PERFORMANCE WORK STATEMENT
TECHNICAL SUPPORT FOR HUMAN HEALTH RISK ASSESSMENT

I. INTRODUCTION[i]

The Office of Research and Development's (ORD) National Center for Environmental Assessment (NCEA) serves as the resource center for the overall process of human health and ecological risk assessment: the integration of hazard, dose-response, and exposure data and models to produce risk characterizations. The organizational structure of NCEA consists of an immediate office located in Washington, DC and three divisions (Cincinnati, OH, RTP, NC and Washington, DC). The Center occupies a critical position in ORD between (a) the researchers in other ORD components who are generating new findings and data, and (b) the regulators in the EPA program offices and regions that must make regulatory, enforcement, and remedial action decisions.

II. PURPOSE AND SCOPE

This contract shall provide NCEA with support for (1) conducting risk assessments on environmental stressors (i.e., physical, chemical, microbial, or other agent forms), and (2) developing state-of-the-art methods, models, and guidance documents for human health risk assessment. The Contractor shall provide support for assessments and for research to improve the science and practice of risk assessment in two key areas: single stressor risk assessment, and stressor combinations or mixture risk assessment. All work performed under this contract will be ordered through work assignments issued by the Contracting Officer (CO).

The Contractor shall furnish all supplies, personnel, facilities, and equipment necessary to complete the specific areas of each work assignment. All delivered documents and reports shall be submitted in draft form for Agency's review. Required revisions may be provided by the Agency to the Contractor for incorporation into final documents.

III. SPECIFIC AREAS OF WORK

The Contractor shall provide all technical support within the scope of this Performance Work Statement. The Contractor shall perform tasks, as specified by individual work assignments issued by the Contracting Officer, in the following program areas: Methods Development, Assessment Development, and Risk Assessment Guidance and Support. The Contractor shall be capable of performing a range of risk assessment tasks in each of the four elements of the National Academy of Science's risk assessment paradigm: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

The tasks commonly require expertise in multiple disciplines such as epidemiology, toxicology (see specialized disciplines identified in A.1 (a) below), pharmacology, physiology, pathology, microbiology infectious disease epidemiology, public health, decision analysis, quantitative dose-response assessment,

quantitative uncertainty analysis, human health economics, exposure modeling, statistics, biostatistics, chemistry, and mathematical modeling including Benchmark Dose (BMD) modeling, physiologically-based pharmacokinetic (PBPK) modeling, exposure modeling, and computational toxicology modeling.

In many tasks, scientific needs are highly specialized requiring expert personnel having the knowledge and ability to fully and critically evaluate study methodologies and results in the technical disciplines identified above. Analyses must be scientifically sound and sufficiently documented to withstand intensive critical examination and review by other experts in the relevant disciplines.

A. Assessment Issues and Documents

The Contractor shall develop, revise, review and update, and/or evaluate various scientific documents and reports used by NCEA to assess the nature and degree of risk posed by contaminants (chemical, physical, mixtures and biological/microbial) in a variety of media. National and international scientific literature, unpublished studies and investigations still in progress may be sources of information. The Contractor shall conduct literature searches and use EPA's Health and Environmental Research Online (HERO) to retrieve hardcopies or electronic copies of key studies. Specific tasks may include any of the following:

1. Human Health Assessment Documents

a) Prepare, revise or review component or comprehensive chemical hazard or qualitative risk assessment documents that serve as baseline assessment documentation for the development of consensus positions in EPA's Integrated Risk Information System (IRIS). IRIS contains agent-specific summaries of qualitative and quantitative health information in support of the first two steps of the risk assessment process, i.e., hazard identification and dose-response evaluation. IRIS information includes the reference dose (RfD) for noncancer health effects resulting from oral exposure, the reference concentration (RfC) for noncancer health effects resulting from inhalation exposure, and the carcinogen assessment for both oral and inhalation. Combined with specific situational exposure assessment information, the health hazard information in IRIS may be used as a source in evaluating risks from environmental contaminants. All IRIS assessments are developed using basic procedures in current IRIS Standard Operating Procedures (SOPs).

The following activities may be required in development of an IRIS chemical assessment:

- Literature search for health hazard information using the sources specified in the IRIS SOPs, supplemented by other sources specified by EPA or in search strategies proposed by the contractor.
- Development of abstracts for relevant articles found in the literature search.
- Use of HERO tools for literature identification, classification and other bibliographic functions.
- Development of IRIS Toxicological Reviews and other documents, which summarize relevant literature, identify human health hazards, evaluate studies, select studies and endpoints on which to base toxicity, evaluate plausible modes of action and commonalities for cancer and noncancer endpoints, and perform quantitative dose-response assessments

using state-of-the-science methodologies (including BMD modeling, and PBPK analysis where appropriate). Development of these documents will require theoretical and/or empirical approaches and expert scientific judgment. Depending on the chemical, experts are often needed in the areas of epidemiology, toxicology (with specialized expertise commonly needed in fields including, but not limited to, carcinogenesis bioassays and mechanisms, reproductive/developmental toxicology, neurotoxicology, and immunotoxicology, genotoxicity, and pathology, statistics (including dose-response modeling, and biostatistical analysis of epidemiology data), dosimetry and physiologically-based pharmacokinetic modeling and biologically-based dose-response modeling, and biochemistry. In many tasks, scientific needs are highly specialized requiring expert personnel having the knowledge and ability to fully and critically evaluate study methodologies and results in the technical disciplines identified above. Assessment documents must be state of the art scientific work products based on critical evaluation and analyses of the biological effects and health risks of the chemical or other stressor. These assessments must be recognized, nationally and internationally, as scientifically sound and authoritative.

- Summarize comments on IRIS assessments at all stages of the review process including NCEA review, Agency review, Interagency review, and External Peer review. Prepare responses to comments and revise the Toxicological Review as needed to respond to the comments.
- Provide technical editing of IRIS documents. Technical editing may include editing of the document to ensure correct grammar, spelling, punctuation, usage, and appearance of tables and figures; checking references, generating reference lists and related tasks using HERO; page numbers, tables of contents, and like tasks to ensure consistency, checking for correct formatting in conformance with the IRIS SOPs and templates; and other details of style. It may also include substantive editing including rewriting or rearranging sentences, paragraphs, or sections; arranging or rearranging tabular material; redrawing and retouching illustrations; standardizing symbols; checking and standardizing equations, and checking numbers in the text against figures and tables to insure consistency.
- Provide support on addressing cross-cutting issues common to multiple IRIS assessments. Examples of such issues include what criteria to use in selecting critical endpoints for deriving RfDs and RfCs, how to select values for uncertainty factors, how to perform a dose-response assessment for a chemical that produces more than one tumor type, and how to evaluate a database to select a cancer weight of evidence descriptor. Activities may include but are not limited to analyzing entries on the IRIS database to determine past and current practices, developing issue papers, performing statistical analysis, developing mathematical models or adapting models from the literature, and identifying and engaging experts to provide methods and analysis to address the issues.

b) Prepare other human health assessments. The assessment documents shall generally focus on the development of cancer dose-response functions and derivation of oral Reference Dose (RfD) and inhalation Reference Concentration (RfC) values, and may include mode of action descriptions as well as dose-response modeling. Assessments may be limited to one toxic endpoint, such as carcinogenicity or developmental toxicity, or cover multiple endpoints, such as all noncancer health

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endpoints, in a style, scope, and format provided in the work assignment. While most assessments will focus on chronic exposures and related adverse health effects, assessments dealing with acute exposures and their effects may also be required.

c) Develop or revise provisional peer reviewed toxicity value (PPRTV) assessments. PPRTVs are developed in accordance with EPA chemical toxicity assessment practices, generally for less common chemicals with smaller databases. PPRTVs generally identify one critical study and do not incorporate the extensive modeling typical for an IRIS assessment.

d) Prepare, review or revise portions (e.g., chapters or volumes) of large integrated (health plus ecological effects plus exposure assessment) risk assessment documents. These assessments are to be consistent with domestic and international guidelines.

e) Prepare, revise or review documents that conduct quantitative risk assessments for stressor mixtures. These assessments may require both exposure and toxicity evaluations and must be consistent with U.S. EPA Agency guidance documents (U.S. EPA, 1986, 2000). Epidemiological assessments of chemical mixtures may also be included when such data are available.

2. Exposure Assessment Documents for Contaminants, Mixtures, Media- or Site-Specific Cases

a) Determine exposure or potential exposure from pollution/contaminant sources (including background levels) by evaluating measured or modeled biological, chemical, or physical concentrations or gradients at the interface between an organism and an environmental medium of concern as specified in individual work assignments. Estimate internal doses and target organ doses of chemicals; this may include the development of dynamic PBPK models.

b) Estimate or evaluate human populations potentially exposed to pollutants from the sources described in Section III.A.2(a) above, and identify any sensitive subpopulations listed in "Guidelines for Exposure Assessment," EPA 600/Z/92/001, or as otherwise specified in individual work assignments.

c) Estimate or evaluate bioaccumulation and/or bioavailability of pollutants in different media (i.e., air, soil, sediment, ground water, surface water, biosolids, food chain, distribution systems, etc.) to various human populations per "Guidelines for Exposure Assessment," EPA 600/Z/92/001, or as otherwise specified in individual work assignments.

d) Perform various statistical or computational analyses to support the development of specific dose exposure assessments such as: distributions of exposure; human activity patterns; indoor vs outdoor exposures; human migration patterns; gender-specific, age-specific, ethnic specific factors; chemical contact rates and pathways in food/water consumption patterns and habits; and regional or neighborhood exposure patterns.

3. Site or Community Based Risk Assessments

The Contractor shall develop risk values and information that is suitable for various end-uses, including conducting cost-benefit analyses (c.f. Dockins et al. 2004; Rice et al. 2006). The Contractor shall perform these exposure and risk analyses in accordance with guidance specified in individual work assignments. Risk analysis may be conducted in conjunction with different risk management alternatives.

4. Public Health Outcomes

The Contractor shall provide technical expertise in 1) identifying specific and readily identifiable indicators of the health status of humans exposed to environmental contaminants, 2) identifying human health conditions from experimental studies with research animals, humans, and from human population and/or field studies, 3) the ability to link sources of environmental contaminants to human exposures, to quantify human exposures, and to predict the likelihood of individual indicators of health status (human health conditions) resulting from such exposure. The Contractor shall review, interpret, and synthesize economic studies (e.g., valuation studies that estimate benefits of reducing health risks) and shall have an ability to assign health outcomes (i.e., symptoms like fatigue, injury, morbidity effects, death) related to the economically meaningful health effects economic values (weights) in units commonly employed in the estimation of benefits.

5. Integrated Science Assessments

The contractor shall prepare, revise, or review component or comprehensive documents that serve as baseline documentation for development of EPA's Integrated Science Assessments (ISAs). The ISAs and their supporting annexes provide a critical review and integration of multi-disciplinary scientific evidence from a large body of studies on the six criteria air pollutants (ozone, particulate matter, carbon monoxide, nitrogen dioxide, sulfur dioxide and lead). The ISAs provide critical inputs to decision making on the National Ambient Air Quality Standards (NAAQS) that are reviewed every 5 years.

The following activities may be required in development of ISAs:

- Development of literature searches for health and environmental information on the criteria air pollutants.
- Development of abstracts for relevant articles found in the literature searches.
    - Use of HERO tools for literature identification, classification and other bibliographic functions.
- Entry into HERO describing newly published studies to be incorporated into the ISA annex. Should other criteria pollutants be included in the studies, table entries shall be created for those as well.
- Preparation of sections of the ISA. The contractors shall identify scientific and technical authors who are recognized nationally or internationally in their field and have both a general knowledge, as well as the specific knowledge, expertise or experience as specified in the work assignment. The selected author/consultant must have experience that includes authoring several journal articles or other technical documents that specifically relate to research on the criteria pollutant. During the development of the sections, the contractor may be required to meet with EPA and/or the document authors to discuss the document.

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B. Risk Assessment Methods Research and Development

The Contractor shall provide scientific and technical support for the development of innovative human health risk assessment methodologies/procedures or the refinement and improvement of existing ones. Methodologies may be those that are commonly applied in the context of regulatory risk assessment or they may be generated from the broader scientific area of risk analysis. Scientific products must be recognized, nationally and internationally, as scientifically sound and authoritative.

Specific tasks may include any of the following:

1. Research, development and support of methods to improve risk assessment and reduce the uncertainty in the risk assessment approaches for cancer and noncancer toxic endpoints, and for chemical, physical and microbiological stressors. Examples include, but are not limited to, the following:

    a) Develop improved understanding of physiological and biochemical processes and relate this knowledge to conventional EPA or other default approaches.
    b) Improve risk assessment default approaches using physiological, mechanistic information, human and animal molecular biomarker data and conventional toxicological data.
    c) Develop methods and perform route-to-route extrapolations for adverse effect indices such as RfD and RfC and cancer unit risk.
    d) Evaluate plausible modes of action and commonalities for cancer and noncancer endpoints.
    e) Evaluate new methods for acute or subchronic effects assessment as well as their relationship, if any, to chronic effects assessment methods.
    f) Explore ways in which risk values may be made more usable to a wider variety of applications, recognizing the limitation of traditionally calculated values such as RfD.
    g) Development and evaluation of mathematical and statistical methods to address human health or environmental risks. Expert, non-routine statistical analysis of relevant data. Expert development and evaluation of mathematical models to represent biological or environmental systems and processes.

2. Support research, development, and application of new risk assessment methods suitable for either conducting or evaluating cumulative risk, microbial risk, mixtures risk, dose-response assessment (including extrapolation to low dose), exposure assessment, and relevant uncertainty analysis. Examples of such research include, but are not limited to the following:

    a) Characterize, assess, and compare the infectious and acute and chronic disease risks associated with individual or concurrent exposure to pathogens and chemical contaminants.
    b) Evaluate exposure and health hazards from multiple exposure pathways such as those associated with inhalation of vapors and particles, dermal contact, contamination of food chains, person-to-person transmission, and water and food contamination.
    c) Investigate and document the impact of model and parameter uncertainty on cancer and noncancer risk calculations as well as risk characterizations.
    d) Research, develop and investigate approaches for quantitative and qualitative uncertainty analysis.

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e) Validate or develop improvements to existing alternative methods, models, or approaches for risk assessment of single contaminant or mixture (multiple contaminants), or site specific situations.
f) Develop guidance and methodologies for risk assessment, including delineating the range of assumptions, developing or improving upon existing statistical and or biologically-based models, analyzing data that provide the scientific basis for evaluating exposure or risk, and assuring scientific credibility in such endeavors
g) Develop statistical or mathematical models or methods applicable for testing uncertainty or variability in exposure and risk assessment.
h) Conduct statistical analysis of routinely collected environmental health data and data from epidemiologic studies.
i) Development and/or refinement of mathematical/microbiological/biological/ chemical/physical methods/models [e.g., dose-response modeling techniques such as benchmark dose, categorical regression, pharmacokinetics and pharmacodynamic models, or biologically based dose response (BBDR) models, bioavailability, environmental fate of microorganisms].

3. Perform research in exposure assessment:

a) Develop or improve transport and fate models or modeling systems for environmental deposit of pollutants.
b) Define human uptake or that of other species including bioavailability and bioaccumulation.
c) Research to improve identification and delineation of exposure patterns for human receptor populations and variances within subgroups.
d) Develop or adapt extant pharmacokinetic models to address key exposure issues.
e) Identification of cumulative exposure situations and quantification of the duration, intensity and frequency for situations in which people are exposed to multiple chemicals.

4. Perform research in public health outcomes:

a) Identify critical links between source, exposure, and effect.
b) Link human health risk assessment to public health outcomes.
c) Identify human health protection endpoints.
d) Link exposure to health outcomes.
e) Identify the most important environmental causes of disease.
f) Indicators of health status.
g) Risk management decisions.

5. Conduct statistical analyses and modeling, including experimental design, hypothesis testing, power calculations, linear and nonlinear regression modeling, risk characterization modeling, Monte Carlo simulations, outlier analyses, etc. Specific tasks may include, but are not limited to the following:

a) Conducting power calculations for toxicological tests on environmental contaminants.
b) Conducting hypothesis tests on toxicological data.

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c) Using toxicological data, estimating departures from additivity or identifying contributions to toxicity by the unidentified fraction of a complex mixture.
d) Analyzing epidemiological data for statistically significant effects or exposure misclassification.
e) Conducting uncertainty analysis or a sensitivity analysis on environmental models
f) Analyzing chemical mixture data for chemical stability and similarity among mixtures.
g) Analyzing dose-response and/or exposure data for chemicals or microbial agents.

C. Risk Assessment Data Bases and Computer Tools

1. The contractor shall provide technical support for EPA database development and for maintenance of risk information systems, including, but not limited to, Health and Environmental Research Online (HERO), Health Effects Assessment Summary Tables (HEAST), the Mixtures Toxicologic Interactions Data Base (MIXTOX), and IRIS. Technical support may include collecting and entering data, organizing information, evaluating the literature and approaches used, re-evaluating and updating existing information, document meetings and conference calls that pertain to the development of information for databases, preparing tutorials or background materials for database users, supporting the planning and management of database collection and preparing supplementary information, extracting and evaluating information from the literature or documents, reviewing and responding to information from the literature or documents, and reviewing information submitted by outside organizations. Also inquiries and analyses of existing databases to address issues or glean data could be required.

2. The contractor shall develop/refine fate and transport exposure models or exposure modeling systems, integrate into overall methods and guidance, apply models to real and/or hypothetical situations, and/or provide written guidance on use of existing models to characterize direct and indirect exposures.

3. The contractor shall develop or improve upon existing "smart" or user friendly exposure assessment tools and risk characterizing systems, e.g., RISK ASSISTANT, CALTOX.

4. The contractor shall develop or maintain exposure assessment databases using expert data management systems, e.g., Geographic Information System (GIS).

5. The contractor shall conduct, investigate, or validate field studies for purposes of measuring or monitoring.

6. The contractor shall conduct research on hydrogeologic features of contaminant transport, including karst terrains.

D. Analysis, Document and Issue Paper Preparation

The contractor shall develop analyses, white papers or toxicological reviews of specific health/exposure assessment topics. The proposed scientific and technical authors shall be recognized nationally or internationally in their fields and have both the general knowledge, as well as the specific knowledge, expertise or experience specified in the work assignment. The selected author/consultant must have experience that includes authoring several journal articles or other technical documents that specifically relate to the topic. During the development of the documents or issue papers, the contractor may be required to meet with EPA

and/or the authors to discuss the documents or issue papers. Subjects of documents or issue papers vary widely and will be defined specifically by the COR.

E. Risk Assessment Support

1. Science Writing, Risk Communication and Training

The Contractor shall provide scientific and technical support to enable EPA to successfully communicate risk assessment research and assessment information to individuals and organizations both within and outside the risk assessment field. The Contractor shall prepare the information in a variety of formats to meet the specific needs of a range of audiences including scientists, decision-makers, those unfamiliar with risk assessment, and those who are experts in the field. Examples of requested work products may include: announcements, posters, displays, fact sheets, leaflets, and brochures addressing a variety of risk assessment related topics. Information presented in paper form, electronic format (media or online), or video format may also be needed.

The Contractor shall be responsible for presenting information performed under this Performance Work Statement (PWS) in the form of symposia and workshops to the at-large science community.

2. Administration and Technical Support for NCEA Human Health Related Meetings

Contractor support shall include administrative and technical support for NCEA human-health related meetings, such as workshops convened to address specific issues in risk assessment. Support includes securing experts to support the tasks in the PWS, paying for the cost of expert services, including travel and applicable fees, securing facilities and equipment for meetings, serving as coordinator and facilitator of meetings, providing, developing written material for meetings, and preparing summary reports or formal proceedings as necessary.

3. Superfund Health Risk Technical Support Center

The Contractor shall provide Superfund health risk technical support as specified in specific work assignments. The responses prepared by the Contractor shall primarily focus on human health risk characterization, hazard identification and exposure characterization pertinent to single and multiple contaminants at Superfund sites. The types of risk assessment information required typically include chronic and less-than-chronic noncancer risk assessments, cancer risk assessments, and toxicologic risk assessments, and review of site-specific risk assessments. Responses shall also include a review and analysis of the scientific background information and provisional recommendations. Contractor response may be required on a rapid response basis. In terms of turnaround time, a "rapid response" will typically require a response within five (5) working days, but that will depend upon the specific technical issue. When needed, the Contractor shall provide scientific expertise related to site-specific Agency decisions, reviews or on-site reviews.

F. Information Management

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The Contractor shall provide support for data collection and compilation activities pertaining to all sections of the PWS. The Contractor shall be required to enter data into the HERO database and perform quality checks on this data. This will generally involve data extraction from primary and secondary sources and transcription to a conveniently-accessible format. Such formats will include off-the-shelf relational databases, spreadsheets, or word-processing software. This task may involve data evaluation, analysis, and transformation, as necessary for the particular application. The Contractor may also be required to reevaluate, update, document, and otherwise maintain existing or new information systems.

G. Literature Search

1. Specific Reporting Requirements

During the preparation of documents, reports, and other projects, the Contractor shall conduct toxicological, health, economic or exposure-specific literature searches. When such a search is required by a work assignment, the Contractor shall conduct literature searches to avoid missing key studies, retrieve pertinent articles, and provide abstracts and summaries as indicated below unless otherwise directed.

To determine the extent and availability of information germane to specific tasks, the Contractor shall conduct extensive and exhaustive searches of all relevant databases consistent with the project level of effort. A specific plan for the search and retrieval of the relevant information shall be developed for each work assignment. .

a) Search the periodical literature for the period prescribed by the work assignment, using databases specified in the work assignment as well as other available databases.

b) Search for, within the specified period, domestic and international nonperiodical literature, such as books, technical reports, monographs, and conference and symposium proceedings prepared by select committees or bodies (e.g., such as those convened by the National Academy of Sciences, the World Health Organization, the National Science Foundation, the American Association for the Advancement of Science, the EPA Science Advisory Board, and other relevant professional and academic sources). Search for, within the specified period, all secondary sources designated in the work assignment.

c) Search sources such as the Registry of Toxic Effects of Chemical Substances (RETCS), National Cancer Institute, National Institute of Environmental Health Sciences, National Center for Toxicological Research, etc. for unpublished or interim research reports relevant to the subject of the search.

d) Search the proceedings from toxicological, public health, microbiological, ecological and economic conferences, meetings and seminars on risk assessment; pertinent federal and state reports dealing with risk assessment studies including relevant documents available from the Library of Congress, Congressional Reporting Service, the Government Printing Office, academic sources (e.g., published and unpublished dissertations and theses), and all other published and unpublished or interim research reports relevant to the risk assessment subject matter detailed in the work assignment.

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e) As required in individual work assignments, the Contractor shall prepare an abstract of 150-300 words for each relevant article found. The abstract shall include the purpose, summarize major findings, and provide principal conclusions and recommendations.

f) Use HERO to acquire and maintain literature used during the project. All literature shall be the property of the U.S. EPA and be governed by the copyright laws of the United States. Contractor shall have temporary use of the literature under the Fair Use Clause.

g) When specified, the Contractor shall explore the application of newer web-based software developed for the linking of ideas and concepts within a selected body of literature.

h) Where appropriate, the Contractor shall explore and apply methodologies for quantitatively summarizing related literatures on specific subject areas.

i) Results of literature searches shall identify relevant scientific information and likewise exclude information that is not relevant to the science task. Contractor shall implement procedures to efficiently screen out studies that may, for example, have key words in common with search criteria, but which do not provide information on search subject goals. The literature screened out shall be tagged and maintained by the Contractor in HERO.

j) All search and screening strategies and results shall be saved and entered into HERO to enhance transparency.

2. Quality Assurance Requirements for Literature Review

During examination of the identified literature, the Contractor shall place primary emphasis upon the adequacy of study design, quality control, and interpretation of results of each study, and determine the article's relevance to the assessment of actual or projected exposure to the pollutants or subject under study. Primary literature sources shall be used exclusively except in rare, extenuating circumstances. The work assignment shall include the details of the search strategy. The literature search and results – whether screened out or included – shall be maintained in HERO, along with the reasons why.

H. Physiologically-Based Pharmacokinetic (PBPK) Model Technical Support

Each work assignment from EPA for pharmacokinetic (PK), PBPK, or biologically-based dose response (BBDR) model technical support will identify the purpose/objective of the work requested. For each specific area of interest, the Agency may request any or all of the following types of support in individual work assignments:

1. Initial PBPK Model Scoping and Evaluation

The Contractor shall provide an initial determination (or scoping) to identify available open source PK, PBPK, or BBDR models for a chemical of interest, the adequacy and appropriateness of the model(s) for

potential use in the human health assessment, and what, if any, additional work might be needed to modify a model for a specific use.

Examples of topics and issues that shall be addressed in the initial scoping include the following:

- What is known about the toxicokinetics of the chemical of interest?
- What open source PK or PBPK model(s) are available for the chemical of interest, and what level of QA/QC have they undergone (e.g., peer review publication, regulatory agency review, etc.)?
- What are likely sensitive endpoints for the chemical under review, and what are the test species, exposure regimens, and routes of exposure from the initial identification of critical studies?
- Are identified models parameterized for the relevant test species (and/or humans), and for the potential route(s) of exposure that are relevant to humans?
- Are any of the identified models proprietary source models (i.e., where the code, data, or supporting documentation is not available to the public; this relates to requirements for transparency)?
- How extensively has the model been used and/or evaluated, what were the outcomes, and what documentation is available to review?
- Is further model development needed for each potential use in the assessment?
- What are the estimated time and people resources needed for full retrieval of model documentation, for evaluation, and for suggested modifications of the model for use in the assessment?

The Contractor shall conduct an initial survey of the literature to identify the extent and nature of the toxicokinetic data and hazardous effects data for specified chemicals, as well as available PK/PBPK models that have potential applications in the assessment. This work is not intended to be a full search and retrieval of all relevant studies, rather a broad overview of the literature sufficient to make an initial determination of the key features of the kinetics relative to the most sensitive endpoint(s) for hazardous effects, and an initial identification of potential candidates for the critical studies (and in particular, the species and strain of test animals) that could be used for derivation of a reference value. This information shall then support prioritization and selection of any available PBPK models for a more detailed model evaluation.

2. Detailed Model Evaluation

Selected models shall be further evaluated for quality and appropriateness for specific uses. Broad criteria presented in Clark et al. (2004), Chiu et al. (2007), and McLanahan et al., (2012) shall be used to evaluate the overall quality of the model, and specific chemical toxicokinetic hazardous effects data shall be used to evaluate the appropriateness of the model for potential use in the assessment. This evaluation shall include model runs in the appropriate software (as specified by EPA; e.g., acslX, MatLab) to reproduce published results, and to assure that the model code and computer implementation support model analysis and use. The evaluation may also include sensitivity analysis, and more specialized analyses (e.g., Monte Carlo, Bayesian) to duplicate previous results or to evaluate the model structure or parameter values. This work shall also include organizing and formatting the model code, supporting documentation, and data for entry into a model archive maintained at EPA (details on the format requirements will be provided).

Based on the model evaluation results, the Contractor shall recommend which PBPK models are currently sufficient for specific uses in each assessment, and if not sufficient, what further development or

needed modifications would be needed for specific uses in the assessment, along with an estimated level of effort to conduct that work.

3. Model Modification and Development

Based on review of the evaluation reports, EPA will identify specific models for application or for further development. The Contractor shall support EPA in this work that could include additional literature and data compilation, modifications to the model structure, recalibrating and testing of the model against new data (or combinations of new and previous data), and application of the model for specific use in an assessment. As required, the Contractor shall also evaluate and support the use of quantitative structure-activity relationship (QSAR) models in the estimation of PBPK model parameters where chemical specific parameter values are not available, and a QSAR approach would further support the use of a PBPK model in the derivation of a reference value.

4. Information Resources and Methods Development or Support

The use of PK, PBPK, and BBDR models in risk assessment remains a relatively new approach, and there is need for readily accessible and high quality resources to support model evaluations and development. Critical information resources that are being or have been developed at EPA include: 1) a compilation of frequently used physiological parameter values (e.g., tissue volumes, blood flows, respiratory rates) and chemical specific toxicokinetic parameter values (e.g., enzyme activity, absorption, partitioning) in human and nonhuman test species/strains for both the general population and for sensitive lifestages and subpopulations (e.g., early life, aged, pregnant); 2) an archive of PK/PBPK/BBDR models that have been or are being used in the development of health hazard assessments, including the supporting documentation and data used to develop and test the model; and 3) a glossary of PBPK model terms.

The Contractor shall support the maintenance and further elaboration of these resources and develop any additional resources or methods that EPA determines will facilitate the development, evaluation, or use of PK, PBPK, and BBDR models in human health assessment. *Examples* of possible methods development are: approaches to improve the statistical rigor and ability to test hypotheses for model parameter identification and model structure identification; development of computational tools to facilitate the analysis of variability and uncertainty among human populations (i.e., for sensitive subpopulations vs. average, healthy adults); and approaches for facilitating the application of models in health assessments (i.e., to more quickly incorporate and propagate the impact of model changes through the model steps of a health assessment, of which the PBPK model is just one).

Concurrent with the search and retrieval of parameter databases and models, the Contractor shall compile and annotate new model references from the peer reviewed literature or other reputable sources to add to EPA's HERO database of PBPK model references and to further augment the glossary of terms.

IV. PRODUCT QUALITY

A. General Risk Assessment Provisions

In the preparation of any of the scientific documents required by a work assignment, the Contractor may be required to provide the services of experts in the areas of epidemiology, toxicology, pharmacology, physiology, pathology, environmental microbiology, infectious disease epidemiology, public health, decision analysis, quantitative uncertainty analysis, economics, statistics, biostatistics, chemistry, and mathematical modeling including Benchmark Dose (BMD) modeling, physiologically-based pharmacokinetic (PBPK) modeling, and computational toxicology modeling. In many tasks, scientific needs are highly specialized requiring expert personnel having the knowledge and ability to fully and critically evaluate study methodologies and results in the technical disciplines identified above. Unless otherwise specified in a work assignment, products prepared must be state of the art analyses based on expert critical evaluation and analyses of the biological effects and health risks of the chemical or other stressor. As appropriate, the Contractor shall present qualitative and quantitative biological, toxicological or biochemical evidence, as well as statistical analysis and a discussion of the strengths and weaknesses of pertinent studies taking into account current EPA guidance on such matters.

Contaminant or site-specific documents and reports shall provide a scientifically defensible evaluation of the toxic potential of chemical/physical/microbiological pollutants. The quality of work products is expected to accurately reflect the state-of-the-art scientific knowledge and current risk assessment methods, including the approaches used by the US EPA. The Contractor may be required to apply newly developed methods in preparation of the documents.

Contaminant-specific reports may require detailed or concise summaries of available data in the areas of acute, subchronic, and chronic toxicity. Detailed discussions of the chemical, physical, and pharmacokinetic/pharmacodynamic properties may be required. Exposure discussions may also be required depending on the task. These may include summarizing concentrations in the environment and in food sources, rates of release to the environment, levels in human tissues, and exposure estimates for populations. This may involve analyzing pollutant sources and release rates, pollutant transport and fate, exposed populations and activity patterns, standard factors and scenarios, and use of previously determined health and health risk data to calculate overall risk to human health. When appropriate, comprehensive searches of all pertinent literature and data bases shall be performed. The data shall reflect the latest scientific knowledge obtainable. The literature shall be critically evaluated, and accepted EPA risk assessment guidance shall be applied to the data. In the absence of specific EPA guidance, procedures will be developed and applied upon approval by the P.O.

B. Quality Assurance/ Quality Control Requirements

The Contractor is responsible for quality control and quality assurance of all tasks. The Contractor shall ensure that data generated or used for each work assignment is "of the type and quality needed and expected for their intended use" and that all assessment products adhere to a high standard for quality, including objectivity, utility, and integrity. All documents shall adhere to the OMB data quality guidance for federal information and with EPA's Information Quality Guidelines.

As specified in each work assignment and prior to starting any work, the Contractor shall prepare either a Quality Assurance Project Plan (QAPP) or a narrative statement that describes the procedures to be used and a list of the data sources and methods. The Contractor must address in the work plan or QAPP how it is going to

consider the quality of the secondary data that they use and how it is going to consider data uncertainty and variability. Secondary data is defined as the review or use of someone else's environmental or health data that was developed for a different purpose. This includes (but is not limited to) the data used from citations from the literature searches, from hard copies, and computer databases. After work has begun, the Contractor shall discuss and document in HERO the data quality and limitations of all studies used and how each study was determined adequate to serve as input for an assessment (see previous section III F and the list below).

Risk assessment is a technical analysis of many different kinds of scientific information of varying form and quality, all of which are used to characterize the expected risk to public health and the environment. Such risk assessment analyses may result in scientific assessments that are less certain than ideal and, therefore, must be clearly identified as to the inherent strengths and weaknesses of their data quality and conclusions. All risk assessment products provided by the Contractor shall include information that will fully characterize the projected risks to public health and the environment and shall specifically adhere to the following items:

1. Quantitative assessments shall be accompanied by descriptive information that provides an objective and balanced characterization of the results.

2. Key scientific information and controversies on data and methods (e.g., use of animal or human data, extrapolating from high to low doses, use of pharmacokinetics data and certain quantitative methodologies) shall be highlighted along with discussion of uncertainties, particularly those involving the quality of data, along with comments on their influence on the assessment.

3. When describing exposure scenarios, information shall be presented on the range of exposures and on the use of multiple risk descriptors, e.g., measures of central tendency, high end of individual risk, population risk, and important subgroups.

4. When describing stressor effects scenarios, information shall be presented on the range of impacts and on the evidence, incidence and level of physical, chemical or biological stressors.

C. Written and Electronic Products

The Contractor shall provide written and electronic products of high quality, written in a clear, concise style, with a logical organization and presentation of ideas and rationales. The Contractor shall:

1. Use standard formats as specified in "Handbook for Preparing Office of Research and Development Reports," EPA/600/K-95/002, U.S. EPA (1995), or as specified in the work assignment.

2. Perform scientific and technical editing of all products.

3. Provide written products free of grammatical, spelling, and typographical errors, and accurately summarize the information with correct and compete reference citations.

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4. Present scientific information in a consistent style that makes it easy for the reader to follow and pay specific attention to insure consistent and accurate information content, and appropriate data interpretation throughout the document.

5. Electronic products shall be entered into the HERO database or designated website using EPA standards as specified in the work assignment.

Products not adhering to these standards or guidelines or substantially lacking scientific quality will not be accepted. The Contractor shall use current EPA methods and guidelines for performance of work, unless otherwise specified. The Contractor shall provide printed copies and an electronic copy of all completed work assignment documents prepared in Microsoft Word 2003 or a later version if requested on compact disks.

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[i] HUMAN SUBJECTS:
The Contractor must agree to meet all EPA requirements for studies using human subjects prior to implementing any work with human subjects. These requ8rement are contained in 40 CFR section 26. Studies involving intentional exposure of human subjects who are children or pregnant or nursing women are prohibited by Subpart B of 40 CFR section 26. For observational studies involving children or pregnant women and fetuses, refer to Subpart C & D of 40 CFT sections 26. The US Department of Health and Human Services regulations at 45 CFT section 46.101(e) have long required "…compliance with pertinent Federal laws or regulations which provide additional protections for human subjects" EPA regulations 40 CFR section 26 is such a pertinent Federal regulation. Therefore, the Contractor's Institutional Review Board (IRB) approval must state that the Contractor's study meets the EPA regulations at 40 CFR sections 26. No work involving human subjects, including recruiting, may be initiated before the EPA received a copy of the Contractor's IBR approval of the project and the EPA has also approval. Where human subjects are involved in the research, the recipient must provide evidence of subsequent IBR reviews, including amendments or minor protocol changes as part of annual reports.

Guidance and training for investigators conducting EPA funded research involving human subjects may be obtained here: www.epa.gov/phre.