a kinetic model of a miniature pig be developed and sufficiently validated for use in the design of experiments and interpretation of results? (2) Can this model be applied, with appropriate modifications, to human exposure scenarios so as to predict potential target site doses and biological effects?

SCOPE: The scope of this project encompasses the development of a preliminary miniature pig model and if applicable a dynamic model to describe the relationship between chemical exposure (dermal and inhalation) and biological endpoints of interest. Additional aspects of the project include:

- Use of experimentally derived data to evaluate/modify the model as needed,
- Validation of the model for agent and exposure type in preparation for meaningful extrapolation to human,
- Application of the miniature pig model to human exposures by appropriate model modification, scaling and validation, and
- Exploration of the relationship between exposure concentration to specific endpoints or biomarkers.

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for low level exposure to chemical warfare agent (CWA) in minipig. *The Toxicologist* 78 (1-S): 419. AFRL-HEST-WP-AB-2003-0010.

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Gearhart JM, Robinson PJ, Jakubowski EM, Jr., Thompson SA, Genovese RF, Willmore CB, Rockwood GA. 2005. Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Simulation of Low Level GB Exposure Across Multiple Species. Presented at Scientific Conference on Chemical & Biological Defense Research, November, Timonium, Maryland.

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Study Request 131 – Development of a Reference Dose (RfD) for Ammonium Perchlorate

BACKGROUND: Ammonium perchlorate that produces perchlorate anion (ClO_4^-) is used by the DoD as an oxidizer in munitions and in solid propellants for rockets and missiles. Its production and storage have caused the contamination of soil, ground and drinking water on Air Force bases, contractor installations and Western states. These contaminated sites will need remediation, with the US government ultimately responsible for clean-up costs estimated in the billions of dollars. The provisional RfD is extremely low (5 ppb) and this study will provide a model for toxicity and risk assessment based on scientific data rather than to rely on the conservative default values set by regulatory agencies.

QUESTION: (1) Is iodine inhibition in rodents by perchlorate the same as in humans? (2) Is perchlorate kinetics the same between rats and humans? (3) How do rats and humans respond to perchlorate inhibition? (4) Can PBPK/PD models be developed to address these questions of extrapolation of rats to human?

SCOPE: Develop the series of studies that will address the data gaps in the perchlorate toxicity database. Conduct the toxicity studies or facilitate the collection of toxicity data that will permit the determination of a science-based RfD. Proposed studies include pharmacokinetic and pharmacodynamic study in naïve females, pregnant and lactating dams and nursing pups. Develop PBPK/PD models using the data collected. Develop analytical techniques for perchlorate in water, groundwater, soil, and biological matrices such as blood, urine, milk, thyroid and other tissues required for model development. To support remediation efforts, understand the phytoremediation of perchlorate in soil and water.

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Study Request 135 – Intrinsic Cellular Toxicology

BACKGROUND: There have been several *in vitro* methods to evaluate the potential toxicity of a new chemical. However, there are no appropriate methods for screening toxicity of a given chemical based on an *in vitro* model. For example, at the earliest stage of pharmaceutical discovery, when least is known about the properties of the new molecule, simple predictive screens are appropriate. Such a first level of screen needs to be established for potentially toxic chemicals, such as propellants, under development by the Air Force.

QUESTION: (1) What biochemical assays should be used to evaluate the initial toxicity screening of a chemical? (2) What cell type models should be used to screen for toxicity that would be able to predict toxicity *in vivo*? (3) What bench mark chemical should be used as a positive control?

SCOPE: Initially hydrazine will be used as the positive control. Develop a profile for toxicity screening or a toxicity report card based on biochemical assays and cell models determined to answer the above questions. Incorporate genomic fingerprinting as part of the profile.

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Study Request 136 – Genomic Assessment of Chemicals for Deployment Toxicology

BACKGROUND: In light of today's expeditionary armed forces, which involve rapid deployment of personnel to remote, uncharacterized environmental hazardous sites, a single-chemical analysis approach will not be adequate to provide field commanders with timely risk information to make decisions regarding deploying troops into potentially hazardous environments. Furthermore, it must be assumed that these uncharacterized environments contain contaminants that represent complex mixtures. Rapid risk assessment of uncharacterized environments and chemical mixtures will require the development of new testing methodology.

Toxicogenomics is the study of the function of genes in adverse responses of biological systems to chemicals. Our goal is to use toxicogenomics to quickly detect the presence of chemicals and chemical mixtures in operational areas of deployed forces. This will be accomplished by establishing *in vitro* toxicity "fingerprints", or gene expression profiles, of known mixtures and components of chemical mixtures (i.e., fuels, hydraulic fluids, pesticides) expected to be encountered in deployed environments. Biomolecular profiling tools will be used to evaluate changes in gene expression in response to chemical or mixture perturbation. Bioinformatic tools will then be used to categorize patterns of gene expression in response to chemical or mixture exposure and relate them to mechanism of action. Once experimental gene expression profile databases are established (*in vitro* and *in vivo*) for different chemical classes comprising various environmental mixtures expected in deployed sites, military personnel can be monitored for changes in their gene expression profiles before, during and after deployment. It is envisioned that this approach to risk assessment will minimize mission degradation due to environmentally related adverse health effects by 1) allowing alternate site selection, 2) minimizing individual deployment time in hazardous environments, and 3) identifying proper levels of protective equipment.

QUESTION: (1) What is the *in vitro* dose-response relationship for select mixture components (nonane, m-xylene, napthelene, etc.)? (2) What is the gene expression profile of individual mixture components and the mixture at the no observable and effective concentration 20 (EC20) dose levels? (3) What is the composite gene expression profile of a mixture? (4) Are there, and to what extent, interactions between mixture components?

SCOPE: This project will require molecular biological techniques to answer a majority of the above questions. Molecular methods for *in vitro* and *in vivo* RNA extraction and isolation will be required. Molecular methods to measure gene expression will also be needed. In addition, tools for biomolecular

profiling will be required to assess changes in gene expression. Finally, bioinformatics tools will be needed to categorize patterns of gene expression in response to chemicals or chemical mixtures to relate them to mechanism of action. The project will also require a mathematical modeler for development of predictive model for complex mixtures.

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Study Request 140 – Chemical Mixtures Toxicology

BACKGROUND: Concurrent and sequential exposure to multiple chemicals and other stressors are the rule rather than the exception in deployment exposure scenarios. In some cases, even single "substances" such as JP-8 are in themselves complex mixtures of individual chemicals and their metabolites. In order to develop real-world health risk assessments, interactions between individual components and the biological system and with each other need to be understood and incorporated into a quantitative, predictive framework (PBPK/PD model). In addition, for complex mixtures consisting of hundreds or thousands of components, interactions cannot be fully characterized and new modeling techniques need to be developed. The objective of this effort is to develop and validate mechanistic descriptions and predictive models for military relevant mixtures exposure situations, use these models to identify and assess relevant biomarkers of both exposure and effect, and link exposures to chemical mixtures with adverse health responses in a rational risk assessment framework.

QUESTION: (1) How Can PBPK/PD modeling be adapted to describe the pharmacokinetic and pharmacodynamic behavior of complex mixtures of hundreds of potentially interacting components? (2) How can such models be tested and validated? (3) How can mixtures models be used to facilitate exposure and health risk assessments? (4) How can mixtures models be used to give insight into the mechanisms of environmentally associated disease processes, and thereby be incorporated into cumulative risk assessments involving prior exposures and susceptibility?

SCOPE: The project will require mathematical modeling techniques to answer the above questions. In addition, *in vitro* and *in vivo* studies and analysis will be required for model development and validation.

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Study Request 145 – Biomolecular Network Modeling

BACKGROUND: Finding a better way to evaluate the potential hazards of new chemicals is a goal of the AFRL in order to better serve both the warfighter and civilian community. However, the traditional toxicity testing that requires large numbers of animals are time consuming, costly, and infeasible for every compound considering the vast amount of chemicals that are commercially available. One strategy to reduce the need for these studies involves the development of better tools to predict cellular response to chemical and environmental changes. Over the last decade advances in biotechnology has created new methods to analyze changes in genes (genomics), proteins (proteomics), and metabolites (metabolomics). These new technologies allow scientists to acquire vast amounts of data from a single sample of cells and aid in the building of predictive tools. The field of toxicology has many predictive models; however there is need to develop more comprehensive mathematical models that are based on the integration of genomic, proteomic, and metabolomic data measured from a biological system under control and experimental conditions. Therefore. the strategy of this research program is to create tools that will be utilized to construct mathematical models of complex biomolecular networks.

QUESTION: (1) Can you develop new tools for mathematical modeling of complex biomolecular networks based on advanced technologies, for example genomics and proteomics? (2) How will you integrate these new technologies with more classic biochemical measurements in order to model biomolecular networks?

SCOPE: Develop a research program plan for creating tools for modeling that will include (1) choosing a prototypical biomolecular network in a biologically relevant system which are important to the field of toxicology; (2) performing genomic/proteomic experiments to develop a biomolecular profile of the chosen system; (3) conducting appropriate analyses of relevant experimental endpoints; (4) creating computational tools to integrate the experimental data; and (5) developing a mathematical model of complex biomolecular networks that will help predict cellular response to chemical and environmental changes.

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Kelley-Loughnane, N., Thrash, M.E., Linger, M.E., Soto, A., Pollard, D.H., and Frazier, J.M. 2004. "Modeling the metabolic network of glutathione synthesis in Escherichia coli". Abstract for the International Conference on Systems Biology, Heidelberg, Germany, October.

Geib, C.W., 2005. "Evaluation of E-Cell Version 3: A Biological Modeling and Simulation Tool" Air Force Technical Report (submitted)

Linger, M. 2005. "Construction of a Coupled Transcription – Translation System for the Development of a Mathematical Model Describing the Glutathione Synthetic Biomolecular Network." Poster Presentation, Protein Society meeting, Boston, May.

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Linger, M. 2006. "A Synthetic Genome to Model the Glutathione Biosynthetic Pathway *In Vitro*." Presented at the Protein Society meeting, San Diego, CA, January.

Study Request 149 – Biological Interactions of Nanoparticles

BACKGROUND: Rapid advancements in electronics, sensors, munitions, and propulsion technology have been fueled by developments in nanotechnology. Due to the unique chemical (e.g., very high surface area) and physical characteristics (e.g., spectral characteristics) of nanomaterials, multiple directorates within the AFRL are utilizing nanomaterials to improve weapon systems and military operations. However, full assessment of the novel nanomaterial effects on biological systems has not been completed. Therefore, our research objectives are to characterize the biological interactions of nanoparticles on living cells. Preliminary studies using *in vitro* cell models, such as rat alveolar macrophages and rat liver cells, are revealing the precise range of lethal exposure levels of various nanomaterials as examined with biochemical, toxicological endpoint measures.

QUESTION: (1) Is there a difference in effects and cellular response to a nanoparticle over a range of 15 to 120 nm? (2) What are the physical characteristics of nanoparticles including protein binding characteristics? (3) What is the sub-cellular compartmentalization of specific nanomaterials?

SCOPE: Conduct further studies using *in vitro* cell models such as the cellular responses elicited by human T cells and rat/human macrophages after exposure to different sizes of nanomaterials composed of diverse compounds, such as nanoaluminum. Attempt to describe the cellular mechanisms induced as a consequence of selected cell exposure and provide initial insight on some of the mechanisms activated by the immune system in response to metal/metal oxide nanoparticles with respect to size and chemical composition.

ABSTRACTS, PRESENTATIONS, TECHNICAL REPORTS, AND JOURNAL PUBLICATIONS (listed chronologically):

Hussain, S.M. and Geiss K. 2003. Dose Range Finding Of Chromophore Powder: A Summary Report. Human Effectiveness Directorate, AFRL, WPAFB

Hess, K.L. 2004. "Biological Interactions of Nanomaterials (BIN)". Presented to the AFOSR, WPAFB, Ohio, February.

Hess, K.L. 2004. "Biological Interactions of Nanomaterials (BIN) / New 6.1 Funded Proposal". Presented at the HEPB Internal Review, WPAFB, Ohio, May.

Hess, K.L. 2004. "Biological Interactions of Nanomaterials". Presented at the HE Internal Basic Science/Research Review, WPAFB, Ohio, June.

Hess, K.L. 2004. "Application of Real Time RT-PCR for the BIN Project". Presented to U.S. ARDEC, WPAFB, OH, September.

Hess, K.L., Hussain, S.M., Gearhart, J.M., Mattie, D.R., and Schlager, J.J. 2004. "Potential Hazardous Effects of Nanomaterials". Presented at the JANNAF Interagency Propulsion Committee 32nd Propellant & Explosives Development and Characterization and 21st Safety & Environmental Protection Subcommittee Joint Meeting, Seattle, WA, July.

Hess, K.L., Hussain, S.M., and Schlager, J.J. 2004. "Nanocellular Toxicity: Biological Interactions of Nanomaterials" Presented at the AFOSR/MURI Nanotoxicology Kickoff Meeting, University of Rochester, Rochester, NY, July.

Hussain SM, Gearhart JM, Hess KL, Schlager JJ. 2004. In vitro toxicity of nanoparticles in BRL 3A rat liver cell lines. AFRL-HE-WP-TR-2004-0048.

Hussain, SM, Hess, KL, Gearhart, JM, Geiss, KT, and Schlager, JJ. 2004. In Vitro Toxicity of Nanoparticles in BRL 3A Rat Liver Cells. Presented at the Toxicology and Risk Assessment Conference – "Population Protection in a Dynamic Environment", Cincinnati, Ohio, April.

Hussain, S.M., Hess, K.L., Gearhart, J.M., Geiss, K.T., and Schlager, J.J. 2004. In Vitro Toxicity of Nanoparticles in BRL 3A Rat Liver Cells. Presented at the In Vitro Toxicology Meeting, Zegrze, Poland, September.

Hussain, S.M., Hess, K.L., Gearhart, J.M., and Schlager, J.J. 2004. In Vitro Toxicity of Nanoparticles in BRL 3A Rat Liver Cells. Technical report submitted to Dr. Jonathan Kiel (AFRL/HEPC – Brooks AFB).

Braydich-Stolle, L., Hussain, S.M., Schlager, J.J. and Hofmann, M. 2005. A Germline Stem Cell Line as a Model Cytotoxicity of Nanoparticles in Vitro. *The Toxicologist* 84(S-1): 331.

KL Hess, SM Hussain, R Jones, DR Mattie, and JJ Schlager. 2005. "Nanocellular Toxicity: Biological Interactions of Nanomaterials (BIN Project)". Presented at Air War College Tour, WPAFB, OH, August, to OVALS visitors, WPAFB, OH, March, and to NRC-AFOSR visitors, WPAFB, OH, February.

Hussain, S.M., Hess, K., Gearhart, J.M., Geiss, K.T., and Schlager, J.J. 2005. Toxicity Assessment of Silver Nanoparticles (Ag 15, 100 nm) in Alveolar Macrophages. *The Toxicologist* 84(S-1): 350.

Hussain, S.M., Hess, K.L., Gearhart, J.M., Geiss, K.T., and Schlager, J.J. 2005. In Vitro Toxicity of Nanoparticles in BRL 3A Rat Liver Cells. *Toxicol. In Vitro* 19: 975-983.

Hussain SM, KL Hess, DR Mattie, and JJ Schlager. 2005. "Nanocellular Toxicity: Biological Interactions of Nanomaterials". Presented at the MURI Nanotoxicology Meeting, Rochester, NY, May.

Amato C., S. Hussain, K. Hess, and J. Schlager. 2006. Interaction of Nanomaterials with Mouse Keratinocytes. *The Toxicologist* 90(1): 168.

Hess, K.L., Hussain, S.M., Mattie, D.R., and Schlager, J.J. 2006. "Evaluation of the Potential Toxic Characteristics of Nanoparticles." Presented at the JANNAF Interagency Propulsion Committee 33rd Propellant & Explosives Development and Characterization and 22nd Safety & Environmental Protection Subcommittee Joint Meeting, Destin, FL, March.

Wagner A., S. Hussain, K. Hess, C. Bleckmann, E. England, and J. Schlager. 2006. *In Vitro* Toxicology of Aluminum Nanoparticles in Rat Lung Macrophages. *The Toxicologist* 90(1): 353.

Hess, K.L., Hussain, S.M., Jones, R.L., Mattie, D.R., and Schlager, J.J. "Characterization of T Cell Response Post Exposure to Silver and Aluminum Nanoparticles." (Manuscript in progress.)

Hussain, S.M., Hess, K.L., Jones, R.L., Mattie, D.R., and Schlager, J.J. "In Vitro Toxicity of Nanoparticles in Rat Alveolar Macrophages." (Manuscript in progress.)

SECTION 3 – MAJOR SUBCONTRACTS

Table 2

Major Subcontracts (≥ $5,000) Under Alion SAIC Joint Venture Contract

JV Study Request Number	Organization/ Company/ Consultant	Principal Investigator	Period of Performance	Deliverables
103	Haverstick Consulting (formerly AF Kelly)	Paul Bloomer	3/16/01 – 3/15/06	Provide monthly financial reports and quarterly technical progress reports of computer support operations per SOW 2.5, 4.4.1, and 4.5.4
115	Hyperion Biotechnology	John Kalns, PhD	11/1/01 – 12/31/03	Provide quarterly progress reports of results of research experiments on effects of hyperbaric oxygen on blood loss, trauma and infectious disease.
127	Huntingdon Life Sciences	Gary Hoffman	8/1/05 – 11/30/05	Provide detailed study protocol and schedule for 90-day inhalation toxicity study with perfluoro-n-butyl iodide
129	Jeff Fisher	Jeff Fisher, PhD	9/1/04 – 9/30/05	Review and evaluate program documents for USAF Low Level Chemical Warfare Agent Toxicology Program
129	ENVIRON	Harvey Clewell	9/1/04 – 9/30/05	Review and evaluate program documents for USAF Low Level Chemical Warfare Agent Toxicology Program
131	University of Georgia (Athens)	Valentine A. Nzengung, PhD	10/1/01 – 6/30/02	Provide technical report of experimental results of feasibility and mechanisms of phyto-remediation of mixed-contaminants of perchlorate and chlorinated organic solvents
141	Wright State University	Nicholas Reo, PhD	1/1/05 – 1/31/05	Provide technical progress reports of results of NMR analysis of samples provided by AFRL/HEPB; publications when appropriate
143	Toxicology Excellence in Risk Assessment	Andy Maier, PhD	4/1/03 – 12/31/03	Develop a work plan for project, provide logistics and facilitation of expert TCE panel discussions, provide progress reports of meetings, and provide final report (TCE white paper).
145	Indiana University	Frank Witzmann, PhD	6/1/04 – 5/31/05	Provide technical progress reports of proteomic analysis of samples provided by AFRL/HEPB; publications when appropriate
145	Los Alamos National	Steen Rasmussen,	11/2/04 – 11/1/05	Provide technical report on systematically review of molecular

	Laboratory	PhD		modeling algorithms and a variety of molecular simulation techniques using a select algorithm
145	University of California, Santa Barbara	Francis J. Doyle III, PhD	6/1/04 – 5/31/05	Provide technical report of results of research of experimental design protocols using identifiability theory to determine parameters
151	University of Cincinnati – Genome Research Institute	Irwin Simon, PhD; Detlef Schumann, PhD	3/1/05 – 2/28/06	Provide technical progress reports of proteomic analysis of samples provided by AFRL/HEPB; publications when appropriate
401	Rebecca Clewell	Rebecca Clewell	1/16/05 – 8/30/05	Prepare a manuscript suitable for peer review publication on perchlorate kinetics across life stages in the human
501	The University of Nebraska Medical Center	Edward Ramspott	8/1/03 – 12/31/03	Develop a pre-symposium work plan, coordinate a 3-day Perchlorate State-of-the-Science symposium, and provide a consensus report on symposium results

SECTION 4 – PERSONNEL

Table 3

Alion SAIC Joint Venture Staff 2001-2006

Name	Company - Current (Former)	Title (Per Contract)	Years on Contract
Angell, Mary Ann	Alion (ManTech)	Administrative	2001-2006
Bailey, Therlo	SAIC (Geo-Centers)	Laboratory Animal Technician	2001-2006
Batie, Nadine	Alion (ManTech)	Laboratory Animal Technician	2005-2006
Bausman, Tim	Alion (ManTech)	Animal Health Care Technician	2001-2006
Bloomer, Paul	Haverstick (A.F. Kelly)	Network Analyst	2001-2006
Brown, Christine	(Geo-Centers)	Jr. Level Technician	2001-2001
Buttler, Gerry	(ManTech)	Sr. Level Technician	2001-2003
Chan, Victor	Alion (ManTech)	Sr. Level Research Scientist	2001-2006
Clewell, Rebecca	(Geo-Centers)	Sr. Level Technician	2001-2003
Coleman, Clint	(ManTech)	Jr. Level Technician	2001-2002
Courson, Dave	(Alion/ManTech)	Interm. Level Technician	2001-2005
Deak, Terrence	(ManTech)	Jr. Level Research Scientist	2001-2001
Dixon, Janelle	(ManTech)	Administrative	2001-2001
Dodd, Darol	Alion (ManTech)	Laboratory Program Manager	2001-2006
Etchison, John	(Haverstick/A.F. Kelly)	Sr. Network Analyst	2001-2003
Frazier, Sharion	(Geo-Centers)	Laboratory Animal Technician	2001-2003
Garrett, Carol	(Geo-Centers)	Sr. Level Technician	2001-2002
Gearhart, Jeff	Alion (ManTech)	Sr. Level Research Scientist	2001-2006
Geib, Christopher	SAIC (Geo-Centers)	Interm. Level Research Scientist	2003-2006
Geiss, Kevin	(Geo-Centers)	Jr. Level Research Scientist	2001-2002
Godfrey, Richard	Alion (ManTech)	Sr. Level Technician	2001-2006
Grove, Tara	Alion (ManTech)	Administrative	2001-2006
Harker, Brent	(ManTech)	Interm. Level Technician	2001-2002
Hess, Krista	SAIC (Geo-Centers)	Jr. Level Research Scientist	2003-2006
Hussain, Saber	Alion (ManTech)	Interm. Level Research Scientist	2001-2005
Kelley-Loughnane, Nancy	SAIC (Geo-Centers)	Interm. Level Research Scientist	2001-2006
Kozlowski, Jennifer	(ManTech)	Sr. Level Technician	2001-2001
Linger, Marlin	SAIC (Geo-Centers)	Sr. Level Technician	2003-2006
Liu, Sheng	(ManTech)	Jr. Level Research Scientist	2002-2004
Mahle, Deirdre	(ManTech)	Sr. Level Technician	2001-2004
Malcomb, Willie	(ManTech)	Interm. Level Technician	2001-2002
McDougal, James	(Geo-Centers)	Sr. Level Research Scientist	2001-2001
Merrill, Elaine	SAIC (Geo-Centers)	Sr. Level Technician	2002-2006
Minnick, Darin	(ManTech)	Jr. Level Technician	2001-2004
Narayanan, Latha	SAIC (Geo-Centers)	Sr. Level Technician	2001-2006
O'Lear, John	Alion (ManTech)	Interm. Level Research Scientist	2001-2006
Parish, Margaret	Alion (ManTech)	Interm. Level Technician	2001-2006
Pollard, Dan	(Alion/ManTech)	Interm. Level Research Scientist	2001-2005
Prugh, Amber	Alion (ManTech)	Interm. Level Technician	2001-2006

Robinson, Peter	Alion (ManTech)	Sr. Level Research Scientist	2001-2006
Rogers, James	(Geo-Centers)	Sr. Level Technician	2001-2003
Rudnicki, Denise	(ManTech)	Jr. Level Technician	2002-2003
Sandoval, Melissa	(ManTech)	Jr. Level Technician	2001-2001
Schimmel, Brenda	(Alion/ManTech)	Vivarium Coordinator	2002-2005
Sklar, Ian	(ManTech)	Sr. Level Technician	2002-2004
Stapleton, Andrea	Alion (ManTech)	Interm. Level Technician	2003-2006
Soto, Armando	(Alion/ManTech)	Interm. Level Technician	2001-2005
Thornburg, Christopher	Alion (ManTech)	Sr. Level Technician	2005-2006
Thrash, Marvin	(ManTech)	Interm. Level Research Scientist	2003-2004
Torok, Connie	Alion (ManTech)	Laboratory Animal Technician	2005-2006
Veth, Sarah	(Geo-Centers)	Sr. Level Technician	2001-2002
Wallen, Bobby	Alion (ManTech)	Laboratory Animal Technician	2005-2005
Wang, Charles	(ManTech)	Interm. Level Research Scientist	2001-2001
Young, Susan	(ManTech)	Animal Health Care Technician	2001-2002
Zelik, Steve	(ManTech)	Interm. Level Technician	2003-2003

APPENDIX A

ADDITIONAL PRODUCTS OF THE ALION SAIC JV STAFF

Abstracts, Presentations, Technical Reports, and Journal Publications
(listed alphabetically)

Chou, S., McDougal, J., and Wilson, J. 2002. A Proposed Approach for Deriving Dermal Minimal Risk Levels. AFRL-HEST-WP-PO-2002-0001.

Clewell, H.J., III, Gentry, P.R., Gearhart, J.M., Allen, B.C., Andersen, M.E. 2001. Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model. *Sci Total Environ* 274:37-66.

Clewell, H.J., III, Gentry, P.R., Gearhart, J.M., Covington, T.R., Banton, M.I., Andersen, M.E. 2001. Development of a physiologically based pharmacokinetic model of isopropanol and its metabolite acetone. *Toxicol. Sci.* 63:160-172.

Coleman, C.A.., Hull, B.E., McDougal, J.N., and Rogers, J.V. 2003. The Effect of m-xylene on Cytotoxicity and Cellular Antioxidant Status in Rat Dermal Equivalents. *Toxicol Lett* 142: 133-142. AFRL-HEST-WP-JA-2002-0014

Courson D.L., and Kimmel E.C. 2002. Particulate Fraction Analysis of Pyrolized Carbon Graphite/Epoxy Advanced Composite Material. Presented at the Society of Environmental Toxicology and Chemistry Conference Salt Lake City, UT, 16-20 November.

Courson, D.L., Kimmel, E.C., Reboulet, J.E., Jung, A.E., and Reinhart, P.G. 2003. Exposure of Rat Lung Macrophages to JP-8 Jet Fuel. *The Toxicologist* 72(S-1): 289.

Courson, D.L., Kimmel, E.C., Reboulet, J.E., Jung, A.E., and Reinhart, P.G. 2003. Exposure of Rat Pulmonary Alveolar Macrophages to JP-8 Jet Fuel. Presented at the Society of Environmental Toxicology and Chemistry Conference San Antonio, TX, 9-13 November.

Courson D.L., Kimmel E.C., and Still K.R. 2001. Particulate Fraction Analysis of Pyrolized Carbon Graphite/Epoxy Advanced Composite Material(s). Presented at the American Industrial Hygiene Conference and Exposition, Toxicology session, New Orleans, LA, 2-7 June.

Courson, D.L., P.G. Reinhart, J.E. Reboulet, and E.C. Kimmel. 2004. Time Course of Pulmonary Effects from Exposure to Advanced Composite Material Combustion Atmospheres. *The Toxicologist* 78(1-S): 434.

DelRaso, N.J., Foy, B.D., Gearhart, J.M., and Frazier, J.M: 2003. Cadmium Uptake Kinetics in Rat Hepatocytes: Correction for Albumin Binding. *Toxicol. Sci* 72: 19-30. AFRL-HEST-WP-JA-2002-0012.

Dodd, D.E. 2001. "Toxicology". Presented at the School of Medicine, Wright State University, Dayton, OH, 30 August.

Dodd, D.E., ed. assist. 2001. Preface to "Toxicology and Risk Assessment Approaches" *The Science of the Total Environment*, Volume 274, Nos. 1-3, p. 1.

Dodd, D.E. 2002. Toxicity Profiles for Four Halon Replacement (Fire Suppression) Candidates. AFRL-HEST-WP-CL-2002-0007.

Dodd, D.E., ed. assist. 2002. Preface to "Issues and Applications in Toxicology and Risk Assessment" *The Science of the Total Environment*, Volume 288, Nos. 1-2, p. 1.

Dodd, D.E. 2003. Toxicity Profile for Potassium Carbonate. AFRL-HEST-WP-CL-2003-0001.

Dodd, D.E., guest ed. 2004. Preface to "2003 Conference on Toxicology and Risk Assessment" *J. Toxicol. Environ. Health, Part A: Current Issues* Volume 67, Numbers 8-10, pp. 607-610.

Dodd, D.E., K.L. Bonnette, and G.M. Hoffman. 2001. Acute toxicity, primary irritancy, and dermal sensitization studies on an explosive formulation. *Toxicologist* 60(1): 320. Presented at the Society of Toxicology Meeting, San Francisco, CA, March. AFRL-HEST-WP-PO-2001-0004.

Dodd, D.E., and W.J. Brock. 2006. Fluorocarbon Alternatives - Methodologies for Special Studies and Results. In: H. Salem and S.A. Katz, eds. *Inhalation Toxicology*, Second Edition, Chapter 32, pp. 825-850. CRC Press: Boca Raton

Dodd, D.E., G.M. Hoffman, and Hardy, C.J. 2004. Perfluoro-n-butyl iodide: acute toxicity, subchronic toxicity and genotoxicity evaluations. *Int. J. Toxicol.* 23:249-258.

Dodd, D.E, M. Ivankoe, P. Ferlazzo, and J. Niles. 2001. PAX-21 reduced sensitivity energetics toxicology. In: *Proceedings of 2001 Insensitive Munitions and Energetic Materials Technology Symposium*, pp. 253-268. NDIA/Club Murat: Bordeaux, October. AFRL-HEST-WP-PC-2001-0002.

Dodd, D., and McDougal, J. 2001. Recommendation of an Occupational Exposure Level for PAX-21. AFRL-HE-WP-TR-2001-0103.

Dodd, D.E., S. Sharma, and G.M. Hoffman. 2002. Genotoxicity and 90-day/developmental toxicity studies on an explosive formulation. *Toxicologist* 66(1-S): 267. Presented at the Society of Toxicology Meeting, Nashville, TN, March. AFRL-HEST-WP-AB-2002-0001 and AFRL-HEST-WP-PO-2002-0017.

Dodd, D., Wolfe, R., Pollard, D., Merrill, E., Sterner, T., Bekkedal, M., and English, J. 2004. 90-Day Oral Toxicity Study on n-Nonane in Female Fischer 344 Rats and Male C57BL/6 Mice. AFRL-HE-WP-TR-2002-0137.

Fisher, J., Lumpkin, M., Boyd, J., Mahle, D., Bruckner, J., and El-Masri, H. 2003. PBPK Modeling of the Metabolic Interactions of Carbon Tetrachloride and Tetrachloroethylene in B6C3F1 Mice. *The Toxicologist* 72(S-1): 181. AFRL-HEST-WP-AB-2003-0001.

Frazier, J., Dodd, D., and Nikiforov, A. 2003. Data Development Strategy for Evaluation of Occupational Health Hazards of New Chemicals of Interest to the Air Force. AFRL-HE-WP-TR-2003-0144.

Garrett, C., Rogers, J., Wang, C., and McDougal, J. 2002. Transcriptomic profiles in rat skin following dermal exposure to sodium lauryl sulfate. *The Toxicologist* 66(1-S): 161-162. AFRL-HEST-WP-AB-2002-0009 and AFRL-HEST-WP-PO-2002-0012.

Geiss, K., Abdulla, R., and Frazier, J. 2001. Assessment of Oxidative Stress in Primary Rat Hepatocytes Following Exposures to Volatile Halogenated Methanes Utilizing a Unique *In Vitro* Exposure System. *The Toxicologist* 60(1): 301-302. AFRL-HEST-WP-PO-2001-0005.

Gearhart, J.M. 2001. "Pharmacokinetics of toxic chemicals in breast milk". Presented at "Toxic Chemcials in Breast Milk: A National Workshop to Assess the Hazards to Children's Health of Chemical Contaminats in Breast Milk", New York Academy of Medicine, New York, NY, 5 October.

Gearhart, J.M. 2002. "Pharmacokinetics of toxic chemicals in breast milk". Presented at the Workshop on Chemicals and Drugs in Breast Milk, sponsored by NICHD/FDA/OWH-DHHS, Rockville, Maryland, 24-25 April.

Geiss, K., and Frazier, J. 2001. QSAR Modeling of In Vitro Oxidative Stress Caused by Halogenated Aliphatics. AFRL-HEST-WP-AB-2001-0001, AFRL-HEST-WP-AB-2001-0004 and AFRL-HEST-WP-PO-2001-0037.

Geiss, K., and Frazier, J. 2001. Oxidative Stress in Primary Rat Hepatocytes Following Exposures to Volatile Halogenated Methanes. AFRL-HEST-WP-AB-2001-0005 and AFRL-HEST-WP-PO-2001-0039.

Geiss, K., and Frazier, J. 2002. Halogenated Hydrocarbon Toxicity in Primary Rat Hepatocytes: Induction of Oxidative Stress and a Novel Toxicity Ranking Method. AFRL-HEST-WP-AB-2002-0012 and AFRL-HEST-WP-PO-2002-0005.

Geiss, K., and Frazier, J. 2002. Development of an Integrated Toxicity Assessment System for use in Operational Deployment and Materials Development. AFRL-HEST-WP-AB-2002-0021.

Geiss, K.T., J.M. Frazier, and D.E. Dodd. 2002. Toxicity screening of halogenated aliphatics using a novel *in vitro* volatile chemical exposure system. In: *Proceedings of the 12th Halon Options Technical Working Conference*, http://www.bfrl.nist.gov/866/HOTWC, Albuquerque, April. AFRL-HEST-WP-PC-2002-0001 and AFRL-HEST-WP-AB-2002-0022.

Gunasekar, P., Rogers, J., Kabbur, M., Garrett, C., Brinkley, W., and McDougal, J. 2001. Comparative Study of Molecular Mechanisms of Skin Irritation after Acute Exposure to m-Xylene in Rats and Guinea Pigs. AFRL-HE-WP-TR-2001-0090.

Gunasekar, P.G., Rogers, J.V., Kabbur, M.B., Garrett, C.M., Brinkley, W.W., and McDougal, J.N. 2003. Molecular and histological responses in rat skin exposed to m–xylene. *J Biochem Mol Toxicol* 17: 92-94.

Hussain, S.M. 2001. "*In vitro* toxicity evaluation of a new series of high energy chemicals in primary rat hepatocytes". Presented at the conference - Issues and Applications in Toxicology and Risk Assessment, Fairborn, OH, 23-26 April.

Hussain, S.M. and Frazier, J.M. 2001. *In vitro* toxicity evaluation of a new series of high energy chemicals in primary rat hepatocytes. *The Toxicologist* 60(1): 43. AFRL-HEST-WP-PO-2001-0018 and AFRL-HEST-WP-PO-2001-0028.

Hussain, S.M. and Frazier, J.M. 2001. *In vitro* assessment of high energy chemicals in rat hepatocytes. *Sci. Total Environ.* 274, 151-160.

Hussain, S., Frazier, J., and Brown, C. 2002. Mechanistic Toxicology of Hydrazinium Nitrate in Primary Rat Hepatocytes. *The Toxicologist* 66(1-S): 119. AFRL-HEST-WP-AB-2002-0002 and AFRL-HEST-WP-PO-2002-0014.

Hussain, S., Gao., P., Mattie, D., and Frazier, J. 2003. In Vitro Rat Hepatocyte Toxicity and Bacteria Genotoxicity Evaluation of High Energy Chemicals for Replacement of Hydrazine. AFRL-HE-TR-2003-0077.

Hussain, S.M., Mattie, D.R., and Frazier, J.M. 2002. Studies on newly synthesized propellants: toxicological assessment. CPIA Pub 698, JANNAF 18th Safety & Environmental Protection Subcommittee Meeting.

Hussain, S.M., Sharma, S., Gao, P., Mattie, D. and Frazier, J. 2003. Rat Hepatocyte Toxicity and Bacteria Genotoxicity Evaluation of High Energy Chemicals for Replacement of Hydrazine. AFRL-HE-WP-TR-2003-0077.

Kelley-Loughnane, N., Sabla, G., Aronow, B.J., Bezerra, J.A. 2001. Developing livers display an unique transcriptional program with minimal overlap with hepatic regeneration. Poster presented at the AASLD Annual Meeting, November. (designated as President's Choice)

Kimmel, E.C. and Courson, D.L.. 2002. Characterization of Particulate Matter in Carbon-Graphite/Epoxy Advanced Composite Material Smoke. Presented at the J. Am Ind. Hyg. Assoc. Conference, August.

Kimmel, E. C., Prues S.L., Reboulet J.E., and Courson D.L. 2004. Tracheobronchial and Nasal Compartment Clearance of 1.0 Micron Particles in the Rat: Comparison with a Typical Path Tracheobronchial Clearance Model. *The Toxicologist* 78(1-S): 437.

Kimmel, E.C., Reboulet, J.E., Courson, D.L., and Still, K.R. 2002. Airway reactivity response to aged carbon-graphite composite material smoke. *J. Appl. Toxicol.* 22(3):193-206.

Kimmel E.C., Reboulet J.E., Courson D.L., Whitehead G.S., and Reinhart P.G. 2003. Pulmonary Function Following Exposure to Carbon-Graphite/Epoxy Composite Material. *The Toxicologist* 72(S-1): 43.

Lipscomb, J.C., Mattie, D. and Dodd, D.E., guest eds. 2005. Introduction to "2004 Toxicology and Risk Assessment Conference" *J. Toxicol. Environ. Health, Part A: Current Issues*, Volume 68, Numbers 11-12, pp. 833-836.

Mahle DA, Gearhart JM, Godfrey RJ, Mattie DR, Cook RS, Grigsby CC. 2005. Determination of Partition Coefficients for a Mixture of Volatile Organic Compounds in Rats and Humans at Different Life Stages. AFRL-HE-WP-TR-2005-0012.

Mahle, D.A., Godfrey, R.J., Buttler, G.W., and Fisher, J.W. 2004. Metabolism of perchloroethylene and 1,1,1,2-tetrachloroethane after carbon tetrachloride pretreatment in B6C3F1 mice. AFRL-HE-WP-TR-2001-0133.

Mahle, D.A., Godfrey, R.J., Buttler, G.W., Narayanan, L., Taylor, A., and Fisher, J.W. 2001. Pharmacokinetics and metabolism of dichloroacetic acid and trichloroacetic acid administered in drinking water in rats and mice. AFRL-HE-WP-TR-2001-0059.

Mahle, D.A., Grigsby, C.C., Godfrey, R.J., Gearhart, J.M., Barton, H.A., Lipscomb, J.C., and Cook, R.S. 2004. Comparison of partition coefficients for a mixture of volatile organic compounds in rats and humans at different life stages. *The Toxicologist* 78(1-S): 22. AFRL-HEST-WP-AB-2003-0008.

Mattie, D., Cooper, J., Sterner, T., Schimmel, B., Bekkedal, M., Bausman, T., and Young, S. 2004. Developmental Neurobehavioral Effects of JP-8 Jet Fuel on Pups from Female Sprague-Dawley Rats Exposed to Oral Gavage. AFRL-HE-WP-TR-2001-0186.

Mattie, D., Sterner, T., Bekkedal, M., Schimmel, B., Bausman, T., Young, S., and Cooper, J. 2001. Developmental Neurobehavioral Effects of JP-8 Jet Fuel on Pups from Female Sprague-Dawley Rats Exposed by Oral Gavage. *The Toxicologist* 60(1): 217. AFRL-HEST-WP-PO-2001-0019.

Mattie, D.R., Sterner, T.R., Merrill, E.A., and Clewell, R.A. 2006. Using Human Life Stage PBPK/PD Model Predictions of Perchlorate-Induced Iodide Inhibition to Inform Risk Assessment in Sensitive Populations. *The Toxicologist* 90(1): 261.

McDougal, J., Pollard, D., Davis, R., and Dodd, D. 2001. Dermal Absorption of Comp B and CRB-12 in Isolated Rat Skin. AFRL-HE-WP-TR-2001-0058.

Mukerjee, D., D. Mattie, and D. E. Dodd. 2001. Introduction to "Theories and Practices in Toxicology and Risk Assessment" *Toxicol. Ind. Health*, Volume 17, Numbers 5-10, p. 144.

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