Umbrella Quality Assurance Project Plan (QAPP) for Dosimetry and Mechanism-Based Models

Prepared

for

U.S. Environmental Protection Agency
Office of Research and Development
Center for Public Health and Environmental Assessment

Prepared by
U. S. EPA Pharmacokinetics Workgroup (PKWG)

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Effective Date: December 16, 2020

ORD QA Category A

INTRODUCTION

The U.S. Environmental Protection Agency (EPA) requires the coordinators of any given EPA project to develop a quality assurance project plan (QAPP) that establishes procedures for assessing the quality of products (outputs of the project) and for documenting the execution of these procedures. This document provides an "umbrella" QAPP that covers projects involving dosimetry and mechanism-based models, including physiologically based pharmacokinetic (PBPK) models, classical pharmacokinetic (PK) models, models of in vitro systems, and biological response or pharmacodynamic models, as well as collection and curation of data related to calibration and evaluation of such models. This QAPP applies to modeling projects coordinated in the Center for Public Health and Environmental Assessment (CPHEA) related to the evaluation of exposure-dose-response relationships (or related chemical or particle kinetics) for use in chemical risk assessment at the EPA. A diagram of the workflow for application of the QAPP to a specific model is shown in Figure 1. While the QAPP also addresses QA of data collection and curation related to modeling, that process is considered sufficiently straight-forward that a separate workflow diagram is not provided. Finally, a diagram of the overall model evaluation, review, and application process, of which this QA process is a part, is provided in Figure 2. This QAPP conforms to EPA QAPP guidance (U.S. EPA, 2002a) and is an internal guidance document that supports EPA's Human Health Risk Assessment (HHRA) research program.

Although this QAPP applies to a more general class of models, it primarily focuses on the evaluation of PBPK models. A PBPK model is a mathematical description of the disposition of one or more chemicals in the body of a human or experimental animal. Organs or tissue groups are represented as compartments linked by blood flows that carry the chemical(s) between compartments. In other words, a PBPK model is a quantitative statement of a set of hypotheses regarding the major determinants of absorption, distribution, metabolism, and excretion (ADME). These models are valuable to quantitative chemical risk assessments in that they can be used for dosimetry extrapolation between species (e.g., animal to human), across routes (e.g., inhalation to oral), and among exposure scenarios (Krishnan and Andersen, 1994), all of which can be used to facilitate human health risk evaluation and the setting of regulatory exposure levels. In addition to PBPK models, simpler PK models with more empirically derived parameters can be used for the same types of extrapolation. Either form of PK model (PBPK models being a subset of all PK models) can be linked to a model describing some level of biological response, in which the combined dosimetry-response model is referred to as a biologically based dose-response (BBDR) model. This QAPP applies to all mathematical models based on chemical and physical processes and various biological mechanisms.

Guidance on the use or application of PBPK models in EPA risk assessments is not the subject of this document, but is provided in a separate report (U.S. EPA, 2006). Other publications and regulatory documents describing best practices for PBPK and other types of models are listed in APPENDIX C. This list is not meant to be comprehensive. This QAPP has been developed

specifically to address the Office of Research and Development (ORD) Policy on Modeling Quality Assurance and Documentation[1], which is consistent with EPA's Guidance for Quality Assurance Project Plans (U.S. EPA, 2002a). Guidance and publications from other organizations may be useful supplements but may not fulfill EPA- and ORD-specific requirements.

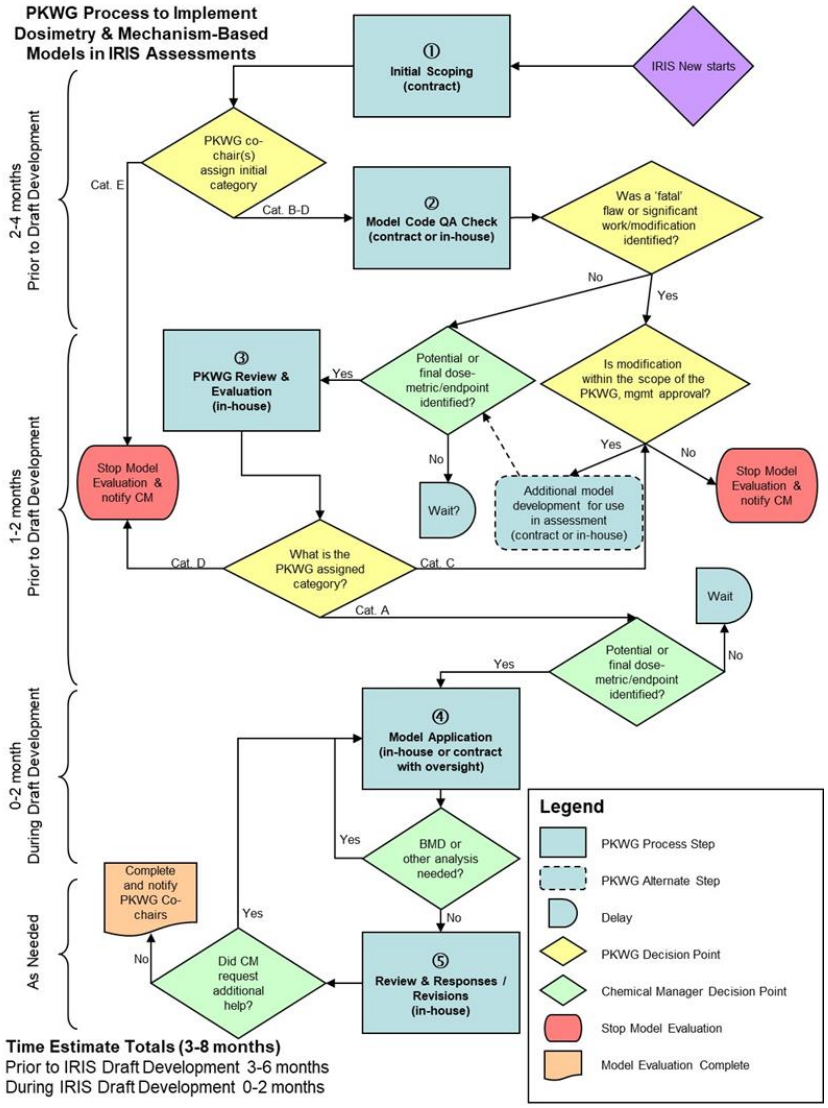

Figure 1. Decision workflow for review and application of a specific computational model. The labels "Cat A" through "Cat E" represent "categories" for models that are used by the PKWG in evaluating adequacy of models for use in chemical risk assessment. The labels "Cat A" through "Cat D" mean that a PBPK model is available for the chemical of interest. The label "Cat A" implies the model is useful; the label "Cat B" implies the model needs further evaluation to determine its adequacy; the label "Cat C" implies significant work will be required before the model could be used; and the label "Cat D" implies that the model is inadequate for human extrapolation.

[1] https://intranet.ord.epa.gov/policy/modeling-quality-assurance-and-documentation

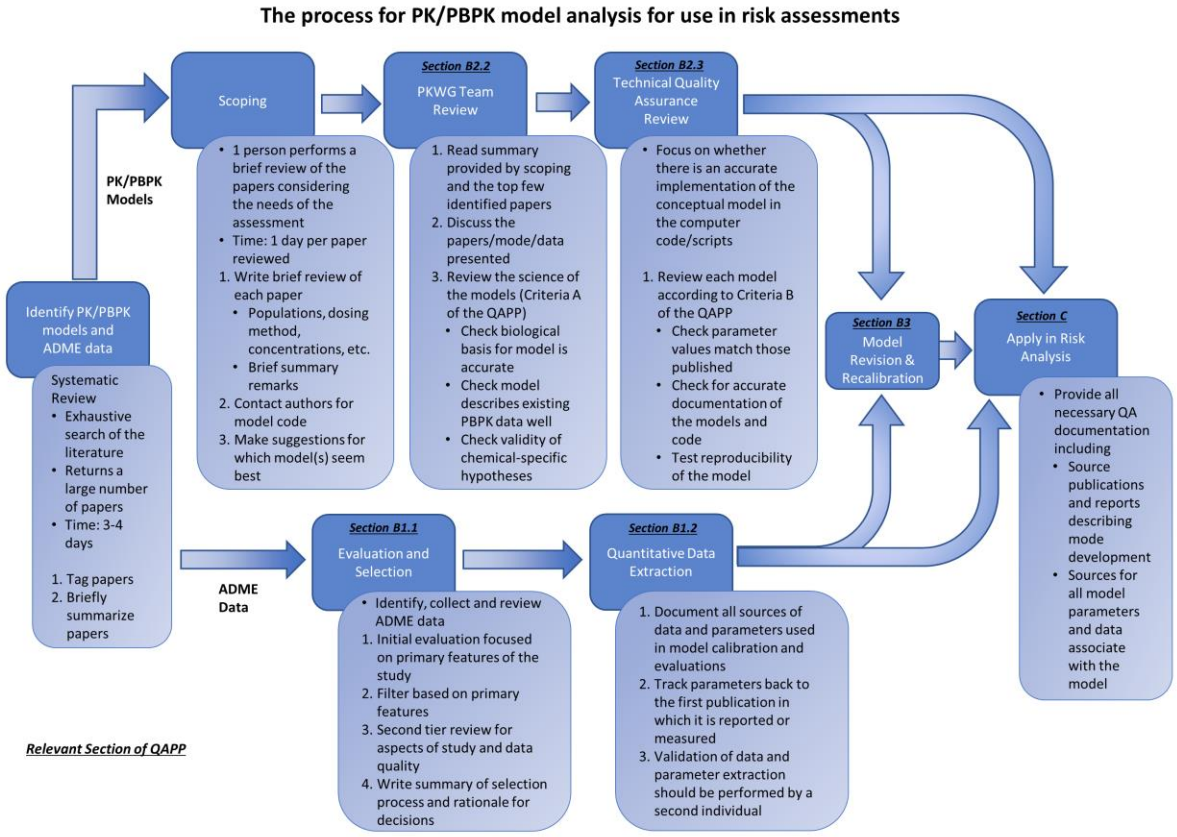

Figure 2. Workflow for identification, selection, and application of dosimetry and mechanism-based models (e.g., PBPK models) and related quality assurance procedures. Underlined names specify sections of this document.

Other EPA models and modeling tools, such as the high throughput toxicokinetic (HTTK) suite of models (Pearce et al., 2017), have their own QAPPs specific to the EPA research projects under which they were developed. If CPHEA seeks to use such a model, its scientific validity and appropriateness for use in an IRIS Toxicological Review or other risk analysis would need to be evaluated as part of this QAPP, since the model may originally have been developed for another purpose. For example, the PKWG might determine that the HTTK predictions for a specific chemical are sufficiently sound for use in an IRIS assessment. Since the HTTK models have been subjected to QA review under their own ORD QAPP, the model codes and parameter sets would be assumed to have already satisfied those criteria, obviating the need for a detailed review of the computer code under this QAPP, though the rationale for general scientific quality and applicability would still need to be evaluated.

In order to adequately evaluate the quality of a PBPK model, a comprehensive understanding of a chemical's ADME processes (to the extent possible) is needed, which requires a review of all available PK data. For large PK datasets, an initial systematic review should allow for a selection of the publications which are most informative for PBPK modeling (i.e., a representative subset from among multiple publications containing similar information). For example, measurement of the total excretion in a 24-hour urine sample is less informative than time-course urine concentration data. Furthermore, if multiple publications report similar data, then the data from one or two of these might be adequate for model evaluation. The selection and grouping of representative datasets should also be documented and checked, along with details of data extraction from the representative sets.

Once PK data has been extracted from the literature, QA procedures described herein can be applied to ensure the fidelity of these data. The data will be evaluated for accuracy and consistency and any apparent discrepancies will be resolved or explained. These procedures should be applied to any datasets used in development or calibration of a mechanistic model but may include other datasets that might be used for evaluation of the model. For example, evaluation data can be used to determine whether a common set of values of the model parameters can consistently yield predictions that agree with the datasets (or whether, perhaps, parameter values must be varied in order to yield predictions of datasets that differ for explainable reasons).

Each model is defined by a specific set of model equations and a number of model parameters which must be chosen appropriately to match the chemical, physical, physiological, pharmacokinetic, or other data. If a model is to be used to support human health risk assessment, the model must first be evaluated for quality, to assure that:

(1) it properly represents the underlying chemistry, physics, or biology, given the assumptions stated or implied in the scientific reference(s) describing the model (the model equations are correct);
(2) values of the model parameters taken directly from the scientific literature have been transcribed accurately and appropriately applied;
(3) the model yields predictions that reasonably agree with all of the datasets (as described in the report or paper, with the datasets having undergone QA review), or sound explanations can be provided when this is not the case.

Regarding (3), it is generally desirable that model predictions fall within a factor of two of any data, but agreement of model predictions should be evaluated across an entire data set. Additional details on that aspect of evaluation are provided later in this document. An example where a large data discrepancy might be ignored is when the model describes some data quite well, in particular at exposure levels in the range of application, but does not fit other data (e.g., at less relevant exposure levels). In some cases, the data may exhibit a high degree of variability that cannot be explained by strain, gender, or other experimental differences, making it impossible for any model to fit all the data with high precision. In this case, strain- or gender-specific parameter sets might be used (applied in the analysis of corresponding toxicity studies). If the differences

between two datasets cannot be explained, then alternate model parameter sets can be obtained by fitting each of them separately and the resulting range of parameters treated as a range of uncertainty. Both sets of parameter values can be tested in the model application to evaluate the impact of this uncertainty.

It should also be noted that each model includes code (implementation software), associated parameter values, and data. Because parameter values may be set or key calculations may be performed in a model script separate from the file which defines the primary model equations, the term "model" as used here refers to the entire set or "package" of such files. An accurate model of human workplace exposure, for example, requires not only that the body weight, tissue fractions, and metabolic parameters be set properly for an adult human, but also the respiration rate and cardiac output expected in the workplace and corresponding exposure levels as they vary during the day. The "model," then, includes equations, parameter values, and data, which are all addressed in this QAPP

A model can be implemented in any of a number of software languages, such as R, MCSim, Berkeley Madonna, Python, MATLAB, and Octave. A model implementation is the translation of the mathematical description, parameter values, and data used into one or more software languages, recorded in a set of computer files and scripts. These model files and scripts are then executed in an appropriate programming environment, which often is referred to by the same name as the language. For example, there is a MATLAB language, which consists of a set of rules for syntax and structure that one must use when implementing models in MATLAB, and a MATLAB environment, where specific simulations and other model-based calculations are executed. This QAPP addresses the implementation of specific models and model applications into the corresponding computer files and scripts irrespective of the language used.

Evaluation of the quality of the programming environments and evaluation and maintenance of their technical and user documentation is beyond the scope of this QAPP and is not the responsibility of the Pharmacokinetics Work Group (PKWG) (see Section A5: PKWG Background and Description) or individuals involved in developing and/or evaluating PBPK models as described here. Each of these programming environments is assumed to be fit for the purpose of scientific computing and documentation is assumed to be accurate as provided, though any evidence of errors or inaccuracy should be documented and reported to the software developer immediately.

On the other hand, if code packages (sets of files) or tools are developed to facilitate mechanism-based modeling for EPA applications, (i.e., that integrate with and extend a programming environment), then those packages or tools should be evaluated using this QAPP even if they are not models themselves. For any specific PBPK project, an addendum to this umbrella QAPP may be produced that specifies additional details pursuant to its specific work plan.

SECTION A: TASK MANAGEMENT

This section addresses task management including roles and responsibilities, background and description, quality objectives and criteria, training, documentation, and record keeping.

A1: Title and Approval Page

Title of the Plan: Umbrella Quality Assurance Project Plan (QAPP) for Dosimetry and Mechanism-Based Models
Signatures indicate approval of this QAPP and a commitment to follow the applicable procedures noted therein.
Effective Date: December 16,2020

VIKTOR MOROZOV Digitally signed by VIKTOR MOROZOV Date: 2020.12.17 08:55:04 -05'00'

Viktor Morozov, PKWG Management Liaison Date

DUSTIN KAPRAUN Digitally signed by DUSTIN KAPRAUN Date: 2020.12.16 18:00:53 -05'00'

Dustin Kapraun, PKWG Co-Chair Date

Schlosser, Paul Digitally signed by Schlosser, Paul Date: 2020.12.17 08:40:16 -05'00'

Paul Schlosser PKWG Co-Chair Date

YU-SHENG LIN Digitally signed by YU-SHENG LIN Date: 2020.12.17 09:07:55 -05'00'

Yu-Sheng Lin, PKWG member Date

ALAN SASSO Digitally signed by ALAN SASSO Date: 2021.01.06 11:17:48 -05'00'

Alan Sasso, PKWG member Date

TODD ZURLINDEN Digitally signed by TODD ZURLINDEN Date: 2020.12.22 19:12:21 -05'00'

Todd Zurlinden, PKWG member Date

CHERYL ITKIN Digitally signed by CHERYL ITKIN Date: 2020.12.17 18:52:33 -05'00'

Cheryl Itkin, CPHEA Director of Quality Assurance for CPAD and HEEAD Date

SotoHernandez, Jessica Digitally signed by SotoHernandez, Jessica Date: 2020.12.17 20:23:49 -05'00'

Jessica Soto-Hernandez, CPAD Quality Assurance Manager Date

A2: Table of Contents

TABLES

FIGURES

A3: Distribution List

The individuals in Table 1, along with all members of the PKWG, will receive copies of the approved QAPP and subsequent revisions.

Table 1. QAPP distribution list

Name	Role	Organization	Contact Information
Paul Schlosser	PKWG Co-Chair	ORD/CPHEA/CPAD	schlosser.paul@epa.gov (919) 541-4130
Dustin Kapraun	PKWG Co-Chair	ORD/CPHEA/CPAD	kapraun.dustin@epa.gov (919) 541-4045
Viktor Morozov	PKWG-Management Liaison	ORD/CPHEA/CPAD	morozov.viktor@epa.gov (202) 564-7561
Yu-Sheng Lin	PKWG member	ORD/CPHEA/CPAD	Lin.Yu-Sheng@epa.gov (202) 564-7253
Alan Sasso	PKWG member	ORD/CPHEA/CPAD	Sasso.Alan@epa.gov (202) 564-2608
Todd Zurlinden	PKWG member	ORD/CPHEA/CPAD	zurlinden.todd@epa.gov (909) 541-4301
Cheryl Itkin	CPHEA Director of QA Assessments for CPAD and HEEAD	ORD/CPHEA/CRPIS	itkin.cheryl@epa.gov (202) 564-6469
Jessica Soto-Hernandez	CPAD QA Manager	ORD/CPHEA/IO	sotohernandez.jessica@epa.gov (202) 564-9896

A4: Task Organization

This section describes the roles and responsibilities for individuals associated with the PBPK Model QAPP.

A4.1: Task Roles and Responsibilities

The overall PBPK Modelling task includes the following roles: PKWG-Management Liaison, PKWG Co-Chairs, CPHEA Director of QA, CPAD QA Manager, and PKWG Project Leads (for specific chemicals or models; may also be the PKWG Chair); Principal Investigator (PI) or Contributing Investigator (CI) (for a specific sub-task; may be the Project Lead). The PKWG Project Lead is expected to manage the overall PBPK modelling task, including application of this QAPP.

Modelling tasks may also involve U.S. EPA staff or contractors not specifically identified in this document, but who are responsible for QA of the task or a sub-task; those individuals are

referred to as the PI or a CI, depending on their role (for example, a contractor PI would be the primary or lead individual employed by a contractor as responsible for providing a work product), and shall be identified in an addendum, which can also describe other changes or additions to this QAPP for a specific model. While a PI or CI may in turn have assistance from other colleagues/staff, the QA responsibility shall not be delegated except to individuals identified as a PI or CI in an addendum. For example, a CI who is supporting the PKWG Project Lead may obtain assistance from a colleague (not identified in an addendum) in extracting data for a PBPK model, but that CI would still be responsible for documentation and QA of the extracted data.

The PKWG-Management Liaison is responsible for the following:

- approving the QAPP;
- providing an avenue of communication between CPAD management and the PKWG Chair(s);
- supporting the corresponding activities of the CPAD QA Manager and the PKWG Chair(s);
- ensuring implementation of QA corrective actions within the task when appropriate;
- facilitating project formulation, including defining desired outcomes and outputs; and
- working with CPAD (and higher) management to allocate resources needed for model QA evaluations as described by this QAPP.

The CPAD QA Manager is responsible for:

- providing technical QA leadership for the task;
- ensuring all individuals developing or using a model have appropriate QA training (e.g., by taking the Quality Assurance Program Overview course in SkillPort);
- approving any supplemental model-specific amendments to the QAPP;
- advising the CPAD Director of QA and other managers on QA-related issues requiring their attention;
- reviewing, approving, and documenting QA product review in STICS and QA tracking systems;
- performing Technical System Audits (TSAs) ensuring corrective actions are completed as needed;
- reviewing and approving QA documents generated by the task; and
- serving as the QA expert on QA activities pertaining to research.

The PKWG Co-Chairs and Project Lead are responsible for:

- planning and identifying desired outcomes and outputs to be delivered for projects;
- ensuring that the quality system is properly implemented;

- ensuring that the quality-related documents (e.g., QAPPs, reports) are developed, approved, and implemented as appropriate;
- completing QA training;
- informing the appropriate chemical manager and others listed in Table 1 as appropriate of any model quality-related issues;
- communicating with management, Project Leads, Directors, and Center Director and resolving conflicts when necessary;
- obtaining the CPAD QA Manager's approval for quality-related documents;
- reviewing and approving the QA documentation (amendments) for specific models;
- participating in TSAs and implementing any corrective actions;
- ensuring that PIs or CIs are sufficiently qualified and that their contributions meet the QA objectives of this QAPP; and
- providing the model application and supporting documentation to the appropriate CPAD or other EPA staff for subsequent distribution (e.g., inclusion of documentation in a Toxicological Review or posting of model code in HERO).

PIs and CIs are responsible for:

- ensuring that the QAPP is implemented as it relates to their specific tasks; and
- providing full documentation for their modeling tasks and QA activities to the Project Lead.

A4.2: Relationship Between PKWG and Other EPA Organizational Units

Core members of the PKWG, including the co-chairs, are employees in the EPA ORD Center for Public Health and Environmental Assessment (CPHEA). Ad-hoc PKWG members from other ORD centers and EPA program offices also contribute to QA reviews. Figure 3 shows the relationship between PKWG and other EPA organizational units.

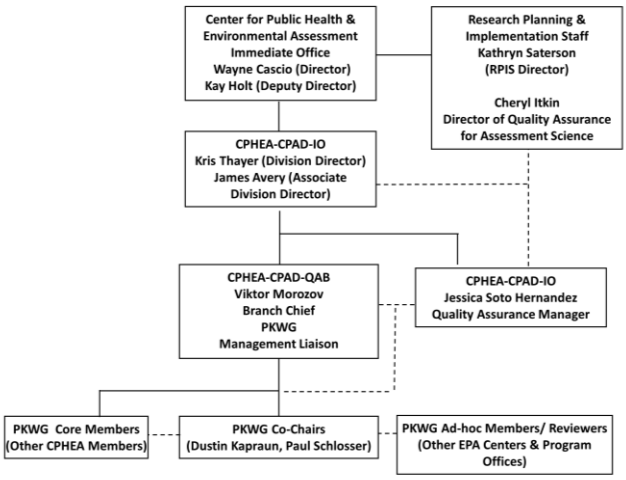

Figure 3. Relationship between PKWG and other EPA organizational units.

A5: PKWG Background and Description

The PKWG exists within the CPHEA to support and promote consistent application of the best science practices in PK data analysis and modeling, including but not limited to PBPK modeling, as applied in human health risk assessment. The PKWG addresses the absorption, distribution, metabolism, and elimination (ADME) of chemicals in humans and laboratory animals, the analysis of in vitro chemical kinetic data to obtain parameters for PK models, as well as the use or implementation of PBPK and other models. The objectives of this workgroup are to:

1. Promote and support the best use of available scientific PK and other quantitative biological data and methods in human health risk assessment in scientific products developed by CPAD for EPA's Integrated Risk Information System (IRIS);

2. As appropriate, promote and support the use of PK data and mechanistic computational models in other scientific EPA assessments and products;

3. Advise EPA management on issues related to PK data and mechanistic modeling in human health risk assessment; and

4. Advance the scientific application of PK and other quantitative data for human health risk assessment through further development and refinement of corresponding computational models, analysis methods and tools, and data resources.

A key part of the PKWG's work is to evaluate data covering ADME and PK, as well as the application of PBPK and other mechanistic models for potential use in IRIS assessments and other EPA products. Occasionally new computational models are developed for use in IRIS, but it is more

often the case that existing models are reviewed (including QA evaluation) and corrected or revised as deemed appropriate. In accord with the ORD Policy on Modeling Quality Assurance and Documentation[2], this QAPP describes the QA documentation needed as a part of model development or review and revision.

A6: Quality Objectives and Criteria

This QAPP seeks to ensure quality by establishing objectives and criteria for the development or elaboration; evaluation and correction; and application of mechanism-based models. The objectives for the QAPP include:

- providing a process that supports confidence and enhances transparency in scientific decisions based upon mechanism-based model application;
- creating a uniform framework for model development, revision, and QA review that is sufficiently flexible to encompass the various models, datasets, software environments, and the needs of the IRIS Program, CPHEA, and EPA program and regional offices likely to occur;
- providing specific guidance for evaluation of PBPK models (e.g., selection of internal dose, incorporation of metabolic saturation as a function of dose or concentration); and
- increasing efficiency for risk assessment activities by minimizing the chances that errors occur in model code, parameter values, or data extraction and that where they exist (i.e., in existing models) they are identified and corrected quickly, as early as possible.

Because computational modeling requires specialized skills and knowledge, including familiarity with specific software, the conventions of PBPK and other mechanism-based modeling, and the related aspects of biology (physiology), biochemistry, chemistry, and mass-transport, the criteria which relate to clarity, transparency, or understandability of a model are understood to apply to an individual with a moderate level of (PBPK) modeling expertise. Quality criteria for this QAPP include:

- complete, transparent model descriptions (i.e., all equations, parameter derivations, and calculations of data are completely and accurately described);
- model code and scripts that can be understood (i.e., have sufficient annotation) and used by an individual with moderate expertise in the selected programming language and environment;
- model accuracy and reliability:
    - equations in the model code accurately represent the model as described in supporting scientific papers, reports, or other documentation, with any discrepancies explained or resolved;
    - parameters in the model match those listed in supporting documents;
    - model parameters are accurately copied or extracted from scientific sources;

[2] https://intranet.ord.epa.gov/policy/modeling-quality-assurance-and-documentation

- data used to calibrate or evaluate model predictions have been accurately copied or extracted from scientific sources; and
- model results (numerical outputs, including tables and figures) can be replicated to at least the precision given in assessments and other documents where they are reported or used.

While not required, it is suggested that an accompanying 'readme' file be provided to guide model users and reviewers. The readme file should briefly describe each file in a code package; for example, the function or output of each accompanying script and the data contained in data files. For models in software environments such as R, where supplemental code packages in addition to the base installation are needed, and placement in the computer's file directory may be important, guidance on the installation should also be provided.

In addition to the quality objectives above, there are EPA, ORD, and CPHEA policies and plans that guide quality activities including the following:

- ORD Quality Management Plan.
- CPHEA/CPAD Quality Management Plan (an appendix of the ORD Quality Management Plan).
- Chapter 13 of the ORD Policy on Modeling Quality Assurance and Documentation[3].
- Requirements for Quality Assurance Project Plans (QA/G-5).
- Scientific Integrity Policy (www2.epa.gov/osa/policy-epa-scientific-integrity).
- EPA Information Quality Guidelines (https://www.epa.gov/quality/epa-information-quality-guidelines).
- EPA Peer Review Handbook (https://www.epa.gov/osa/peer-review-handbook-4th-edition-2015).

A7: Training and Certification

CPHEA employees take appropriate Quality Assurance Training courses prior to working on modeling activities. CPHEA QA staff provides QA training to researchers. There is no specific certification for PBPK modeling. Those who have signed this umbrella QAPP make a commitment to follow it.

A8: Documentation and Records

This section discusses how and where the documents and records relating to a modelling task are maintained. The PKWG Chair(s), Project Leads, contributing EPA staff, and contractor PI should maintain documents and records associated with this task. For each model, or task associated with a model, a specific individual (either EPA employee or contractor) shall be identified, who will have primary responsibility for the documentation associated with that model

[3] https://intranet.ord.epa.gov/policy/modeling-quality-assurance-and-documentation

or task. Documentation listed in A8.2: Documents and Records shall be maintained in EPA "cloud" storage, such as an OneDrive, SharePoint site, project site, in databases, or in version control repositories.

A8.1: QAPP Distribution

The PKWG Chair(s) maintain(s) the final approved version of this QAPP in the PKWG-Umbrella QAPP SharePoint folder. The PKWG Chair(s) and PK Project Leads maintain a final version of any addenda for the chemical/assessment on which they are a lead. The approved QAPP, including revisions, updates and any addenda are delivered electronically to the individuals listed in Section A3: Distribution List and any other EPA staff of contractor PIs supporting mechanism-based computational modeling. The final approved QAPP and subsequent versions and addenda are stored by the PKWG Chair(s) or the PK Project Leads in the PKWG-Umbrella QAPP SharePoint folder.

A8.2: Documents and Records

The PKWG Project Lead for a chemical/assessment, with assistance from any modeling PIs and CIs is expected to keep documents relating to the computational modeling task. Information includes:

- the source publication(s) or report(s) describing development of the model, in particular the choice of any features or model components that are not standard to PBPK modeling;
- the sources for all model parameters and data associated with the model, including page and table or figure numbers within a citation; these may also include spreadsheets or other files received from authors of publications and reports, but should generally be the sources cited in the paper or report where the model is described;
- comments or other documentation (e.g., spreadsheets or software scripts) sufficient to reproduce any conversion of published data to the actual values used in a model;
- the model code and any scripts (preferred) used to generate any plots, tables, or other results, or sufficiently detailed descriptions of the steps used to produce each plot, table or other result to allow it to be reproduced;
- a readme file (preferred) to guide model users regarding the primary components, features, and function of any scripts; the readme can presume a moderate level of PBPK modeling expertise;
- detailed descriptions of any changes made from a computational model as published in the scientific literature, including the rationale for the changes and indication of its impact on model predictions; and
- a master document that summarizes QA for the various pieces or individual files (e.g., QA checklists) in the set or package associated with each model.

This information should be maintained in shared electronic folders or databases. While copies of original publications or reports may just be kept in EPA's HERO database and only cited in

the model's QA package, all other pieces should be organized together into a single folder or zip file at the end of the QA process.

A8.3: Project Management Plan (PMP) for IRIS Projects

During the planning phase of the PBPK work to be done for IRIS projects (Toxicological Reviews), the PKWG Project Lead works with the IRIS Chemical Manager and other participants to ensure the IRIS PMP includes a description of the PBPK modeling work to be performed in support of the IRIS chemical assessment. IRIS PMPs are maintained for IRIS project management purposes. All Chemical Managers (CM) will keep the PMP as part of the IRIS project file.

A8.4. Documents and Records Related to Peer Review

Typically, PBPK models are incorporated into IRIS Toxicological Reviews, in which they are peer reviewed along with the Toxicological Review as a whole. In this case, documents and records related to peer review are the responsibility of the chemical manager(s) and defined by that peer review process. If a PBPK model is being used as published in the peer-reviewed scientific literature, with only minor modification or corrections, then it is assumed that model was selected by the process described in the IRIS Handbook (i.e., by discussion and agreement among the PKWG, chemical managers, and other management personnel as appropriate), and no additional peer review (beyond that of the Toxicological Review) is necessary.

If a model is being developed de novo or a previously published model is being substantially altered by PKWG members or other staff (and submitted for journal publication separate from its use in a Toxicological Review), then an additional peer review process may be used. Corresponding documents and records may include:

- Internal Peer Review Plans
- Federal Register Notice(s), if generated
- Charge to Reviewers
- PBPK Model packages
- Logistical Fact Sheets
- Peer Review Reports or individual comments from reviewers.
- Disposition of comments.

These documents are kept by the PKWG Project Lead the PKWG SharePoint drive[4] and are the official peer review records. Public documents, such as manuscripts intended for peer-reviewed scientific journal publication, go through the CPHEA/CPAD clearance process using the STICS online database where copies of these documents can be found in that database.

[4] https://usepa.sharepoint.com/sites/ORD/pkwg/Shared%20Documents/Forms/AllItems.aspx

A8.5: Other Documentation

Other key documents associated with PBPK tasks include IRIS standard operating procedures, the IRIS Handbook, and software user manuals and documentation (i.e., provided by the software developer such as MATLAB or R source-code providers). While it is not the responsibility of the PKWG, PI, or CI to maintain master copies of these documents, it is helpful for them to have copies readily available on their computers or via internet links (e.g., to software documentation on the manufacturer's or developer's website).

SECTION B: STANDARD OPERATING PROCEDURES (SOPs) FOR IDENTIFICATION, ORGANIZATION, AND EVALUATION OF ADME AND PK STUDIES AND COMPUTATIONAL MODELS

B1: Data Review, Verification, Validation, and Usability

Section B1 reviews the data and parameters used to create a pharmacokinetic or similarly structured biologically based model. Here, the usability of data for informing the model is reviewed, and model parameter values obtained from published sources are cross-referenced against those sources.

B1.1 Data Evaluation and Selection

This section describes the analytical process by which information from ADME and other chemical process studies is identified, evaluated and selected for use in modeling. Before extracting data to electronic files that are used by the computational model, the data sources must be identified and evaluated for study quality and applicability to the model.

Uncertainty in a model is reduced when the most relevant, reliable, and quantitatively valuable ADME or other relevant studies are identified and given precedence over studies that provide limited information. It is essential to locate all relevant, scientifically sound ADME data to provide the best possible basis for PK model calibration and evaluation. One would want to know how well a model describes any existing data, and the more data used in model evaluation and calibration, the lower the uncertainty in model predictions. On the other hand, for chemicals with extensive available databases (there are hundreds of ADME studies for some chemicals), one will wish to identify a smaller, manageable set of ADME studies representative of the more extensive database.

PBPK models serve to quantify inter- and intra-species PK differences, so they are developed for specific animal species or humans. Therefore, the most relevant ADME studies are conducted in those species, and it is generally acceptable to ignore studies from other species not being modeled. However, mechanistic information may be derived from other species, so a qualitative summary of those data can be helpful. ADME studies are used to: identify the parent

chemical and metabolite(s) found in test species and humans; demonstrate metabolic pathways; identify metabolizing enzymes and kinetic constants (e.g., K_m, V_{max}); characterize metabolic competition (i.e., when multiple chemicals compete for the same metabolic enzyme); indicate primary routes/methods of elimination, and identify data gaps toward which future research may be targeted. Given that nearly all PK reports have some level of intrinsic value, the considerations described below will help determine the level of detail at which these reports might be summarized.

For the purpose of PBPK modeling, optimal ADME studies are those that have been peer reviewed, have been conducted in humans or the species/strain of animal being modeled, and have employed a range of doses that span those used in key toxicological studies or are relevant to human exposures. The most useful ADME studies report the time course for amounts or concentrations of a parent compound of interest and specifically identified metabolite(s), providing information on the parent chemical's overall fate and mass balance. For human ADME studies, doses in the range of the benchmark dose point of departure (POD) are ideal for informing animal-to-human extrapolation. In vitro studies, including those that evaluate a given metabolite formation, may also have value concerning reporting enzyme kinetic parameters such as K_m and V_{max}.

While there is no formally established approach to categorize ADME studies based on their data type and depth of detail, a conceptualized "tiered approach" may be a useful tool to consider value of each study. For example, the initial evaluation may focus only on the primary features, such as the species, strain, sex, developmental stage, and exposure route. A regimen of administration, sample timing, extent to which metabolites are identified and distinguished analytically from the parent chemical, and the number of time-points evaluated. The most promising studies identified by applying filters to this first tier of information (e.g., those conducted in the species, sex, strain, and developmental stage being modeled, and which are dosed via the route(s) of interest) can then be evaluated more carefully in a second-tier review for aspects of study and data quality. The second-tier review might identify the studies which quantify levels of the parent compound and key metabolites, demonstrate the relationship between exposure and internal dose, provide time-course data in target tissues or blood, and employ sound analytical and statistical methods. The points identified under the general considerations for in vitro and in vivo studies below should be used when evaluating study quality and whether a tiered approach is used.

It should be recognized that many chemicals produce multiple toxicities, through different MOAs, with other dose-response functions and that a PBPK model may be used to help interpret results for multiple endpoints. It is recommended that ADME study and data selection focus not only on the apparent key effect (i.e., based on external dose-response and severity considerations), but other endpoints that are triggered by exposures within an order of magnitude of the most sensitive one.

The extent to which ADME reports address the following questions impacts their value for PK modeling. While answers to all these questions are not strictly required, they are all valid and useful for ranking such studies. For chemicals with many ADME publications, greater application of these questions will aid in selecting the best data for modeling.

General considerations:

- Have toxicity studies identified a responsive test animal species (e.g., Sprague-Dawley rat) and the target organ or tissue (liver, thymus, kidney, brain)? Does the ADME investigation evaluate (tissues or samples from) the identified test species/strain or human? If not, to what extent can the species and tissue investigated be deemed an appropriate surrogate?
- Are the results based on chemical-specific identification and quantitation (e.g., gas chromatographic, high-performance liquid chromatography [HPLC], or mass spectral identification) or on general measures of chemical distribution (e.g., radiolabel quantitation)?
- For data from/in humans, is the characterization of exposure sufficient to inform qualitative or quantitative conclusions?
- To what extent can adverse outcome(s) be attributable to the parent chemical, metabolism of the parent chemical (via a specific pathway), or an identified metabolite? If the parent chemical or a key metabolite or pathway has been identified, to what extent does an ADME study inform the dosimetry of the parent chemical, specific metabolic pathway, or identified metabolite?
- To what extent can human data be used to characterize inter-individual PK variability?
- Are valid analytical methods utilized and described in sufficient detail to enable interpretation of the data; are limits of detection and/or quantification provided?
- To what extent has the report been subjected to a peer review? Is the document accessible in whole or in part?

For in vitro ADME investigations:

- To what extent has the concentration of the agent been localized (e.g., measurement in cells versus media) and characterized (e.g., parent chemical disappearance, metabolite formation)?
- Are non-biological sources of loss accounted for (e.g., volatilization, solubility, binding to non-biological test system components)?
- To what extent does the range of concentrations studied enable an evaluation of events at non-saturating and saturating conditions of metabolism, binding, or transport?
- What evidence is available to determine whether in vitro concentrations have in vivo relevance, both in studies conducted in animal models and in human environmental exposures?
- What is the biological level of organization of the in vitro system? How much extrapolation is required to convert from units observed (e.g., pmol product formed per minute per pmol enzyme) to values representative of the intact system? Do multiple bioprocessing steps or bifurcations in downstream or upstream metabolic processes complicate the extrapolation?

- If metabolic rates have been determined using recombinantly expressed enzymes, has a relative activity factor been determined?
- If metabolic rate constants have been derived and presented by the authors, are the underlying data available for evaluation?

For in vivo ADME studies:

- Was the route and method (e.g., inhalation, oral drinking water, oral bolus) of administration consistent with the route and method of exposure used in the toxicity evaluations?
- How likely is it that differences between the vehicle used in the toxicity study and the ADME study may have introduced PK differences between the two studies?
- Is it likely that manipulations of the animal have altered the underlying anatomy, physiology, or biochemistry related to related ADME processes (e.g., could anesthesia have altered important functions like respiration and chemical metabolism)?
- Are time-course and/or exposure-dose PK data reported?
- What is the relationship of doses evaluated to the POD?
- Do the data demonstrate mass-balance? Or, do they focus on a single pathway or step in a complex overall metabolic pathway?

After considering the set of available ADME studies against the various factors described above, it should be possible to sort the studies according to their relevance to the intended PBPK model development and application (e.g., test species, route of exposure), type of information (studies that identify ADME mechanisms vs. those providing quantitative data useful for calibration and validation), and study quality. (which may enable ranking and selection of studies with apparently discordant results or identify those most useful for PK modeling).

In cases of apparently conflicting PK datasets, an analysis of the methods and details will be conducted to either resolve the discrepancy or decide which of the datasets is/are most likely to be correct. For example, there are sometimes significant strain- or gender-related differences in PK among laboratory animals. If apparent data discrepancies appear to be due to such differences, then a PBPK model would only be expected to fit a strain (or sex), and, for risk assessment application, this should be the one with critical dose-response data. Alternatively, model parameters might be identified for each strain, gender, life stage, or other sub-population for which analysis is to be conducted. Discrepancies between datasets might also occur due to different analytical methods, in which case evaluation of the methods might lead to the identification of certain datasets as unreliable. In each case, the rationale for the selection or grouping of datasets will be recorded.

Once this is complete, the qualitative information can be summarized (or used to evaluate the quality and completeness of an existing summary) and the studies from which data should be extracted for model calibration or validation identified. While it is beyond the scope of this PQAPP to specify in detail how the summarization and study selection should be conducted, a written summary describing the approach used (e.g., tiered evaluation, with selection process at each tier)

and the rationale for study selection should be prepared, allowing for the process to be independently reviewed and possibly reproduced.

B1.2: Extraction of Quantitative Data and Model Parameters

After the sets of data or sources of parameters to be used for a model have been identified and evaluated for general scientific quality, as described in Section B1.1 Data Evaluation and Selection, the data must be obtained or extracted from those sources and parameters transcribed as described below.

All sources of data and parameters used for model calibration and evaluation will be documented in text tables, Excel workbooks, or other electronic records with a level of detail to allow easy validation. Specific table numbers, figure numbers, or page and paragraph/line numbers should be provided. If multiple entries in a table report alternate values of a quantity (e.g., measured by different techniques), then further detail shall be provided. If a model is obtained without documentation of ADME data and model parameters described here, such documentation shall be generated as part of the model QA evaluation.

Model Parameters:

Identifying a model parameter source as a publication describing a previous model where the parameter is taken from an earlier source, is not enough since that practice can lead to the propagation of errors. The parameter value should be tracked back to and checked against the publication in which it is first reported or measured. This can include, however, articles and reports which comprehensively review and report physiological parameters, such as Brown et al.(1997), and ILSI (1994). However, for such comprehensive reviews, different values for the same parameter may be reported in different tables. Hence it is imperative to identify the specific table (and column/row) from which the parameter is taken. Table 2 provides an example template for reviewing parameters used from previous publications. This assumes the parameter used is not altered or recalibrated in the current model.

Where calculations are used to convert reported parameters or data to values/units consistent with a model, sufficient detail to replicate the calculations shall be provided. Preferably, calculations and conversions are set up in computational scripts or Excel spreadsheets using embedded formulas. For example, suppose a tissue mass fraction is calculated from a reported tissue weight (TW) and body weight (BW). In that case, the TW and BW are entered into adjacent columns, exactly as reported in the reference. The resulting fraction (TW/BW) is calculated in a third column (e.g., the entry is '= C1/B1') rather than entered as a numerical value. Comment text (and column headers in spreadsheets) would identify the data source(s), as described above, and provide details for more complex calculations.

When parameters are derived by more elaborate means, for example, a regression analysis, details sufficient to replicate the result should be provided; this can be readily accomplished by embedding the analysis in a script. Simple regressions can also be performed directly in Excel plots,

with the equations shown, allowing for easy validation. If a regression is performed by other means (e.g., using the Solver function in Excel), then a plot of the resulting curve can be generated along with the data for visual comparison, which makes it immediately evident when a significant numerical error has occurred. Table 3 provides an example template for review parameters calibrated from existing data.

Data:

When data are received directly from the researcher(s) or the author(s) of a publication, a copy of the data file shall be saved with "as received" and the date received or saved in the file name. Subsequent manipulations of the data file shall be done using copies of this original file, with that dependence documented in the copies or an accompanying text file.

If original data files are not available from the person(s) who generated the data (as is often the case for older data), they should be validated against the published sources and the process should be documented. Data provided in numerical form from an intermediate source (e.g., a model author) can be plotted and compared to a published figure as described below to ensure accuracy.

Validation:

All data and parameter extraction should be validating by having an individual other than the person who performed this initial extraction check the values against the original sources. If data were initially extracted by the authors of a publication, then a single reviewer (other than the person(s) who originally extracted the data) can perform the check. For datasets with less than 20 entries, all entries should be checked. For larger datasets a minimum of 20 entries or 20% of the entries should be checked, whichever is greater.

When data are digitized from a published figure, a preferred method of validation is to plot the data in Excel using identical axis types and scaling (e.g., linear vs. log scales) and a transparent background for the plot. This generated plot can then be placed on top of an image of the plot taken from the original publication. The two overlain images can be stretched or compressed to give exact alignment of the axes, and smaller symbol sizes or alternate colors can be used in the Excel-generated plot to provide contrast. It can be seen that the reproduced plot points closely match those in digital image (to within a few percent precision). If the initial extractor creates such a plot, then a reviewer only needs to visually examine the plot and check that the data values in the spreadsheet cells used by the plot match the values in files read or otherwise used for the model – the reviewer does not need to re-create the plot to check its accuracy.

B2: Review, Verification, and Validation of Existing Computational PBPK/PK Models

Section B2 reviews the pharmacokinetic model structure to ensure an accurate mathematical description of the underlying biology. The PK model review in Section B2 includes equation review, calibrated parameter replication, and model fitting replication to ensure results are consistent across the entire modeling process.

B2.1: General Approach for Model Evaluation

Criteria for judging the quality of a model provided here are separated into two categories: scientific and technical, which are respectively described in "Section B2.2: Model Structure and Documentation (Criteria A)" and in "Section B2.3: PBPK/PK Model In-Depth Technical Evaluation (Criteria B)." In summary, the scientific criteria (primarily included in Criteria A) focus on whether or not the model structure and equations appropriately represent the biology, chemistry, and other information available for the chemical MOA(s)(or the subset of those being described by a specific model). The scientific criteria can be judged based on the (draft) publication or report that describes the model and does not require evaluation of the computer code. Criteria A also includes preliminary technical criteria, such as the computer code (if obtained from an outside source) and apparent completeness of parameter listing and documentation. The in-depth technical and remaining scientific criteria (Criteria B) focus on the accurate implementation of the conceptual model in the model code and scripts, use of correct or biologically consistent parameters in the model, and reproducibility of model results reported in journal publications and other documents. Any datasets incorporated into the model should be evaluated for quality and documented as described in Section B1: Data Review, Verification, Validation, and Usability.

The data evaluation and selection are described in Section B1.1 Data Evaluation and Selection and their accuracy is described in Section B1.2: Extraction of Quantitative Data and Model Parameters.

While the criteria presented here are in part a component of the current IRIS process, similar scientific criteria have also been successfully applied and are described in greater detail by Chiu et al. (2007), Mclanahan et al. (2012), IPCS (2010), and Clark et al. (2004). This approach stresses: (1) clarity in the documentation of model purpose, structure, and biological characterization; (2) validation of mathematical descriptions, parameter values, and computer implementation; and (3) evaluation of each plausible dose metric. Such transparency and documentation are important for compliance with the Agency's information quality guidelines (U.S. EPA, 2002b).

B2.2: Model Structure and Documentation (Criteria A)

It is assumed here that a journal article, report, or other scientific document describing the model structure, underlying science, and sources or methods for identifying all model parameters is available (need not be a peer-reviewed publication), and that a copy of the corresponding computer code has been obtained, along with permission for its use and subsequent public distribution. For QA evaluation, a brief report is prepared summarizing the key features of the model and its likely utility for use in a risk assessment. For example, one can quickly determine if a PBPK model has been calibrated for oral and/or inhalation exposures, and hence whether it is suitable for specific routes of exposure. This information is important for evaluating the potential applicability of a given PK or PBPK model. For example, if it is thought that a key toxic endpoint results from

metabolism to a reactive metabolite in a target tissue, then a model that doesn't predict that rate (dose metric) is less useful than a model that predicts the rate. The model QA report should evaluate the following criteria, based on the model description in publications or reports.

As mentioned in the introduction, if a computational model (set of code) has previously been subject to a QA review that satisfies the ORD Policies and Procedures, then the QA review of the code to satisfy the Technical Criteria below need not be repeated. This would apply in the case of a general model code or model template where only the parameters need to be evaluated for each implementation. Evaluation of the Scientific Criteria, just below, would still be needed, but that could be conducted quickly if the model structure has already been evaluated for another chemical in the same class. If targeted changes are made in a previously reviewed model, the QA can focus on those changes.

Scientific criteria for mechanism-based models:

- Biological/mechanistic basis for the model is accurate:
  - Model equations are consistent with chemical, physical, or biochemical understanding and biological plausibility.
  - Consistent with mechanisms that significantly impact the process being modeled.
  - Describes critical behavior, such as nonlinear kinetics in a relevant dose range.
  - PK models predict dose-metrics expected to be relevant and to be better correlated with toxicity or risk than applied doses.
  - PK models are applicable for the relevant route(s) of exposure.
- Model should describe existing data reasonably well:
  - Shape: matches curvature or nonlinearity, inflection points, peak concentration time, etc.
  - Quantitative value: model predictions preferably within a factor of 2–3 of the data.
  - Confidence/Credible intervals: If the model presents uncertainty in parameter estimation through Bayesian inference or similar methods, model predictions should also include a prediction envelope with the 90% or 95% intervals shown.
- Validity of chemical-specific hypotheses:
  - Standard PBPK model compartments incorporate a limited number of hypotheses regarding ADME processes that have been tested and shown consistent with multiple datasets, for multiple chemicals, and therefore do not require in-depth consideration.
  - However, hypotheses specific to a particular chemical or chemical class, which are not supported by PBPK or other model type agreement with data for other chemicals, should be evaluated more carefully, in particular when a hypothesis leads to prediction of much lower risk in humans than experimental animals (i.e., corresponding to a human-equivalent dose or concentration that is on the order of 100–fold or more greater than a toxicological point of departure in animals).

        - For example, if it is hypothesized that a specific metabolic pathway operates in an experimental animal species (in a target tissue), making that species (tissue) particularly sensitive, then one should determine if there are ADME data for that metabolite (in the target tissue) in both sensitive and non-sensitive animal species demonstrating dosimetric differences commensurate with sensitivity, and dosimetric data in humans (or human tissues) demonstrating a lack of production.
        - Another example is the hypothesis that reactive metabolites formed in the liver will not have an impact on other tissues. But a moderately reactive metabolite with a half-life of minutes is sufficiently stable to be transported between tissues or cell types within a tissue, even if it is too reactive to measure in tissue samples from in vivo PK studies, so this hypothesis needs careful evaluation.
    - PBPK models which incorporate alternate hypotheses (e.g., some systemic distribution for a metabolite vs. none) may be equally consistent with the ADME data, but lead to very different risk predictions, and the resulting range of uncertainty should be considered.

Technical criteria for mechanism-based models (evaluate if scientific criteria are met):

- Well-documented model code.
- Parameters are clearly identified, including origin/derivation (validated as described in Section B1.2: Extraction of Quantitative Data and Model Parameters).
- Parameters do not vary unpredictably with dose or concentration (e.g., any dose-dependence in absorption constants is predictable across the dose ranges relevant for animal and human modeling).
- For probabilistic human models, evaluate parameter distributions in the model versus full human variability. For example, Bayesian calibration applied to human data taken from only healthy adults, and with physiological parameters representing that group, may not be sufficient to describe the entire population. When specific factors such as a genetic polymorphism are known to impact human variability, an analysis which fails to incorporate them would not be considered sufficient to replace default uncertainty factors. Generally, all segments of the population should be included when evaluating the distribution of the Human Equivalent Dose (HED) or Human Equivalent Concentration (HEC) but limiting the analysis to only the most sensitive group can be considered.
- Sensitivity and uncertainty analysis have been conducted for relevant exposure levels (local sensitivity analysis is sufficient, although global sensitivity analysis is more informative).
    - If a sensitivity analysis was not conducted, then one should be performed as part of the QA evaluation.
    - A sound explanation should be provided when sensitivity of the dose metric to model parameters differs from what is reasonably expected based on experience.

B2.3: PBPK/PK Model In-Depth Technical Evaluation (Criteria B)

The following technical criteria address the computational implementation, including checking the code versus published or implied equations, and attempting to reproduce published figures and tables.

- Model equations and parameters specified in computer code match those published or implied[5] in the peer-reviewed manuscript or report.
- Published figures and tables of model simulations are reproducible to within 10%.
- The most rigorous approach to validating that a particular model implementation accurately represents the mathematical and conceptual model as described in a publication or report (or implied, if not all equations are explicitly listed) is to independently replicate coding of the model; e.g., in a different programming language/environment. Such re-coding, while not necessary for acceptance and application of a model, may also facilitate transparency and communication of the model for internal and external scientific reviewers and other stakeholders and interested parties.
- If errors in the model implementation (equations or parameters) are found and corrected, and the correction or change alters the evaluated model predictions (plots or tables showing model agreement with data) by less than 10% on a linear scale, the error is considered small enough to not invalidate the model or any other parameter value, even if model predictions outside the range of the data change by more than 10%. (If data are currently plotted on a log scale, these can be converted to a linear scale to a linear scale to evaluate the impact of a change).
    - Since model quality is judged by comparing model predictions to data, the impact of an error on model quality is evaluated only by determining the impact in the range of the data. The error is considered *de minimis*, hence acceptable, if the impact in the range of the data is less than 10%.
    - An impact greater than 10% outside the range of any data may indicate uncertainty in model extrapolation to that range but does not alter the evaluation of its technical quality.
- If scientifically justified, a new version of the model equation or parameter may be documented and used in place of a published version (even if errors/corrections in the original version do not result in changes greater than 10%).
- For corrections resulting in changes greater than 10% in the range of the data, or significant changes in model structure (vs. only revising parameters), the revised model should be evaluated as a new model version; key conclusions may be unchanged, but the quality cannot be judged based on results of the previous version.

B2.4: Documentation of Model Evaluation

Documentation of a model evaluation, in particular the technical evaluation (Criteria B) should be generated and saved on a network drive/folder specific to the model being evaluated, as described in section A8.2. A master checklist of items being evaluated (e.g., model parameters, model data, model equations) should be created, to include summaries of the initial evaluation, corrective actions, and final decision with respect to overall model quality or acceptability. For sets of model parameters or data, which can be large in themselves, dependent documents (checklists) can be generated. For example, the master checklist would identify "Model parameters" as one item,

[5] Some publications assume familiarity with the standard forms or equations for PBPK model compartments and may only describe them in the text and provide the associated parameters, without listing the specific equations. In this case the equations are implied.

with a parameter checklist document identified therein. Evaluation of each parameter is then documented in the parameter checklist. Table 4 provides an example template for evaluating model files and equations within those files.

B3: Development of New Models, Significant Revisions of Existing Models, and Other Computational Analyses

While Section B2: Review, Verification, and Validation of Existing Computational PBPK/PK Models specifically addresses the evaluation of existing models, development of new models, significant model revision, and other computational analysis (e.g., estimation of exposure from biomarker levels) should be subject to the same scientific criteria and conducted in a way that satisfies the quality criteria. Specifically:

- Parameters and data should be collected and documented consistent with Section B1.2: Extraction of Quantitative Data and Model Parameters, with a second individual checking the values/extraction for accuracy.
- Complete details of unit conversions and other data manipulations, regressions, and the derivation of any non-ty*pic*al model equations should be provided, with algebraic calculations embedded in Excel worksheets (using formulas) or in scripts (with comments).
- Model equations should be described in complete detail in a text document (e.g., a report or appendix), such that a reviewer can ascertain that the equations in the model code represent a correct mathematical translation of the model;
    - comments should be provided within the code and scripts to facilitate review and QA (i.e., describing what lines or sections of code do) and at the top of model scripts to summarize their function;
    - a second individual should check the model code and any accompanying scripts line-by-line to assure that the code matches the text description; or
- An accompanying “readme” file should be created to provide an overview and general directions for users. Instructions in this file should contain sufficient detail such that any person moderately experienced with programming and PBPK modeling can reproduce model results.
- Documentation of the QA evaluation in the form of tables or checklists as described in Section B2.4: Documentation of Model Evaluation, listing all items checked, should be created and stored.

B4: Model Environment Conversion

In order to support transparency and to facilitate external peer and stakeholder review of PBPK models, all such models should be made available in a freely available programming environment, such as R, MCSim, or Octave. If a model is already available in such an environment, then no conversion is required. However, when a model is converted from another environment it is expected that all numerical outputs (e.g., results reported in tables) and graphical outputs (plots) should be matched between versions. Numerical results should match to at least three significant

figures and there should be essentially no observable discrepancy in graphical output, beyond those that result from formatting choices. In the process of checking and assuring this level of consistency between software environments, errors in model equations or parameters may be found. Thus, software environment conversion facilitates QA evaluation. Therefore, it may be desirable to convert a highly influential model to an alternate environment, or independently code the model in the same environment, even when that is not needed for model sharing and review. All files defining the model equations and parameters, and any other scripts for each equivalent model version, should be made available for review and evaluation.

SECTION C: ASSESSMENT AND OVERSIGHT

This section describes quality assessments and other reviews that are conducted to determine whether this QAPP is being implemented as approved.

C1: Assessments and Oversight

The PKWG is responsible for oversight for any ADME evaluation or PBPK modeling task being conducted in support of IRIS Toxicological Reviews. The PKWG provides overarching direction, ideas, and suggestions with respect to PBPK model-specific application features and methodology, although the primary work may be performed by other EPA modelers or contactors. The PKWG also evaluates PBPK model theory and the mathematical formulas used for model calculations and reviews draft documents produced for ADME evaluation or PBPK modelling. With the agreement of CPHEA/CPAD management, the PKWG may also provide guidance, oversight, or direct support for PBPK modeling tasks being conducted by U.S. EPA program offices. The PKWG may also evaluate software platforms and provide feedback on usability, clarity, coding issues, and the correctness of application output, although full validation of large software packages is beyond the scope of this QAPP.

The CPHEA/CPAD Director of QA conducts TSAs on the PBPK task. The Director of QA may inspect electronic files and documents stored by the PKWG Chair(s) and Project Leads on their individual computers or shared network folders for the purpose of implementing this QAPP. Issues are discussed with the responsible individuals following the TSA. The PKWG Chair(s) and Project Leads, with assistance from any PIs or CIs, implement any corrections resulting from the TSA. The CPHEA/CPAD Director of QA monitors implementation.

C2: Reports to the PKWG and Management

Copies of reports and draft documents evaluating ADME/PK studies or other data or describing model development or revision, testing results, findings, and corrective actions developed to support IRIS Toxicological Reviews should be provided to the corresponding PKWG Project Lead and/or Chair(s). While the PKWG may not be providing direct support for a particular

assessment, this communication will help the PKWG fulfill its oversight and review role, and to provide feedback on the materials in a timely manner.

The PKWG Chair(s) or Project Leads provide summary reports on QA reviews to the CPHEA Quantitative Assessment Branch Chief and chemical assessment managers as these are developed or completed. Meetings are held as needed, including other individuals working on the PBPK models and/or QA review, and others in CPHEA/CPAD management as appropriate, to discuss findings and how they will be addressed.

The CPHEA/CPAD Director of QA provides TSA reports to management. The TSA report includes areas of exceptional compliance and areas for improvement. The report also includes proposed corrective actions for findings contained in the report. Any corrective action that is implemented and completed is reported to the chemical manager and others in management by the PKWG Project Lead or Chair(s).

C3: Federal Register Notices (FRNs)

When draft or final model files and supporting documents are being announced in an FRN (i.e., for public comment), the PKWG Project Lead should check and assist with composing the draft FRN to assure accuracy.

C4: Model Reconciliation with Needs and Intended Use

The PKWG Project Lead is responsible for identifying any aspects of a model that does not meet the objectives and criteria listed in this QAPP or the needs of the intended application. The potential strengths and limitations of the model should be communicated clearly. A discussion with management may then occur to determine whether a model should be revised to address the shortcomings or if the model application should be discontinued or adjusted to facilitate the identified weaknesses or limitations.

APPENDIX A

Template Tables for Completing QA of a Model

Table 2. QA review of model parameters from outside source. In this context, <original model> represents previously published model, i.e. "source publication" while <EPA model> represents the EPA model document. Cited publication is the 3rd party citation for the source publication

Model parameter description	EPA model source code symbol	Units	Value from original model source code[a]	Value from original model publication[b]	Value citied in original model publication	Value in EPA model source code[c]	Notes and determination
Body mass	BWinit	g	315 (L26)	315 (T3)	315[†] (T2)	315 (L217)	

[a]Value (line number) in the file "source_parameter_file", which is associated with the publication of <original model>.

[b]Value (table # or page #) in the publication of <original model>.

[c]Value (line number) in the file "EPA_parameter_file" which is associated with the current publication (<EPA model>).

[†]3rd party publication citation.

Table 3. QA review of model parameters generated for new EPA model. Here, <EPA publication> is the EPA document containing the new parameter values

Model parameter description	EPA model source code symbol	Units	Value source	Value in EPA model source code[a]	Notes and determination
SC thickness	TSC	cm	10–50 µm[†] (in text pg. 1,700)	0.003	Median value of range used in current model
Absorption rate	ka	1/s	Maximum Likelihood Estimation	0.21	Determined using MLE methods outlined in <EPA publication>

[a]Value from the current publication (<EPA publication>). It has been verified that this value matches the value reported in Table XX of the current publication (<EPA publication>).

[†]Parameter source for current EPA publication.

Table 4. QA review of files and parameter definitions from model code. For parameter values, "Notes and determination" provided the calculation for that parameter

File or variable	Definition	Notes and determination
File_provided_for_EPA_publicaiton	Script to generate c code from **example.model**	Utilizes *compile_model* function from RMCSim.R.
example.model –model file containing PBPK equations and default parameters		
Initial bloc (for MCSim model files)		
VTDR, VTDO1, VTDO2, VTVR1, VTVR2, VTPL, VTCA, VTPU	Volumes epithelial tissue	Surface area X tissue thickness

APPENDIX B

ADME/PBPK Science Inventory Tables

Tabular presentation of PK and ADME data can provide the reader with a means of rapidly understanding the depth and breadth of available data. Emphasis should be placed on communicating the study design, including in vitro or in vivo, the range of doses and time points studied. Additional information should convey the species, strain and sex of animals studied and the time points evaluated. When available, the identification of parent compound and metabolites should be included. Finally, the conclusions supported by the available evidence should be communicated along with any notable limitations of the study.

Almost all ADME studies provide information that is at least qualitatively useful, and it is rarely the case that there are competing mechanistic hypotheses for ADME. Every chemical undergoes absorption, distribution, and elimination, and most undergo metabolism, so rather than evaluating "evidence" for such processes, we are evaluating how well they can be characterized and quantified. Hence the set of tables which summarizes the available studies for ADME will be referred to as inventory tables.

Because ADME studies vary quite widely in study design and details, a somewhat simple but flexible table structure provides a framework for presenting an overview of the literature. Three somewhat different structures will be used to list key information in the following categories: Animal In-Vivo, Human In-Vivo, and In-Vitro. Examples are given below. Publications describing PK/PBPK models will be listed in the Animal or Human In-Vivo tables, as appropriate. A list of ADME or information that is useful for PBPK modeling follows.

Table 5. Type of ADME information for PBPK modeling

ADME Info Type	Specific Information
Absorption	Bioavailability Absorption rate(s) Uptake rates
	Tissue location of absorption (stomach vs. intestine, nasal vs. lung, etc.) Blood: air partition coefficient (PC) Irritant/respiratory depression
	Overall mass transfer coefficient Gas-phase diffusivity Gas-phase mass transfer coefficient
	Liquid- (or tissue) phase mass transfer coefficient Deposition fraction Retained fractions
	Tissue burdens Computational fluid (airway) dynamics
Distribution	PCs for the target (or surrogate) tissue and all other relevant tissues Storage tissues or tissue components (e.g., blood) and the binding coefficients Transporters (active and passive) Lipophilicity (or other parameters used to estimate the volume of distribution)
Metabolism	Enzymes involved Rate of metabolism; Vmax, Km Potential for inhibition; Ki Metabolic saturation/non-linearities
	Key organs involved in metabolism Key metabolites (if any)/pathways Metabolites measured Species differences in enzyme activity or expression
	Site-specific activation (may be toxicologically significant, but little systemic impact) Induction / inhibition Cofactor (e.g., GSH) depletion
Elimination	Pathway(s) for parent and metabolites; urine, fecal, exhalation, hair, etc. Rate(s) Mechanism(s)
Other	Time course data for various routes Influence of dose level Species/strain, BW, number, gender, age, etc.
	Measurements: what is measured (parent/metabolite), method of analysis, and limits of detection/quantification. Determination of study quality (to inform the use of data and substitute info if necessary--standard body weights, infusion rates, etc.) Alterations in any of the ADME due to chemical speciation, chemical formulation, subject age, health status, etc.
	Exposure levels Exposure regimen (e.g., # h/d; d/w) Enterohepatic circulation Particle diameter and distribution

Example of ADME Inventory Tables

Table 6. Animal In-Vivo ADME inventory tables

Bragt, PC, van Dura, EA. (1983) Toxicokinetics of hexavalent chromium in the rat after intratracheal administration of chromates of different solubilities. Ann Occup Hyg, 27:315-22.			
Animals	Rat, Wistar, male, 165–200 g		
Route	Oral (intratracheal)	Duration	Single dose; body/tissues to d 51; urine/feces to d 10
Analyte(s)	Gamma radioactivity (total chromium)	Matrices	Urine, feces, blood, heart, lungs, spleen, kidneys, liver, pancreas, testes, bone marrow (femur)
Exposure	Water solutions containing 0.4-6.0 uCi ^{51}Cr; 20 µL given Sodium chromate: 69 ug Cr; zinc chromate: 66 ug Cr; lead chromate: 38 µg Cr		
Notes	"Numerical analysis of the whole-body chromium elimination was performed by assuming a two-compartment open kinetic model." Biphasic elimination; half lives depend on chemical form. Sodium chromate doses of 280 and 1,120 µg Cr had same distribution and excretion of chromium, as percentages of the dose given, at 24 h (data not shown).		
Thomann RV, Snyder CA, Squibb KS. (1994). Development of a pharmacokinetic model for chromium in the rat following subchronic exposure. I. The importance of incorporating long-term storage compartment. Toxicol Appl Pharmacol 128:189-198.			
Animals	Rat, F-344, male, 200g (8 weeks at exposure initiation)		
Route	Oral (drinking water)	Duration	Exposed 6 wks, 12 & 20 wks post exposure obs
Analyte(s)	Total chromium*	Matrices	Blood, liver, kidney, spleen, bone & total carcass**
Exposure	100 ppm Cr (VI) as potassium chromate in drinking water		
Notes	*by atomic absorption **12-week study: blood, liver, kidney, spleen at 1, 3, 6 wks of exposure and postexposure at 6 & 24 h, 3, 5 & 7 d, and weekly at wks 2-12. **20–week study: as above plus bone and total carcass. Sampled twice weekly to wk 11, then weekly through wk 20. **PK Model:** Three compartments: blood input to compartment A (lumped liver, kidney, spleen) and compartment B (storage in bone, carcass). Blood Cr reached LOD at 35 d post exposure. Authors estimate a time to steady state of 200 d. Model structure and equations given; model calibrated to this original data, but not validated against other data. Graphic presentation of al data, e.g., time-dependent Cr accumulation to 6 wks with level highest in kidney > spleen > liver > blood		
Cavalleri, A, Minoia, C, Richelm, P, Baldi, C, Micoli, G. (1985) Determination of total and hexavalent chromium in bile after intravenous administration of potassium dichromate in rats. Environ Res 37:490-6.			
Animals	Rat, Wistar, male, 2–240 g		
Route	Intravenous	Duration	Single dose; 2 hr (samples at 15 min intervals)
Analyte(s)	Total Cr; Cr (VI)	Matrices	Bile, whole blood, plasma
Exposure	Intravenous, potassium dichromate: 0, 0.5, and 1 mg Cr		
Notes	• Peak in total biliary Cr at 30 min (2nd time point). For Cr (VI) peak was at first time point, only 2% of total Cr at highest (1 mg) dose. Declines rapidly to 1%, then more slowly. After 2 h total Cr excreted in bile was 1.4–2.2% of the dose, Cr (VI) ~ 0.01%. • Minimal reduction of Cr (VI) found to occur in rat bile ex vivo: 13% in 60 min. • In whole rat blood (in vivo) 94% of Cr (VI) was reduced in 1 min, 98% in 5 min. In plasma (in vivo) 98% was reduced in 1 min, 99.5% in 5 min.		
National Toxicology Program (NTP). (2008) NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate in F344/N Rats and B6C3F$_1$ Mice (Drinking Water Studies). Toxicity Report Series Number 546, NIH Publication No. 08-5887.			
Animals	Rat, F344/N, male, 10/group, 6 wks–1 yr Mouse, B6C3F$_1$, female, 10/group, 6 wks–1 yr		
Route	Oral (drinking water)	Duration	4, 11, 180, and 369 d + 2 d wash-out (all times)

Analyte(s)	Total chromium	Matrices	Urine, feces, erythrocytes, plasma, liver, kidney, glandular stomach, and forestomach
Exposure	Water concentrations (mg = $Na_2Cr_2O_7 \bullet 2H_2O$ unless "Cr") (estimated dose rates) Male rat: 0, 14.3, 57.3, 172, or 516 mg/L (= 0, 5, 20, 60, or 180 mg/L Cr; ~ 0.6, 2.2, 6, or 17 mg/kg BW/d) Female rat*:* (same concentrations as males; ~ 0.7, 2.7, 7, or 20 mg/kg/d) Male mouse: 0, 14.3, 28.6, 85.7, or 257.4 mg/L (= 0, 5, 10, 30, or 90 mg/L Cr; ~ 1.1, 2.6, 7, or 17 mg/kg/d) Female mouse: 0, 14.3, 57.3, 172, or 516 mg/L (~ 1.1, 3.9, 9, or 25 mg/kg/d)		
Notes	Water ingestion measured à estimated dose rate 2-day wash-out limit's utility		
National Toxicology Program (NTP). (2007) NTP Technical Report on the Toxicity Studies of Sodium Dichromate Dihydrate Administered in Drinking Water to Male and Female F344/N Rats and $B6C3F_1$ Mice and Male BALB/c and am3-C57BL/6 Mice. Toxicity Report Series Number 72, NIH Publication No. 07-5964.			
Animals	Rat, F344/N, male, 4/group, 6–10 wks Mouse, $B6C3F_1$, male, 4/group, 6–10 wks Guinea pig, Hartley, male, 4/group, 6–10 wks		
Route	Oral (drinking water)	Duration	21 d + 2 d wash-out
Analyte(s)	Total chromium	Matrices	Blood, kidney, and rat femur
Exposure	Concentrations: 0, 2.87, 8.62, 28.7, 86.2, 287, or 862 mg/L sodium dichromate dihydrate (= 0, 1,3,10, 30, 100, or 300 mg/L chromium)		
Notes	Water ingestion not measured / dose rate not estimated 2-day wash-out limit's utility		

Table 7. Human In-Vivo ADME inventory table

Kerger BD, Paustenbach DJ, Corbett GE, and Finley BL. (1996) Absorption and Elimination of Trivalent and Hexavalent Chromium in Humans Following Ingestion of a Bolus Dose in Drinking Water. Toxicol Appl Pharmacol, 141:145-58			
Subjects	7 male volunteers aged 21–66 yrs; 1 female volunteer aged 28 yrs		
Route	Oral (drinking water)	Duration	2 wks
Analyte(s)	Total chromium	Matrices	Urine, plasma, and RBC
Exposure	Drink Cr in 0.5 L drinking solution in 2 min -5 mg Cr (III) [chromic chloride] in 0.5 L DW; (n = 4) -5 mg reduced Cr (III)-OJ [potassium dichromate] in 0.5 L orange juice (OJ); (n = 4) -5 mg Cr (VI) [potassium dichromate] in 0.5 L DW; (n = 4)		
Notes	• Bioavailability (% of oral absorption) was Cr (VI) > Cr (III)-OJ > Cr (III) (6.9%, 0.6%, 0.13%) • Urinary excretion t½ was Cr (VI) > reduced Cr (III)-OJ > Cr (III) [39 h, 17 h, 10 h) • The magnitude and duration of elevations of chromium in plasma and RBC were Cr (VI) > reduced Cr (III)-OJ > Cr (III)		
Kerger BD, Finley BL, Corbett GE, Dodge DG and Paustenbach DJ. (1997) Ingestion of chromium (VI) in drinking water by human volunteers: absorption, distribution, and excretion of single and repeated doses. J Toxicol Environ Health, 50:67-95			
Subjects	5 male volunteers aged 30-44		
Route	Oral (drinking water)	Duration	Single-Dose: 2 wks; Multi-Dose: 3 wks
Analyte(s)	Clinical (see notes)	Matrices	Urine, plasma, and RBC
Exposure	Drinking solution: Cr (VI) [potassium dichromate ($K_2Cr_2O_7$) or potassium chromate (K_2CrO_4)] in DW -Single-Dose: 5 mg Cr (VI)/0.5 L, drinking in 2 min (n = 4) -Multi-Dose: 5 mg Cr(VI)/L, drinking 333 mL/time, 3 time/day, for 3 d; after 2-3 day intermission, then 10 mg Cr(VI)/L, 333 mL/time, 3 time/day, for 3 d (n = 3)		

Notes	• After a single bolus dose, the average t½ of urinary chromium excretion was 39 h, and the excretion pattern was fairly consistent among the volunteers. • 4-d total urinary chromium excretion and peak concentrations in urine and blood varied considerably among 5 volunteers. • Chromium uptake/excretion was slower in the subjects took multi-doses than those took a single bolus dose. • >99.7% of Ingested Cr (VI) was reduced to Cr (III) before entering the blood stream.		
Finley, BL, Scott, PK, Norton, RL Gargas, ML and Paustenbach, DJ. (1997) Urinary chromium concentrations in humans following ingestion of safe doses of hexavalent and trivalent chromium: Implications for biomonitoring, J Toxicology Environ Health, 48:479-99			
Subjects	4 males, 2 females, aged 25–39		
Route	Oral (capsules)	Duration	18 d
Analyte(s)	Total chromium	Matrices	Urine
Exposure	Given via capsules using the following regime: d 1–7, 200 µg/d chromium picolinate; d 8–10, Cr (VI) ingestion at EPA reference dose of 0.005 mg/kg/d; d 11–13, no dose period; d 14–16, Cr (III) ingestion at the EPA reference dose of 1 mg/kg/d; and d 17–18, post-dose period.		
Notes	Urine was analyzed for total chromium using graphite furnace atomic absorption spectroscopy with Zeeman background correction.		
Finley, BL, Kerger, BD, Katona, MW, Gargas, ML and Paustenbach, DJ (1997) Human ingestion of chromium (VI) in drinking water: pharmacokinetics following repeated exposure, Toxicol Appl Pharmacol, 142:151-9			
Subjects	5 white male participants, aged 30–54		
Route	Oral (solution)	Duration	4 d per dose
Analyte(s)	Total chromium; clinical observations	Matrices	Blood, urine
Exposure	• Oral [drinking solution] – Cr (VI) [potassium chromate ($K_2Cr_2O_7$) in deionized water. Multiple doses were ingested 5 different concentrations over the duration of the study (0.1, 0.5, 1.0, 5.0 and 10.0 mg Cr (VI)/L). One liter of each was consumed so that the ingested daily doses were 100, 500, 1,000, 5,000 and 10,000 µg Cr (VI)/day, respectively. • Each dose was ingested for 3 consecutive d. A no-dosing period of at least 1 day was observed between consumption of the different concentrations		
Notes	• Blood and red blood cells were also collected and analyzed for chromium. • Urine voids were collected starting from day 1 (beginning with the first morning void) through the last day of study (including the last void before bedtime) and analyzed for chromium. • Clinical tests were done to screen for significant alterations in hematology, blood chemistries or urinalysis that might have been due to Cr (VI) ingestion.		
Kirman CR, Aylward, LL, Suh M, Harris MA, Thompson CM, Haws LC, Proctor DM, Lin SS, Parker W, Hays SM. (2013) Physiologically based pharmacokinetic model for humans orally exposed to chromium. Chem Biol Interact 204:13–27.			
Subjects	Human TK data from literature; multiple studies		
Route	Oral	Duration	Single dose to 12 wks exposures; some 90-d data
Analyte(s)	Cr (VII), Cr (III)	Matrices	Blood, plasma, urine, stomach contents
Exposure	Multiple; TK data from previously published studies		
Notes	**PBPK model:** Report described development of human PBPK model based on previously published human plasma, RBC and urine data. Kirman et al determined Cr (VI) to Cr (III) reduction kinetics in human stomach contents ex vivo (this report). Authors calculated second order rate constant for reduction of Cr (VI) to Cr (III), k, of 44.5 L/mg /h. Model coded in ACSL with excel interface. Model validated against separate human TK dataset; sensitivity analysis presented.		

Table 8. In-Vitro ADME inventory table

Proctor DM, Suh M, Aylward, LL, Kirman CR, Harris MA, Thompson CM, Gurlyuk H, Gerads R, Haws LC, Hays SM. (2012) Hexavalent chromium reduction kinetics in rodent stomach contents. Chemosphere, 89:487-93.	
Species	Adult female B6C3F$_1$ mice and F344 rats
System(s)	Gastric juice: stomach contents from untreated, ad libitum-fed rats and mice, early morning sacrifice time
Exposure	Initial concentrations: 1–400 mg/L (mice) & 1–144 mg/L (rats) Cr (VI) as sodium dichromate dehydrate (C(VI)), incubated 16 s to 1 h
Analyte(s)	Disappearance of Cr (VI) and appearance of Cr (III).
Notes	Authors calculated second order rate constant for reduction of Cr(VI) to Cr(III), k, for rats of 0.3 L /mg/h and 0.2 L/mg/h, and concluded that at DW concentrations above 21 mg/L for mice and above 60 mg/L for rats, reduction capacity was saturated in rodents. First order model failed, used a mixed second-order model to estimate kinetics. Authors estimate 16 mg Cr (VI) reducing capacity per animal in rats and mice.
De Flora S, Camoirana A, Bagnasco M, et al. (1997) Estimates of the chromium (VI) reducing capacity in human body compartments as a mechanism for attenuating its potential toxicity and carcinogenicity. Carcinogenesis, 18:531–7	
Species	Human
System(s)	• Heparinized venous blood: Cr (VI) sequestering capacity • Intestinal bacteria: Cr (VI) sequestering capacity. • RBC lysates & liver homogenates (with NADPH generating system): reducing ability.
Exposure	Varying amounts of sodium dichromate, dissolved in PBS, pH 7.4, at 0.625, 1.25, 2.5, 3.75, 5.0, 7.5 or 10 µg Cr(VI) equivalents per vial (50 µL), were mixed either with liver homogenates (6.25, 12.5, 25, or 50 µL per vial), RBC lysate soluble fractions (6.25, 12.5, 25, or 50 µL per vial), whole blood (100 µL per vial), concentrated intestinal bacteria (100 µL per vial), or equivalent volume of their diluting solvents.
Analyte(s)	Cr (VI)
Notes	An NADPH generating system (S9 mix) was added to liver homogenates and RBC lysates. After 60 min of gentle mixing at 37°C, the mixtures were evaluated for the amount of residual Cr (VI), both by using the colorimetric method by s-diphenylcarbazide and/or by assessing mutagenicity in strains and TA102 of *Salmonella typhimurium* (13). Due to the turbidity of mixtures, the mutagenicity test system, used as a 'biological spectrophotometer," was applied in the case of liver homogenates and RBC lysates. The amounts of residual Cr(VI), and consequently the amounts of reduced or sequestered Cr(VI) was eliminated daily with sequestered Cr(VI), were calculated from the regression lines relating the fecal bacteria initial amounts of Cr(VI) to the loss either of colorimetric reactivity or mutagenic activity.

Gammelgaard B, Jensen K, Steffansen B. (1999) In vitro metabolism and permeation studies in rat jejunum: Organic chromium compared to inorganic chromium. J Trace Elements Med Biol, 13:82-8.	
Species	Rat/Sprague-Dawley/F, 22–24 wks
System(s)	• Artificial gastric juice, pH 1.2 • Everted gut sac permeation model – rat small intestines
Exposure	• Artificial gastric juice - Initial concentration of 100 µg/L of potassium dichromate or chromium picolinate, at 37°C for 4 h (n = 4–6) • Everted gut sac permeation model - Initial concentration of 500 µg/L of chromium chloride, chromium nitrate, or chromium picolinate, incubated at 37°C for 120 min with rat intestine segments (n = 6)
Analyte(s)	Cr (III) and Cr (VI)
Notes	• For everted gut sac, sampling was from surrounding solution • In artificial gastric juice: Cr (VI) [potassium dichromate] was reduced followed first-order kinetics; t½ = 23 min; Cr (III) [chromium picolinate] was stable for 4 h • For everted gut sac with chromium chloride, chromium nitrate, or chromium picolinate: the permeability coefficient was 0.7 ± 0.3, 1.0 ± 0.4, or 9.6 ± 2.2 µm/min the penetration was 165 ± 59, 160 ± 26, or 127 ± 36 ng total Cr/g rat jejunum

APPENDIX C

Publications and Reports Addressing the Quality, Reporting, and Application of PBPK Models in Regulatory Settings

Chiu et al. (2007) (Evaluation of physiologically based pharmacokinetic models for use in risk assessment)

Clark et al. (2004) (Framework for evaluation of physiologically based pharmacokinetic models for use in safety or risk assessment)

Dewoskin et al. (2001) (Improving the Development and Use of Biologically Based Dose Response Models (BBDR) in Risk Assessment)

Mclanahan et al. (2012) (Physiologically Based Pharmacokinetic Model Use in Risk Assessment—Why Being Published Is Not Enough)

Tan et al. (2020) (PBPK model reporting template for chemical risk assessment applications)

IPCS (2010) (Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment)

REVISION HISTORY

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0	December 2020	New document released in 2020; supersedes pre-organization PBPK Umbrella QAPP

REFERENCES

Brown, RP; Delp, MD; Lindstedt, SL; Rhomberg, LR; Beliles, RP. (1997). Physiological parameter values for physiologically based pharmacokinetic models. Toxicol Ind Health 13: 407-484. http://dx.doi.org/10.1177/074823379701300401

Chiu, WA; Barton, HA; Dewoskin, RS; Schlosser, P; Thompson, CM; Sonawane, B; Lipscomb, JC; Krishnan, K. (2007). Evaluation of physiologically based pharmacokinetic models for use in risk assessment [Review]. J Appl Toxicol 27: 218-237. http://dx.doi.org/10.1002/jat.1225

Clark, LH; Setzer, RW; Barton, HA. (2004). Framework for evaluation of physiologically-based pharmacokinetic models for use in safety or risk assessment. Risk Anal 24: 1697-1717. http://dx.doi.org/10.1111/j.0272-4332.2004.00561.x

Dewoskin, RS; Barone, S, Jr; Clewell, HJ; Setzer, RW. (2001). Improving the development and use of biologically based dose response models (BBDR) in risk assessment. Hum Ecol Risk Assess 7: 1091 - 1120. http://dx.doi.org/10.1080/20018091094871

ILSI (International Life Sciences Institute). (1994). Physiological parameter values for PBPK models. Washington, DC: U.S. Environmental Protection Agency.

IPCS (International Programme on Chemical Safety). (2010). Characterization and application of physiologically based pharmacokinetic models in risk assessment. (Harmonization Project Document No 9). Geneva, Switzerland: World Health Organization. http://www.inchem.org/documents/harmproj/harmproj/harmproj9.pdf

Krishnan, K; Andersen, ME. (1994). Physiologically based pharmacokinetic modeling in toxicology. In AW Hayes (Ed.), Principles and Methods of Toxicology (3rd ed., pp. 149-188). New York: Raven Press, Ltd.

Mclanahan, ED; El-Masri, HA; Sweeney, LM; Kopylev, LY; Clewell, HJ; Wambaugh, JF; Schlosser, PM. (2012). Physiologically based pharmacokinetic model use in risk assessment--Why being published is not enough. Toxicol Sci 126: 5-15. http://dx.doi.org/10.1093/toxsci/kfr295

Pearce, RG; Setzer, RW; Strope, CL; Sipes, NS; Wambaugh, JF. (2017). Httk: R package for high-throughput toxicokinetics. J Stat Softw 79: 1-26. http://dx.doi.org/10.18637/jss.v079.i04

Tan, YM; Chan, M; Chukwudebe, A; Domoradzki, J; Fisher, J; Hack, CE; Hinderliter, P; Hirasawa, K; Leonard, J; Lumen, A; Paini, A; Qian, H; Ruiz, P; Wambaugh, J; Zhang, F; Embry, M. (2020). PBPK model reporting template for chemical risk assessment applications [Review]. Regul Toxicol Pharmacol 115: 104691. http://dx.doi.org/10.1016/j.yrtph.2020.104691

U.S. EPA (U.S. Environmental Protection Agency). (2002a). Guidance for quality assurance project plans. (240R02009). http://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=20011HPE.txt

U.S. EPA (U.S. Environmental Protection Agency). (2002b). Guidelines for ensuring and maximizing the quality, objectivity, utility, and integrity of information disseminated by the Environmental Protection Agency. (EPA/260/R-02/008). Washington, DC: U.S. Environmental Protection Agency, Office of Environmental Information. https://www.epa.gov/sites/production/files/2017-03/documents/epa-info-quality-guidelines.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2006). Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment (Final Report) [EPA Report] (pp. 1-123). (EPA/600/R-05/043F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668