

STATEMENT OF WORK
POTENTIAL FOR ENVIRONMENTAL AND THERAPEUTIC AGENTS TO INDUCE
IMMUNOTOXICITY
DATED OCTOBER 6, 2004

INDEPENDENTLY, AND NOT AS AN AGENT OF THE GOVERNMENT, THE CONTRACTOR SHALL PROVIDE ALL THE NECESSARY SERVICES, QUALIFIED PERSONNEL, MATERIALS (INCLUDING ANIMALS), EQUIPMENT, AND FACILITIES NOT OTHERWISE PROVIDED BY THE GOVERNMENT AS NEEDED TO EXAMINE THE IMMUNE SYSTEM IN LABORATORY ANIMALS FOLLOWING EXPOSURE TO XENOBIOTICS. THE GOVERNMENT SHALL ONLY PROVIDE THE CHEMICALS OR THERAPEUTICS DESCRIBED IN TASKS I - IV ON AN AS NEEDED BASIS TO BE DETERMINED BY THE PROJECT OFFICER. THE AS NEEDED BASIS REFERS TO THE CHEMICALS OR THERAPEUTICS THAT CANNOT BE PURCHASED THROUGH COMMERCIAL SOURCES AND MUST BE FURNISHED BY THE GOVERNMENT.

TASK I – EVALUATION OF THE POTENTIAL TO INDUCE IMMUNOTOXICITY

I-A: RANGE-FINDING STUDIES ON IMMUNOMODULATION

THE CONTRACTOR SHALL TEST FOUR XENOBIOTICS PER YEAR USING TESTS DESCRIBED IN TASK I A-1-5. EXPOSURE REGIMEN WILL NORMALLY (BUT NOT ALWAYS) CONSIST OF DAILY DOSING FOR 28 DAYS EMPLOYING ORAL GAVAGE, DRINKING WATER, INTRATRACHEAL, FEED OR INTRAPERITONEAL INJECTION OF THE TEST ARTICLE (ROUTE TO BE DETERMINED BY THE PROJECT OFFICER) AT 5 DOSE LEVELS IN ADDITION TO A VEHICLE CONTROL. EIGHT ANIMALS PER TREATMENT GROUP SHALL BE EMPLOYED FOR THE TESTS DESCRIBED IN ITEMS A-E. PREVIOUS STUDIES AT THE NIEHS HAVE SHOWN THAT CERTAIN OF THE DISCUSSED ASSAYS CAN BE PERFORMED FROM TISSUE DERIVED FROM THE SAME ANIMAL. APPROPRIATE POSITIVE AND VEHICLE CONTROLS SHOULD BE USED FOR EACH IMMUNE ASSAY, WITH THE UNDERSTANDING THAT THE POSITIVE CONTROLS MAY BE DIFFERENT FOR SPECIFIC IMMUNE FUNCTION TESTS. WHEN NECESSARY, AS DETERMINED BY THE PROJECT OFFICER, THE RESULTS FROM THE STUDIES SHALL BE CONFIRMED BY A REPEAT STUDY IN THE CONTRACTOR'S LABORATORY. IN MOST CIRCUMSTANCES, THESE STUDIES SHALL BE PERFORMED IN FEMALE B6C3F1 MICE. FEMALES ARE SUGGESTED SINCE THEY CAN BE GROUP HOUSED AND HAVE BEEN SHOWN TO BE MORE RESPONSIVE THAN MALES IN MANY IMMUNE TESTS. HOWEVER, IN CERTAIN INSTANCES THE MALE B6C3F1 MICE, FEMALE F344 OR SPRAGUE-DAWLEY RAT OR ANOTHER MOUSE STRAIN MAY BE EMPLOYED (TO BE DETERMINED BY THE PROJECT OFFICER) AND WILL BE BASED ON PHARMACOKINETIC CONSIDERATIONS. IN SOME INSTANCES TEST ARTICLE EXPOSURE MAY BE CONDUCTED BY THE NTP AND THE CONTRACTOR WILL RECEIVE APPROPRIATELY TREATED ANIMALS, IMMUNE CELLS AND/OR TISSUES TO

ASSAY FOR IMMUNE FUNCTION.

IF BACKGROUND INFORMATION ON THE CHEMICAL OF INTEREST IS NOT AVAILABLE, AS DETERMINED BY THE PROJECT OFFICER, THE PURITY OF THE CHEMICAL, ANALYSIS OF THE TEST SOLUTIONS, AND/OR PLASMA LEVELS SHALL BE DETERMINED BY THE NIEHS/ETP, THROUGH THE CONTRACT FOR CHEMICAL ANALYSIS. RESULTS OF THESE ANALYSES SHALL BE DISSEMINATED TO THE CONTRACTOR AS SOON AS THEY ARE AVAILABLE.

1. IMMUNOPATHOLOGY - THE CONTRACTOR SHALL MEASURE STANDARD TOXICITY PARAMETERS INCLUDING BODY WEIGHT, SELECTED ORGAN WEIGHTS (SPLEEN, THYMUS, LIVER, AND KIDNEY) AND HEMATOLOGICAL PROFILE (COMPLETE BLOOD COUNT AND DIFFERENTIAL). LIVER, KIDNEY, SPLEEN, BONE MARROW, PROXIMAL AND DISTAL LYMPH NODES AND THYMUS SHOULD BE FIXED IN ACCORDANCE WITH NTP PROTOCOLS FOR LATER HISTOLOGICAL EVALUATION. TISSUES SHOULD BE CUT AND PROCESSED INTO PARAFFIN BLOCKS AND TRANSFERRED TO THE GOVERNMENT FOR EVALUATION UNDER A SEPARATE CONTRACT. APPROXIMATELY 100 MG OF TISSUE FROM THE SPLEEN, THYMUS AND LIVER SHOULD BE FLASH FROZEN IN LIQUID NITROGEN AND STORED AT -80/C UNTIL TRANSFER TO THE GOVERNMENT FOR GENOMIC STUDIES. THE CONTRACTOR SHALL COLLECT AND ARCHIVE SERUM SAMPLES FOR ASSESSMENT OF TEST ARTICLE LEVELS IN THE BLOOD. QUANTITATION OF BLOOD LEVELS WILL BE PERFORMED BY THE GOVERNMENT UNDER A SEPARATE CONTRACT.
2. HUMORAL MEDIATED IMMUNITY - THE CONTRACTOR SHALL ASSESS HUMORAL MEDIATED IMMUNITY BY QUANTITATING IGM (OR IN SOME INSTANCES IGG) SPECIFIC ANTIBODY RESPONSE FOLLOWING I.V. ADMINISTRATION OF SHEEP RED BLOOD CELLS (SRBC) BY ELISA AND AFC PLAQUE ASSAY. IN ADDITION, AS PART OF METHODS VALIDATION EFFORTS, THE CONTRACTOR SHOULD ASSESS THE RESPONSE TO AN ALTERNATIVE T-DEPENDENT ANTIGEN (I.E. KEYHOLE LIMPET HEMOCYANIN) VIA ELISA OR ELISPOT.
3. CELL MEDIATED IMMUNITY - THE CONTRACTOR SHALL QUANTITATE CELL-MEDIATED IMMUNITY BY ASSESSMENT OF THE LYTIC ABILITY OF SPLENIC CYTOTOXIC T LYMPHOCYTES.
4. CELL QUANTIFICATION - SPLENIC CELLULARITY, SPLENIC DIFFERENTIALS, AND B CELL, T CELL, T CELL SUBSETS, NK CELLS AND MONOCYTE ENUMERATION ARE TO BE PERFORMED BY CYTOMETRIC ANALYSIS. FOR SOME TASK I-B STUDIES AN ASSESSMENT OF THE EXPRESSION OF RELEVANT ACTIVATION MARKERS MAY BE REQUIRED.

5. NON-SPECIFIC IMMUNITY - THE CONTRACTOR SHALL ASSESS NONSPECIFIC IMMUNITY BY QUANTITATION OF NATURAL KILLER CELL ACTIVITY AND MACROPHAGE FUNCTION.-

TASK I-B. FULL PROTOCOL STUDIES IN IMMUNOMODULATION – EVALUATION OF HOST RESISTANCE ENDPOINTS

THE CONTRACTOR SHALL TEST TWO XENOBIOTICS PER YEAR THEREAFTER (SELECTED FROM THOSE TESTED IN TASK I-A) REPEATING ALL THE TESTS DESCRIBED IN TASK I-A. THE PROJECT OFFICER WILL SELECT THE CHEMICAL(S). THE EXPOSURE REGIMEN SHALL BE SIMILAR TO THAT DESCRIBED UNDER TASK I-A WITH THE EXCEPTION THAT 3 RATHER THAN 5, TREATMENT LEVELS WILL BE EMPLOYED IN ADDITION TO VEHICLE CONTROL GROUPS. IN MOST CIRCUMSTANCES THESE STUDIES SHALL BE PERFORMED IN FEMALE B6C3F1 MICE. HOWEVER, IN CERTAIN INSTANCES, RATS OR ANOTHER MOUSE STRAIN MAY BE EMPLOYED.

6. HOST RESISTANCE ASSAYS - THE CONTRACTOR SHALL ASSESS THE ABILITY OF AN ESTABLISHED IMMUNOMODULATOR TO ALTER DISEASE RESISTANCE FOLLOWING CHALLENGE WITH AT LEAST TWO ESTABLISHED HOST RESISTANCE MODELS. FOR ALL HOST RESISTANCE STUDIES A MINIMUM OF TEN ANIMALS PER DOSE GROUP AND CHALLENGE LEVEL SHOULD BE EMPLOYED. THE APPROPRIATE TUMOR CELL AND/OR INFECTIOUS AGENT MODELS WILL BE DETERMINED BY THE PROJECT OFFICER IN CONSULTATION WITH THE CONTRACTOR AND MAY INCLUDE, BUT ARE NOT LIMITED TO THE FOLLOWING:

(A) THE GROWTH OF TRANSPLANTABLE SYNGENEIC TUMOR CELLS (PYB6) USING A CELL CONCENTRATION THAT INDUCES A TD20 IN CONTROL MICE.

(B) THE QUANTITATION OF MELANOMA CELLS (B16F10) IN THE LUNG USING CELL CONCENTRATION THAT INDUCES A TD20 IN CONTROL MICE.

(C) LIVER AND SPLEEN BACTERIAL COUNTS FOLLOWING CHALLENGE WITH LISTERIA MONOCYTOGENES (ED20).

(D) MORIBUNDITY OR BACTERIAL CELL COUNTS FOLLOWING CHALLENGE WITH STREPTOCOCCUS (ED20).

(E) MORIBUNDITY OR TISSUE VIRAL LOAD FOLLOWING CHALLENGE WITH INFLUENZA (ED20).

(F) QUANTITATION OF PARASITIZED ERYTHROCYTES FOLLOWING INFECTION WITH PLASMODIUM. (ED20).

MORIBUND ANIMALS WILL BE HUMANELY EUTHANIZED AND DEATH WILL NOT BE USED AS AN ENDPOINT FOR ANY STUDIES.

TASK II - EVALUATION OF THE POTENTIAL TO INDUCE HYPERSENSITIVITY

THE CONTRACTOR SHALL TEST 2 XENOBIOTICS PER YEAR FOR THEIR POTENTIAL TO PRODUCE SKIN HYPERSENSITIVITY IN THE MOUSE USING TESTS DESCRIBED BELOW. THE PROJECT OFFICER WILL SELECT THE CHEMICAL(S). THE DOSES TO BE TESTED FOR DERMAL SENSITIZING CAPABILITY SHALL BE BASED ON SOLUBILITY. FEMALE BALB/C MICE WILL BE USED FOR THESE STUDIES AND A MINIMUM OF 6 ANIMALS PER DOSE GROUP SHALL BE USED.

1. MOUSE EAR SWELLING TEST (MEST) - THE CONTRACTOR SHALL TEST ALLERGENIC OR IMMUNOGENIC POTENTIAL USING THE MOUSE EAR SWELLING TEST. FOR SENSITIZATION IN THE MEST ASSAY, THE COMPOUND SHALL BE ADMINISTERED TOPICALLY BY APPLYING THE APPROPRIATE CONCENTRATION DIRECTLY TO THE SKIN ON THE SHAVEN UPPER BACK FOR THREE DAYS. THE ANIMALS SHOULD BE RESTED FOR APPROXIMATELY FOUR DAYS. FOR CHALLENGE, THE TEST ARTICLE WILL BE APPLIED TO THE EARS. EAR SWELLING SHOULD BE QUANTITATED AT 24 AND 48 HOURS FOLLOWING CHALLENGE. AN APPROPRIATE POSITIVE CONTROL SHOULD BE USED FOR EACH STUDY..

2. LOCAL LYMPH NODE ASSAY (LLNA) - THE CONTRACTOR SHALL EXAMINE THE SENSITIZATION POTENTIAL OF THE TEST ARTICLES OF INTEREST IN BALB-C MICE AND MATCHING CONTROLS USING THE LLNA. THE LLNA SHOULD BE PERFORMED IN ACCORDANCE WITH THE ICCVAM GUIDELINES. THE TEST ARTICLE SHALL BE APPLIED TO THE DORSUM OF THE EAR FOR THREE CONSECUTIVE DAYS. THE ANIMALS SHOULD BE RESTED FOR TWO DAYS AND PROLIFERATION IN THE DRAINING LYMPH NODES EVALUATED ON DAY 6.

TASK III - EVALUATION OF THE POTENTIAL TO INFLUENCE THE DEVELOPMENT AND/OR PROGRESSION OF AUTOIMMUNE DISEASE

THE CONTRACTOR SHALL TEST 1 XENOBIOTIC PER YEAR FOR THE POTENTIAL TO INFLUENCE AUTOIMMUNE DISEASE. THE PROJECT OFFICER WILL SELECT THE CHEMICAL(S). A RODENT MODEL FOR AUTOIMMUNE DISEASE (E.G. NZB MICE FOR HUMAN SLE, NOD MOUSE FOR INSULIN-DEPENDENT DIABETES OR BROWN-NORWAY RAT FOR MERCURY-INDUCED GLOMERULONEPHRITIS) WILL BE ADMINISTERED A XENOBIOTIC AND MONITORED FOR THE DEVELOPMENT OR EXACERBATION OF AUTOIMMUNE DISEASE USING APPROPRIATE PATHOLOGICAL (E.G., HISTOPATHOLOGY OF

TARGET ORGAN) AND BIOCHEMICAL (E.G., CHANGES IN CIRCULATING AUTOANTIBODIES OR OTHER SERUM PROTEINS, CYTOKINES OR CYTOKINE RECEPTORS, GLUCOSE LEVELS) TESTS. IN SOME INSTANCES, THE XENOBIOTIC MAY BE ADMINISTERED PRENATALLY TO ASSESS DEVELOPMENTAL EFFECTS. FOR SOME COMPOUNDS IT MAY BE NECESSARY TO EXAMINE GENDER-SPECIFIC DIFFERENCES IN THE DEVELOPMENT OR EXACERBATION OF AUTOIMMUNITY, BY EVALUATING CHEMICAL EFFECTS IN BOTH SEXES. APPROXIMATELY 25 MICE PER TREATMENT GROUP AND 3 CHEMICAL-DOSE LEVELS SHOULD BE EMPLOYED.

TASK IV – EVALUATION OF IMMUNOMODULATION IN THE DEVELOPING IMMUNE SYSTEM

THE CONTRACTOR SHALL TEST TWO XENOBIOTICS PER YEAR USING TESTS DESCRIBED IN TASK I A-1-5 FOR THE POTENTIAL TO MODULATE THE IMMUNE SYSTEM IN THE DEVELOPING ORGANISM. THE EXPOSURE REGIMEN WILL NORMALLY (BUT NOT ALWAYS) CONSIST OF DAILY DOSING OF PREGNANT FEMALES BEGINNING ON GD 7 AND CONTINUING THROUGH PND 4-7. PUPS WILL BE DOSED DAILY WHEN DOSING OF THE DAMS IS DISCONTINUED ON PND 4-7, DOSING OF THE INDIVIDUAL PUPS WILL COMMENCE AND CONTINUE GENERALLY THROUGH PND 42. ROUTES OF ADMINISTRATION MAY INCLUDE ORAL GAVAGE, DRINKING WATER, AND INTRATRACHEAL, DOSED FEED OR INTRAPERITONEAL INJECTION OF THE TEST ARTICLE (ROUTE TO BE DETERMINED BY THE PROJECT OFFICER) AT 3 DOSE LEVELS IN ADDITION TO A VEHICLE CONTROL. A MINIMUM OF EIGHT PUPS PER TREATMENT GROUP SHALL BE EMPLOYED FOR THE TESTS DESCRIBED IN ITEMS A-E. AS A LITTER IS CONSIDERED A SINGLE UNIT, ALL TREATMENT GROUPS MUST BE COMPOSED OF PUPS FROM DIFFERENT LITTERS. IN MOST CIRCUMSTANCES, THESE STUDIES SHALL BE PERFORMED IN FEMALE B6C3F1 MOUSE PUPS (DERIVED FROM THE CROSS OF FEMALE C57BL/6 AND MALE C3H/HE MICE). HOWEVER, IN CERTAIN INSTANCES THE FEMALE F344 OR SPRAGUE-DAWLEY RAT OR ANOTHER MOUSE STRAIN MAY BE EMPLOYED (TO BE DETERMINED BY THE PROJECT OFFICER) AND WILL BE BASED ON PHARMACOKINETIC CONSIDERATIONS. IN SOME INSTANCES TEST ARTICLE EXPOSURE MAY BE CONDUCTED BY THE NTP AND THE CONTRACTOR WILL RECEIVE APPROPRIATELY TREATED ANIMALS, IMMUNE CELLS AND/OR TISSUES TO ASSAY FOR IMMUNE FUNCTION. THE OFFERORS SHALL SUBMIT ONE COST PROPOSAL WHICH REFLECTS THE TOTAL COSTS FOR THE SUCCESSFUL COMPLETION OF ALL STUDIES INCLUDED IN TASKS I-IV FOR THREE YEARS (BASE CONTRACT) PLUS THE FIVE OPTIONAL YEARS.

SUMMARY OF STUDIES TO BE CONDUCTED UNDER THE BASE CONTRACT

STUDY TYPE	TASK	NUMBER OF STUDIES PER YEAR
IMMUNOMODULATION -RANGE FINDING	I-A	4
IMMUNOMODULATION – FULL PROTOCOL	I-B	2
HYPERSENSITIVITY	II	2
AUTOIMMUNITY	III	2
DEVELOPMENTAL	IV	2

TASK V - EVALUATION OF ADDITIONAL XENOBIOTICS ON AN AS NEEDED BASIS (OPTION II)

The Contractor shall have the capability of performing additional studies on an as needed basis that will not exceed 35% of the total yearly level of effort. The option to conduct additional studies as described above in Tasks I-IV may be exercised **at least once each year** during the life of the contract. **In addition to the cost proposal for the Base Contract described above, the offerors shall submit separate cost proposals for the conduct of one test article evaluation from each of the distinct Tasks (IA, IB, II, III and IV) identified above in the base contract.** Offerors should predicate the anticipated level of effort for performance of Task V studies to be not more than 35% of the basic contract effort in any given year.

TASK VI - DEVELOPMENT AND/OR EVALUATION OF NEW AND IMPROVED TECHNOLOGY (OPTION III)

IMMUNOLOGY IS A DEVELOPING SCIENCE AND, AS SUCH, IT IS EXPECTED THAT NEW AND IMPROVED METHODOLOGY WILL BE REQUIRED TO MAINTAIN STATE OF THE ART EVALUATION. THE CONTRACTOR SHALL CONDUCT METHODS DEVELOPMENT AND VALIDATION ON A CONTINUING BASIS BEGINNING IN YEAR 1 OF THE CONTRACT. THE DIRECTION OF RESEARCH WILL BE DICTATED BY BOTH PREVIOUS RESEARCH AND NEEDS IN THE AREA. FOR EXAMPLE, IT MAY BE NECESSARY TO EVALUATE METHODS TO ASSESS THE RELEVANCE OF CHANGES IN CYTOKINE LEVELS, MONITOR ADDITIONAL CELL SURFACE MARKERS OR QUANTITATE CERTAIN BIOMEDICAL CHANGES IN CHEMICAL MODELS OF AUTOIMMUNE DISEASE. IN ADDITION, THE VALIDATION OF METHODS TO DETERMINE THE POTENTIAL FOR XENOBIOTICS TO INDUCE OR POTENTIATE AUTOIMMUNE DISEASE SHOULD BE GIVEN A HIGH PRIORITY. THE CONTRACTOR WILL BE EXPECTED TO DEVELOP NOVEL STRATEGIES FOR ASSESSING THE CHEMICAL-INDUCED DEVELOPMENT OF AUTOIMMUNE DISEASE IN RODENTS, SUCH AS THE USE OF ACTIVATION MARKERS IN IMMUNE CELL PHENOTYPING OR USE OF IMMUNOPRECIPITATION TO ASSAY FOR AUTOANTIBODIES. ASSESSMENT OF THE UTILITY OF TRADITIONAL SCREENING METHODS OR DEVELOPMENT OF

NEW STRATEGIES TO EVALUATE IMMUNE PERTURBATIONS IN NEONATAL OR AGING ANIMALS SHOULD ALSO BE CONSIDERED. ALTERNATIVE ENDPOINTS FOR DISEASE RESISTANCE ASSAYS, IN PARTICULAR THOSE WHICH REDUCE THE NUMBERS OF TEST ANIMALS NEEDED SHOULD BE STRONGLY CONSIDERED. FOR XENOBIOTICS SHOWN TO BE SENSITIZERS, IT MAY BE USEFUL TO FURTHER CHARACTERIZE SPECIFIC ANTIBODY PRODUCTION INCLUDING CLASSES (E.G., IGE) AND IGG SUBTYPES, OR CYTOKINE PROFILES USING MOLECULAR TECHNIQUES SUCH AS THE RNASE PROTECTION ASSAY. ALTERNATIVELY, FOLLOW-UP STUDIES TO HELP ESTABLISH CELLULAR AND/OR MOLECULAR MECHANISMS OF ACTION FOR IMMUNE PERTURBATIONS OBSERVED DURING TASKS I - IV PERFORMANCE MAY BE APPROPRIATE. DEVELOPMENT OF NOVEL SCREENING STRATEGIES INCLUDING THE USE OF MOLECULAR TECHNIQUES SUCH AS ANALYSIS OF GENE EXPRESSION BY MICROARRAY TO ASSESS XENOBIOTIC-INDUCED IMMUNOLOGIC ALTERATIONS WOULD BE DESIRABLE. A DEFINED PROTOCOL FOR THE SPECIFIC TASK AS IDENTIFIED BY THE CONTRACTOR, SHALL BE PREPARED BY THE CONTRACTOR AND SUBMITTED TO THE PROJECT OFFICER FOR APPROVAL PRIOR TO CONTINUING THE EVALUATION. ALL WORK CONDUCTED UNDER THIS TASK SHALL HAVE PRIOR APPROVAL BY THE PROJECT OFFICER. ACTIVITIES PERFORMED UNDER THIS TASK SHALL ARE EXPECTED TO REQUIRE APPROXIMATELY 10% OF THE BASIC CONTRACT LEVEL OF EFFORT PER YEAR. THE TASK VI PORTION OF THE CONTRACT SHALL BE OPTIONAL BASED ON THE PROJECT OFFICER S DISCRETION AND THE AVAILABILITY OF FUNDS.

PERSONNEL REQUIREMENT AND LEVEL OF EFFORT:

THE CONTRACTOR IS RESPONSIBLE FOR ESTIMATING THE PERSONNEL REQUIREMENTS OF THE PROJECT BASING THE ESTIMATES ON A CAPABILITY OF PROVIDING THE SERVICES REQUIRED IN THE STATEMENT OF WORK. THE GOVERNMENT ESTIMATES THAT THE PROJECT (TASKS I - IV) WILL REQUIRE APPROXIMATELY 2.5 PERSON YEARS PER CONTRACT YEAR AT THE PH.D. PROFESSIONAL LEVEL, 2.0 PERSON YEARS PER CONTACT YEAR AT THE MA/SENIOR TECHNICAL LEVEL, 1.5 TECHNICAL PERSON YEARS PER CONTRACT YEAR; 0.5 PROFESSIONAL SUPPORT PERSON YEARS PER CONTRACT YEAR AND 0.5 ADMINISTRATIVE SUPPORT PERSON YEARS PER CONTRACT YEAR. THE PRINCIPAL INVESTIGATOR SHALL DEMONSTRATE APPROPRIATE DOCTORAL AND POSTDOCTORAL LEVEL TRAINING AND EXPERIENCE IN AREAS RELATING TO IMMUNOTOXICOLOGICAL WORK IN WHOLE ANIMALS AND SHOULD HAVE (1) DEMONSTRATED ABILITIES AND EXPERIENCE IN PLANNING AND CONDUCTING STUDIES OF IMMUNE SYSTEM EVALUATION FOLLOWING CHEMICAL OR DRUG INSULT, (2) DEMONSTRATED ABILITIES AND EXPERIENCE IN PHARMACOLOGICAL, TOXICOLOGICAL AND IMMUNOLOGICAL STUDIES AND (3) EXPERIENCE IN HYPERSENSITIVITY STUDIES. OFFERORS ARE ADVISED THAT THE CORE STAFF INVOLVED IN TOXICOLOGIC RESEARCH MUST BE IN PLACE BY THE DATE OF

CONTRACT AWARD. THE PRINCIPAL INVESTIGATOR, CO-PRINCIPAL INVESTIGATOR AND TECHNICAL STAFF SHALL BE EMPLOYEES OF THE OFFEROR (I.E., NOT CONSULTANTS OR SUBCONTRACTORS). THE DAILY INTERACTION AND CONSTANT COORDINATION OF EFFORTS NEEDED AMONGST THE STAFF THROUGHOUT THE IN-LIFE PORTION OF THE STUDIES MAKES IT CRITICAL THAT THEY BE PHYSICALLY AND ORGANIZATIONALLY TOGETHER.

TASK V PERSONNEL REQUIREMENTS WILL VARY DEPENDING UPON THE NEEDS OF THE GOVERNMENT AND THE NUMBER OF ADDITIONAL TESTS TO BE CONDUCTED IN ANY GIVEN YEAR. THE OFFEROR'S PROPOSAL SHOULD INCLUDE A DISCUSSION ON HOW THE ADDITIONAL STAFFING REQUIREMENTS WILL BE MET IF THE OPTION IS EXERCISED TO THE FULLEST EXTENT: (NOT TO EXCEED) 35% OF THE BASE CONTRACT. SHOULD THIS BE THE CASE. THE TASK V PERSONNEL REQUIREMENTS ARE ESTIMATED TO BE APPROXIMATELY 0.5 PERSON YEARS PER CONTRACT YEAR AT THE PH.D. PROFESSIONAL LEVEL. 0.5 PERSON YEARS PER CONTRACT YEAR AT THE MA/SENIOR TECHNICAL LEVEL. 0.16 PERSON YEARS PER CONTRACT YEAR AT THE PROFESSIONAL SUPPORT LEVEL. 0.08 PERSON YEARS PER CONTRACT YEAR AT THE ADMINISTRATIVE SUPPORT LEVEL. AND 0.5 PERSON YEARS PER CONTRACT YEAR AT THE TECHNICAL SUPPORT LEVEL.

TASK VI PERSONNEL REQUIREMENTS ARE ESTIMATED TO BE APPROXIMATELY 0.25 PERSON YEARS PER CONTRACT YEAR AT THE PH.D. PROFESSIONAL LEVEL, 0.2 PERSON YEARS PER CONTRACT YEAR AT THE MA/SENIOR TECHNICAL LEVEL, 0.1 PERSON YEARS PER CONTRACT YEAR AT THE PROFESSIONAL SUPPORT LEVEL, AND 0.15 PERSON YEARS PER CONTRACT YEAR AT THE TECHNICAL SUPPORT LEVEL.

IT IS DESIRABLE THAT THE PRINCIPAL INVESTIGATOR HAVE SUFFICIENT SUPERVISORY EXPERIENCE TO DIRECT THIS PROJECT. THE PRINCIPAL INVESTIGATOR AND CO-PRINCIPAL INVESTIGATOR MAY CONTRIBUTE APPROXIMATELY 0.75 PERSON YEARS EACH. ADDITIONAL PROFESSIONAL STAFF MUST HAVE DEMONSTRATED ABILITIES AND EXPERIENCE IN PHARMACOLOGICAL, TOXICOLOGICAL OR IMMUNOLOGICAL STUDIES, STATISTICAL ANALYSIS AND EVALUATION AND/OR QUALITY ASSURANCE. THE SENIOR TECHNICAL PERSONNEL SHOULD HAVE SUFFICIENT TRAINING, PLANNING AND SUPERVISORY EXPERIENCE IN CONDUCTING IMMUNOTOXICOLOGICAL STUDIES TO PERFORM THIS PROJECT. IN ADDITION, JUNIOR TECHNICAL PERSONNEL SHOULD HAVE (1) DEMONSTRATED ABILITIES AND EXPERIENCE IN CONDUCTING STUDIES OF IMMUNE SYSTEM EVALUATION FOLLOWING CHEMICAL INSULT, (2) EXPERIENCE IN TOXICOLOGY AND IMMUNOLOGY TECHNIQUES, AND (3) EXPERIENCE IN HANDLING TOXIC AND RADIOLABELED CHEMICAL AND INFECTIOUS AGENTS.

A LIST OF NAMES AND EXPERIENCE RECORDS OF KEY PERSONNEL, INCLUDING TECHNICIANS, PROPOSED FOR ASSIGNMENT TO THE PROJECT MUST BE PROVIDED. THE VITAE SHOULD CLEARLY STATE EDUCATION, EXPERIENCE,

PUBLICATIONS, DUTIES AND RESPONSIBILITIES BY YEAR. EXPERIENCE SPECIFICALLY RELATED TO ELEMENTS OF THE PROJECT SHOULD BE CLEARLY IDENTIFIED.

TRAVEL REQUIREMENTS:

THE PRINCIPAL INVESTIGATOR, SHALL BE EXPECTED TO TRAVEL TO NIEHS AT LEAST ONCE A YEAR FOR A PERIOD OF ONE DAY FOR A CONFERENCE WITH THE PROJECT OFFICER. ADDITIONALLY, THE PRINCIPAL INVESTIGATOR AND ONE PROFESSIONAL OR TECHNICAL STAFF MEMBER MAY ATTEND ONE PROFESSIONAL MEETING EACH YEAR IN ORDER TO PRESENT DATA DERIVED FROM THIS CONTRACT. For costing purposes the offerors should proposed on an annual basis one trip of three days to each of the following three cities: San Francisco, CA; San Antonio, TX; and Washington DC.

GOVERNMENT FURNISHED MATERIALS

THE GOVERNMENT SHALL PROVIDE THE CHEMICALS OR THERAPEUTICS TO BE TESTED AS DESCRIBED IN TASKS I-IV ON AN "AS NEEDED BASIS" TO BE DETERMINED BY THE PROJECT OFFICER. ALL OTHER CHEMICALS, MATERIALS, AND EQUIPMENT SHALL BE PROVIDED BY THE CONTRACTOR.

Reporting Requirements

a. Technical Progress Reports

In addition to the required reports set forth elsewhere, the preparation and submission of regularly recurring Technical Progress Reports will be required in any contract resulting from this solicitation. These reports will require descriptive information about the activities undertaken during the reporting period and will require information about planned activities for future reporting periods.

For proposal preparation purposes only, it is estimated that the number of copies of these reports will be required as follows:

- (1) Status Reports: Monthly, the Project Officer shall receive one brief (1-3 page) electronic summary of the work currently in progress and the status of all agents on the test, reports and manuscripts. The format of the reports will be as follows: Text - MS Word, Spreadsheet - MS Excel, and Database - MS Access. The Contract Specialist shall receive an electronic copy of each report. The report will be due 10 working days after the end of each month.
- (2) Test Article Study Report: A full test article study report should include complete data and summary of individual assays conducted in the testing of agents performed as part of Tasks I-V and conclusions drawn from experimental findings, including potential human significance. It shall also include difficulties encountered and remedial action taken. The quantity shall be one unbound original, one bound original and 3 bound copies. In addition, a full copy of the report including covers and cover pages should be submitted in an electronic format using software as specified at <http://www.niehs.nih.gov/ctb.sorfarch.htm>

with graphics attached in .gif or .jpg formats on floppy disk or CD-ROM. The due date shall be 60 days after completion of each study. Individual animal data for each test conducted in the study should be submitted along with the study report for entry into the NTP database as specified above. The Contract Specialist shall receive an electronic copy of each report. The format of the reports will be as follows: Text - MS Word, Spreadsheet - MS Excel, and Database - MS Access.

- (3) Annual Report: A brief report of the progress made during the previous 12-month period as it pertains only to task VI. The quantity shall be one original and three copies. The due date shall be 30 days after the anniversary date of the contract, beginning in year 2. An annual report will not be required at the end of the final year when a final report is due. The Contract Specialist shall receive an electronic copy of each report. The format of the reports will be as follows: Text - MS Word, Spreadsheet - MS Excel, and Database - MS Access.
- (4) Final Report: This report shall be a comprehensive final report that includes a summary of all experimental findings and conclusions. A draft Final Report shall be submitted to the Project Officer 60 days before the expiration date of the contract for review and comments. The draft report shall be returned in 30 days to the contractor in preparation for the final report due no later than the expiration date of the contract. The quantity shall be one original final report and three copies. The annual report for the final year will not be required. The Contract Specialist shall receive an electronic copy of this report. The format of the reports will be as follows: Text - MS Word, Spreadsheet - MS Excel, and Database - MS Access.

b. Summary of Salient Results

The Contractor will be required to prepare and submit, with the final report, a summary (not to exceed 200 words) of salient results achieved during the performance of the contract. This report will be required on or before the expiration date of the contract.