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1 INTRODUCTION AND PURPOSE

The work plan for Exposure and Dose Assessment Modeling and Evaluation is designed to address data and mechanism interpretation needs related to the RTI/EOHSI NHEXAS Pilot Study. To accomplish this objective, personnel of the Computational Chemodynamics Laboratory of the Exposure Assessment Division of EOHSI will:

- conceptually evaluate and refine/modify existing methodologies for (a) mechanistic human exposure and target tissue dose assessment modeling and for (b) exposure-related data analysis, to optimize these methodologies for the NHEXAS Pilot Study attributes,
- explore various alternatives to existing "standard" methodologies for exposure and dose assessment, and, if necessary, develop prototypes of new techniques for use with the information obtained through the NHEXAS Pilot Study,
- employ data collected through the NHEXAS Pilot Study, and use them in conjuction with both "standard" and "alternative" methodologies, to estimate exposure and dose for individuals and populations, in orderto comparatively test and evaluate these methodologies, and to test various hypotheses concerning attributes of human exposure and dose and of their interrelationships.

By implementing the above tasks it is expected to:

- develop refined estimates of exposure distributions for individuals and populations, associated with multiple pathways and routes of exposure to the chemicals under consideration, that will allow better quantification of statistical exposure measures ranging from expected values and the functional shape of the distributions to order statistics and asymptotic distributions of extremes,
- test the central hypotheses of the Study, that individual or population exposure estimates, determined from case-specific data collected during this Pilot project, will be different from estimates obtained using literature ("default") data, as these data and associated estimates are identified by the Pre-Study Exposure Assessment Project,
- test and evaluate the viability of existing approaches for linking, in a bi-directional mode, (a) exposure estimates and target tissue dose estimates, and (b) related environmental and biomarker information, using data collected by the Study in conjunction with Physiologically Based Pharmacokinetic Modeling. Other, state-of-the-art and exploratory, methods will also be evaluated for their relevance to exposure and dose assessment (statistical inversion and optimal parameter estimation techniques, generalized compartmental and physiological population pharmacokinetics modeling, etc.).

The above analyses are expected to:

- provide information useful for establishing design criteria for the National NHEXAS Study,
- provide modeling and data analysis tools (or at least prototypes of such tools) that will refine various aspects of exposure and dose assessment procedures.

Special emphasis will be placed in developing and evaluating methods - even if only preliminary - for quantifying estimates of uncertainty in exposure and dose assessment, as this is related not only to environmental variation but also to intra- and inter-individual variability of exposure and dose attributes. Another issue of major concern will be the critical evaluation of methodologies for extrapolating short-term exposure and dose estimates to long-term estimates. Methodologies that take into account the effect of variability in exposure as well as the relative magnitudes of sampling and averaging periods are currently under development at the Computational Chemodynamics Laboratory of EOHSI. The methods and techniques to be used for the Exposure and Dose Assessment Modeling and Evaluation tasks will comply with frameworks that have been established and are currently under further development and improvement at EOHSI (Georgopoulos et al., 1993, Georgopoulos and Lioy, 1994; Georgopoulos et al., 1994), as well as various "standard" methods and models for exposure and dose assessment (ATSDR, 1992; Duan, 1982, 1991; Lioy, 1990; Marnicio et al., 1991; McKone and Daniels, 1991; NAS, 1991; Neely and Blau, 1985; NRC, 1987; Pardi, 1992; U.S. EPA, 1991, 1992abc, etc.).

In order to accomplish the above tasks it will be necessary for the collaborators at EOHSI to work closely with members of the RTI staff to ensure the optimal use of resources, the cross-checking and evaluation of data analysis assumptions and data management methods, and the timely prioritization of objectives and needs.

The following sections summarize the specific aims and the approach and methods for the Exposure and Dose Assessment Modeling and Evaluation.

2 SPECIFIC AIMS

The specific aims for the Exposure and Dose Assessment Modeling and Evaluation tasks of the RTI/EOHSI NHEXAS Pilot Study are to:

- develop and evaluate, in collaboration with RTI and EPA personnel, schemes for the analysis, organization, retrieval, visualization and management of the information collected by NHEXAS, that will provided to EOHSI by RTI, based on state-of-the-art computational methods,
- apply, evaluate and refine state-of-the-art methods for assessing human exposure and target tissue dose for individuals and populations using combined environmental, human activity pattern, and biomarker information, and

- evaluate available "standard" exposure and dose assessment methodologies with the databases to be developed through the Pilot Study activities.

3 APPROACH AND METHODS

3.1 Data Management and Analysis

Database management and statistical data analysis and scientific visualization methods, based on both "classical" and on modular and/or object oriented software libraries, as well as Geographical Information systems (GIS) methods, will be evaluated for their applicability to the data of the NHEXAS Pilot Study. Appropriate protocols and formats will be defined in collaboration with RTI and EPA personnel for the uniform and efficient management, transfer and retrieval of data. Universal, non-proprietary, data formats (ASCII, HDF) are expected to be used for backing-up and making generally available the information to be collected and organized. At this point it is also recommended that the following proprietary software systems, which are widely adopted by federal and state agencies, are used for the analysis and visualization of the data:

- SAS, which combines basic database management features with necessary multivariate statistical analysis techniques,
- AVS, which offers useful multi-dimensional data visualization capabilities, and
- ARC/INFO, for basic Geographical Information Systems based types of analysis.

Although the use of a comprehensive GIS may be relatively limited in direct relation to the needs of the Pilot Study, the development of GIS-based techniques, that will eventually allow the integration of various levels of combined environmental and exposure information with powerful modeling and data analysis methods (e.g., Goodchild et al., 1993), can potentially provide a very useful and versatile tool for multi-regional and national NHEXAS-type studies.

The final selection of software platforms will be decided and confirmed in discussions with RTI and EPA personnel.

3.2 Microenvironmental Modeling

If the necessary information is available, microenvironmental modeling, using modules from the Computational Chemodynamics Laboratory software library, that are based on the mechanistic application of physicochemical principles (mass transport, thermodynamic equilibria, transformations), may be selectively applied to test cases, to evaluate our understanding of the accumulation and fate of the chemicals of concern in various indoor and/or outdoor environments.

3.3 Exposure and Dose Assessment: Modeling/Evaluation of Methods

Exposure and dose assessment modeling will be based on the combined application of various prognostic methods, that are available in the literature, as well as of diagnostic methods that have been developed by the Computational Chemodynamics Laboratory of EOHSI.

3.3.1 Prognostic Methods

Prognostic exposure and dose assessment modeling will utilize various components of the information that will be collected by the NHEXAS Study as well as literature data. This information will include environmental and microenvironmental data, information on spatial/temporal human activity patterns, biomarker information, and, as appropriate, various mechanistic and/or empirical parameterizations (physiological and chemical parameters, human uptake and exposure factors, etc.). In the framework of prognostic exposure assessment the biomarker information will be analyzed for its relevance (or lack of relevance) in evaluating internal dose estimates calculated through the combined application of:

- microenvironmental modeling and/or measurements,
- human activity modeling and/or data,
- human uptake modeling, and
- (classical as well as physiologically based) pharmacokinetic modeling.

The prognostic modeling will utilize various concepts, techniques and associated software libraries and packages, that are either available from outside sources, i.e. commercially and in the research literature (e.g. Marnicio et al., 1991; Pardi 1992; Donigian and Mulkey, 1992; Ott, 1982; U.S. EPA, 1991; etc.) or developed locally at the Computational Chemodynamics Laboratory of EOHSI. Locally developed software libraries utilize non-proprietary standards (Objective C and C++, Objective Fortran) and public domain libraries (LSODE, DASSL, etc.), as well as proprietary modeling tools and support libraries (ACSL/SimuSolv, SCoP, Mathematica, Maple, MathCad, Stella, Crystall Ball, HiQ, etc.) on a variety of platforms (X-windows, SunOs/Solaris, IRIX, NeXTStep, Mac, etc.). Mechanistic approaches as well as Monte Carlo simulations will be considered for their applicability to the cases at hand.

3.3.2 Diagnostic Methods

The use of diagnostic methods for exposure assessment, which are based on the inverse application of Physiologically Based Pharmacokinetic Modeling, driven by available biomarker data (Georgopoulos et al., 1993, 1994), will be evaluated with respect to their

applicability to the chemicals considered in the Pilot Study and to the resolution and information content of the databases that will be built by the Study.

3.3.3 Exploration of Novel Techniques: Prognostic-Diagnostic Methods for Individuals and Populations

Physiologically Based Pharmacokinetic Modeling (PBPKM) is traditionally focusing on specific individuals and its application, either in the prognostic or diagnostic, i.e. inverse or exposure reconstruction, mode, requires extensive information on the temporal evolution of biomarker data following exposure. However, information of this type, arising from the pilot Stud,y will be very limited while, on the other hand, there will be information on the biomarker response to exposure for population samples. For this reason the Computational Chemodynamics Laboratory of EOHSI has been exploring the potential of combining traditional population pharmacokinetic models, such as the Nonlinear Mixed Effects Model, NONMEM (Whiting et al., 1986; Boeckman et al., 1992), with PBPK models, to better address the needs of studies such as the NHEXAS program. Since the concept is novel, and because resources dedicated to the Exposure and Dose Assessment Modeling and Evaluation tasks of the NHEXAS Pilot Study may not be adequate for its full implementation, it should be considered as an exploratory effort that could provide additional insight to the overall exposure and dose assessment process. A brief discussion of this concept follows:

Discussion of Population/PBPK Modeling NONMEM is well established as the standard tool for analyzing population pharmacokinetic data. NONMEM employs a user specified *population pharmacokinetic model*, and a user specified *error model*, to analyze population pharmacokinetic data in terms of fixed effects, which are effects that can be attributed to measurable variables, and *inter- and intra-individual random effects*. The population pharmacokinetic model is comprised of a *structural pharmacokinetic model* that governs the pharmacokinetics of individuals within a population, and a *structural parameter model* that accounts for fixed and random inter-individual variations in pharmacokinetic parameters among individuals within a population. At the present time NONMEM incorporates a number of structural pharmacokinetic models, all of which are based upon classical compartmental pharmacokinetic models. These structural models provide the framework for the resolution of random effects into inter- and intra-individual random effects. PBPK models, which are based upon the underlying physiology, have not as yet been used to analyze population pharmacokinetic data. CCL has been studying the development, within the framework of NONMEM, of a generalized structural pharmacokinetic model that incorporates features of both classical compartmental pharmacokinetic models, as well as PBPK models. The development of such a generalized pharmacokinetic model is motivated by a need to view classical compartmental pharmacokinetic models and PBPK models, not as disparate concepts, but as two ends of a continuous spectrum of models. The study in progress aims to evaluate the viability of combing the practical utility of classical compartmental models with the ability of PBPK models to provide insight into the system being studied, such as the prediction of tissue-specific time-concentration profiles. The sophistication of models developed under a general

framework such as this could be enhanced stepwise, as our understanding of the mechanisms involved improves. The mechanistic formulation of PBPK models provides the appropriate basis for the extrapolation of results and can be a useful guide to experiment and field study designs.

3.4 Comparative Evaluation: Case-Specific versus Global Modeling

As discussed earlier, one of the objectives of the Exposure and Dose Assessment Modeling and Evaluation tasks is to test the central hypothesis of the NHEXAS Pilot Study. This hypothesis states that individual or population exposure estimates, determined from case-specific data collected during this Study, will be different from estimates obtained using literature ("default") data. The Pre-Study Exposure Assessment Project, which is independently implemented, is expected to provide such data and associated exposure and dose estimates. Selected cases from Pre-Study Exposure Assessment Project, to be identified in collaboration with RTI and EPA personnel, that correspond directly to information collected trough the Pilot Study will be simulated with the case-specific data and compared with the Pre-Study predictions.

The case-specific datd will also be compared with information available in various exposure databases (Sexton et al., 1992) and the statistical significance of their "agreement" (or "disagreement") with the default or "global" values will be explored.

4 EXPECTED RESULTS

4.1 Study-Specific Results

Expected results from the Exposure and Dose Assessment Modeling and Evaluation tasks of the RTI/EOHSI NHEXAS Pilot Study will include:

- point, order - extreme value (Georgopoulos and Seinfeld, 1982), interval and distributional estimates of exposure and dose for individuals and populations,
- preliminary estimates of uncertainty in exposure and dose assessment due to intra- and inter-individual variability of exposures and to extrapolation from short- to long-term averages of exposure estimates,
- qualitative estimates of uncertainty associated with available data analysis and prognostic modeling methods for exposure and dose assessment.

4.2 Methods and Techniques

In addition the the Pilot Study-specific calculations and analyses it is expected that the Exposure and Dose Assessment Modeling and Evaluation tasks will provide:

- general information as to the applicability and validity of "standard" methods for assessing exposure and dose, as well as

- new approaches, at least in a preliminary form, for analyzing and interpreting exposure-related information, based upon stochastic mechanistic principles and combined environmental and biological information.

5 QUALITY ASSURANCE

The Quality Assurance procedures that will be followed in the implementation of the Exposure and Dose Assessment Modeling and Evaluation tasks of the RTI/EOHSI NHEXAS Pilot Study will focus on the critical implementation and evaluation of basic modeling methods and of the underlying fundamental concepts. These procedures will rely on the full and detailed description and documentation of methods and assumptions employed in the modeling tasks (including physical assumptions, mathematical approximations, numerical algorithms, software code limitations, etc.). The use of standardized methods for electronic media record-keeping as well as the use of proprietary and non-proprietary device- and platform-independent methods for data analysis, data storage, and document processing constitute standard practices at the Computational Chemodynamics Laboratory.

Compatibility requirements with RTI and EPA procedures, standards, formats, methods and devices will be handled in consultation with RTI and EPA personnel and will be followed during the implementation of the project tasks. Specific protocols for record-keeping and model implementation and evaluation procedures may be developed, if necessary, in collaboration with RTI and EPA personnel to satisfy EPA documentation needs.

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