QAPP AMENDMENT FORM

EFFECTIVE DATE: 1-22-14

QAPP Title Quality Assurance Project Plan for Toxicity Assessment for the EPA's *Study of the Potential Impacts of Hydraulic Fracturing (HF) on Drinking Water Resources*
April 2013

AMENDMENT #1

This amendment revises the Project Description and Objectives and the Quality Objectives and Criteria for the reference value and Quantitative Structure Activity Relationship (QSAR) tasks.

1. The list of toxicity reference value data sources now includes qualitative sources, as well as several sources that are not considered "authoritative" for completeness. These new sources are:
    a. US National Toxicology Program Report on Carcinogens (RoC)
    b. International Agency for Research on Cancer (IARC)
    c. American Conference on Governmental Industrial Hygienists
    d. European Chemicals Bureau, Classification and Labeling Annex I of Directive 67/548/EEC
    e. Toxicology Excellent for Risk Assessment's International Toxicity Estimates for Risk Assessment (ITER)
2. Criteria for evaluating the reference value data sources was generated and follows in Appendix 1-1 (attached)
3. TOPKAT developmental toxicity, mutagen, and cancer qualitative results are now being used from the TOPKAT analysis, in addition to the rat chronic LOAEL
4. Criteria for evaluating the TOPKAT results was generated and follows in Appendix 1-2 (attached)
5. Spearman rank correlation will be used to establish how similar the chemical hazard ranking based on the TOPKAT rat chronic LOAEL compares to the hazard ranking based on the IRIS RfD. We will calculate the probability of finding that level of rank correlation, or larger, due to chance using permutation testing.
6. Jaccard's index (this is a measure of agreement) will be used to establish how similar the TOPKAT cancer prediction is to the known or probable human carcinogens (IARC and RoC) or the chemicals where insufficient information exists (IARC) or the chemicals that are known to not be carcinogens (IARC only). We will use permutation testing to identify the probability of finding a Jaccard's index of that level or larger due to chance.

Reason for Amendment:

The QAPP is being amended in response to comments received from Jeanne Briskin following review of our manuscript that resulted from the worked covered by the QAPP, and as a result of the identification of additional values from TOPKAT that we felt would be useful in our analysis. Jeanne specifically requested in a phone call on January 6, 2014 that we consider including additional values, especially qualitative values such as those from IARC, in our analysis. On January 4, 2014, Jeanne also forwarded the URL for a website run by the Environmental Working Group that included additional data sources. We chose additional new sources based on our knowledge of existing reference values, and included some sources that EWG reports to use in their products for completeness.

Sections of QAPP Affected:

Section A6. Project Description and Objectives
Section A7. Quality Objectives and Criteria

Date Implemented:

January 22, 2014

Approvals:

/s/	**1/22/2014**
Lyle D. Burgoon, Ph.D., NCEA HF Project Lead	Date
/s/	**1/22/2014**
Cheryl Itkin, NCEA HF QA Manager	Date
/s/	**1/22/2014**
Reeder Sams, NCEA-RTP Acting Deputy Director, NCEA-RTP	Date
/s/	**1/22/2014**
John Vandenberg, NCEA-RTP Division Director, NCEA-RTP	Date

Appendix 1-1:

Criteria for Inclusion of Hazard Data Sources

The criteria listed below were used to evaluate the quality of the information considered for use in the hazard analyses in support of the hydraulic fracturing research plan. Only data sources that meet these criteria were considered of sufficient quality to be included in the analyses.

1) The following criteria must be met for a source to be deemed of sufficient quality:
    a. The body or organization generating or producing the peer reviewed reference revalues or peer reviewed qualitative assessment must be a governmental or intergovernmental body.
        i. Governmental bodies include sovereign states, and federated states/units.
        ii. Intergovernmental bodies are those whose members are sovereign states, and the subdivisions or agencies of such intergovernmental bodies. The United Nations is an example of an intergovernmental body. The International Agency for Research on Cancer (IARC) is an agency of the World Health Organization, which is itself an agency of the United Nations. Thus, IARC is considered a subdivision of the United Nations.
    b. The data source must include peer reviewed reference values or peer reviewed qualitative assessments.
        i. A committee that is established to derive the reference values or qualitative assessment can have members of that same committee provide the peer review, so long as either the entire committee, or members of the committee that did not participate in the derivation of a specific section of a work product, conduct the review.
        ii. Peer reviewers who work for grantees of the organization deriving the reference values or qualitative assessments are generally allowed, and this will not be considered to constitute a conflict/duality of interest.
        iii. Peer reviewers may work in the same or different office, so long as they did not participate in any way in the development of the product, and these individuals must be free of conflicts/duality of interest with respect to the chemical(s) assigned.
            1. For instance, peer reviewers for Program X, conducted by Office A, may also be employed by Office A so long as they did not participate in the creation of the Program X product they are reviewing.
    c. The reference values or qualitative assessments must be based on peer reviewed scientific data.
        i. There are cases where industry reports that were not published in a peer-reviewed, scholarly journal may be used, if the industry report has been adequately peer-reviewed by an external body (external to the group generating the report, and external to the group generating the peer-

reviewed reference values or peer-reviewed qualitative assessment) that is free of conflicts/dualities of interest.

d. The reference values or qualitative assessments must be focused on protection of the general public.
    i. Sources that are focused on workers are not appropriate as workers are assumed to accommodate additional risk than the general public due to their status as workers.
e. The body generating the values or qualitative assessments must be free of conflicts of interest with respect to the chemicals it derives reference values or qualitative assessments.
    i. If a body generating the reference values or qualitative assessments accepts funding from an interested party (i.e., a company or organization that may be impacted by past, present, or future values or qualitative assessments), then the body has a conflict of interest.
    ii. For instance, if a non-profit organization is funded by an industry trade group, and the non-profit generates reference values or qualitative assessments for chemicals that trade group is interested in, then the non-profit will have a conflict of interest with respect to those chemicals.
    iii. Having a conflict/duality of interest for one chemical is sufficient to disqualify the entire database, as it is assumed that conflicts/dualities of interest may exist for other chemicals as well.

Appendix 1-2

Confidence Analysis. The TOPKAT software generates several measures which we have used to determine our confidence in each QSAR model prediction. As described below, we assigned a value to each metric, and sum these values to create a composite score. We assign high confidence to predictions with composite scores that are within 80% of the maximum. Medium confidence and low confidence are assigned when composite scores are greater than or less than 55%, respectively. The five TOPKAT metrics that we analyze are: prediction probability, optimum prediction space (OPS) score, number of unknown fragments, the Mahalanobis p-value (for the cancer weight of evidence, Ames mutagenicity, and developmental toxicity models only), and for the LOAEL, the estimated rat oral LD_{50} value (which should be higher than the LOAEL value). These measures are described below:

- Model prediction probability is a measure of the probability that the chemical is positive for a qualitative classification (e.g., carcinogen, mutagen, developmental toxicant). We have higher confidence in predictions that a chemical is a carcinogen, mutagen, or developmental toxicant when the prediction probability is between 80-100% and assign these cases a score of 2. Probabilities of 70-80% are assigned a score of 1, and probabilities less than 70% are assigned a score of 0.

- The OPS score is used to encode TOPKAT's certainty that a chemical is within the chemical space of the model's training set of chemicals based on the fingerprints (i.e., chemical substructures). We assign a value of 2 when the chemical is within the OPS, a value of 1 when the chemical is within the OPS with the exception of a marginal value, and a value of 0 when the chemical is likely outside of the OPS.

- Unknown fragments are those which are not represented within the model's training set. Unknown fragments may alter the biological activity in unknown ways. Thus, we have the most confidence (assign a score of 2) when a chemical has 0 unknown fragments, less with 1 unknown fragment (assign a score of 1), and little confidence when more than 1 unknown fragment exists (assign a score of 0).

- The Mahalanobis p-value for carcinogens, mutagens, and developmental toxicants represents the distance from the center of the chemical structure universe in the training set compared to the current chemical's structure. Smaller p-values represent a larger likelihood that the chemical structure is significantly different from the chemical universe used to train the model. Thus, we have the least confidence in p-values between 0 and 10% (score of 0), medium confidence (score of 1) for p-values between 10-90%, and high confidence when p-values range from 90-100% (score of 2).

Quality Assurance Project Plan (QAPP) for

Toxicity Assessment for the
EPA's *Study of the Potential Impacts of Hydraulic Fracturing (HF) on Drinking Water Resources*

A. PROJECT MANAGEMENT

This section addresses project management, including project background and purpose, roles and responsibilities, and key research questions and objectives.

A1. TITLE AND APPROVAL SHEET

QA Category: 1

Date QAPP submitted: April 10, 2013.
Number of Pages: 15 pp
Revision No: 0

Signatures indicate approval of this Quality Assurance Project Plan and commitment to follow the applicable procedures noted.

_____/s/_____ 4/10/2013
Lyle D. Burgoon, Ph.D., NCEA HF Project Lead Date

_____/s/_____ 5/15/2013
Cheryl Itkin, NCEA HF QA Manager Date

_____/s/_____ 5/7/2013
Reeder Sams, NCEA-RTP Acting Deputy Director, NCEA-RTP Date

_____/s/_____ 5/7/2013
John Vandenberg, NCEA-RTP Division Director, NCEA-RTP Date

Disclaimer

EPA does not consider this internal planning document an official Agency dissemination of information under the Agency's Information Quality Guidelines, because it is not being used to formulate or support a regulation or guidance; or to represent a final Agency decision or position. This planning document describes the overall quality assurance approach that will be used during the research study. Mention of trade names or commercial products in this planning document does not constitute endorsement or recommendation for use.

The EPA Quality System and the HF Research Study

EPA requires that all data collected for the characterization of environmental processes and conditions are of the appropriate type and quality for their intended use. This is accomplished through an Agency-wide quality system for environmental data. Components of the EPA quality system can be found at http://www.epa.gov/quality/. EPA policy is based on the national consensus standard ANSI/ASQ E4-2004 *Quality Systems for Environmental Data and Technology Programs: Requirements with Guidance for Use*. This standard recommends a tiered approach that includes the development and use of Quality Management Plans (QMPs). The organizational units in EPA that generate and/or use environmental data are required to have Agency-approved QMPs. Programmatic QMPs are also written when program managers and their QA staff decide a program is of sufficient complexity to benefit from a QMP, as was done for the study of the potential impacts of hydraulic fracturing (HF) on drinking water resources. The HF QMP describes the program's organizational structure, defines and assigns quality assurance (QA) and quality control (QC) responsibilities, and describes the processes and procedures used to plan, implement and assess the effectiveness of the quality system. The HF QMP is then supported by project-specific QA project plans (QAPPs). The QAPPs provide the technical details and associated QA/QC procedures for the research projects that address questions posed by EPA about the HF water cycle and as described in the *Plan to Study the Potential Impacts of Hydraulic Fracturing on Drinking Water Resources* (EPA/600/R-11/122/November 2011/www.epa.gov/hydraulic fracturing). The results of the research projects will provide the foundation for EPA's 2014 study report.

This QAPP provides information concerning the Toxicity Assessment of the HF water cycle as found in Figure 1 of the HF QMP and as described in the HF Study Plan. Appendix A of the HF QMP includes the links between the HF Study Plan questions and those QAPPs available at the time the HF QMP was published.

The needs and capabilities for the HF toxicity work have changed; therefore, there is no need to fulfill the original toxicity QAPPs. This QAPP replaces all previous HF toxicity QAPPs (QAPP-NCEA-IO-HFS-HTT/2012/02-r00), generated by NCEA. The toxicity work NCEA is doing for the HF study has changed to the work described in this document.

A2. TABLE OF CONTENTS

LIST OF ACRONYMS

ANSI	American National Standards Institute
ASQC	American Society for Quality Control
DQA	Director of Quality Assurance
EPA	Environmental Protection Agency
HFS	Hydraulic Fracturing Study
LOAEL	Lowest observed adverse effect limit
NCEA	National Center for Environmental Assessment
NCCT	National Center for Computational Toxicology
OP	Operating Procedure
ORD	Office of Research and Development
OSIM	Office of Science Information Management
PPRTV	Provisional Peer-Reviewed Toxicity Value
QA	Quality Assurance
QAM	Quality Assurance Manager
QAPP	Quality Assurance Project Plan
QC	Quality Control
QMP	Quality Management Plan
RTP	Research Triangle Park
SSWR	Safe and Sustainable Water Resources
TSA	Technical Systems Audit
US EPA	United States Environmental Protection Agency

A3. DISTRIBUTION LIST

This QAPP will be distributed to the US EPA employees/Toxicity Assessment staff, their management, and the HF Study Coordinator listed in Table 1.

Table 1. QAPP distribution list.

Name	Role in Synthesis Report	Organization	Contact Information
Jeanne Briskin	HF Study Coordinator	ORD/OSP	briskin.jeanne@epa.gov (202) 564-4583
Lyle Burgoon	HF Study Lead, NCEA	ORD/NCEA	Burgoon.lyle@epa.gov (919) 541-7808
Keith Houck	HF Study Co-Lead	ORD/NCCT	Houck.keith@epa.gov
Cheryl Itkin	HF QA Manager, NCEA	ORD/NCEA	Itkin.Cheryl@epa.gov (703) 347-8557
Vicki Soto	HF QA Manager (alternate), NCEA	ORD/NCEA	Soto.Vicki@epa.gov (703) 347-0290
Lora Johnson	Director of QA, ORD	ORD/OSIM	Johnson.Lora@epa.gov (513) 569-7299
Michelle Henderson	HF Program QA Manager (PQAM)	ORD/NERL	Henderson.Michelle@epa.gov (513) 569-7353
Stephen Little	HF QA Manager, NCCT	ORD/NCCT	Little.Stephen@epa.gov (919) 541-0963
Ila Cote	Senior Science Advisor, NCEA	ORD/NCEA	Cote.Ila@epa.gov
Rob Dewoskin	Health & Toxicity Team, NCEA-RTP	ORD/NCEA	Dewoskin.rob@epa.gov (919) 541-1089
Ann Richard	Health & Toxicity Team, NCCT	ORD/NCCT	Richard.ann@epa.gov (919) 541-3934
EPA Management			
Reeder Sams	Acting Deputy Division Director, NCEA-RTP	ORD/NCEA	Sams.Reeder@epa.gov (919) 541-0661
John Vandenberg	Division Director, NCEA-RTP	ORD/NCEA	Vandenberg.John@epa.gov (919) 541-4527
Debra Walsh	Acting Deputy Director, NCEA-RTP	ORD/NCEA	Walsh.Debra@epa.gov (919) 541-7659
Kevin Crofton	Acting Deputy Director, NCCT	ORD/NCCT	Crofton.Kevin@epa.gov (919) 541-2672

A4. PROJECT/TASK ORGANIZATION

ORGANIZATION AND RESPONSIBILITIES

The Office of Research and Development Hydraulic Fracturing Study Research Team is managed by the National Program Director (NPD) for the Safe and Sustainable Water Resources Research Program (SSWR). The work products covered by this QAPP will be generated by the NCEA Toxicity Assessment Team, part of the larger Toxicity Assessment Team. The Toxicity Assessment Team is co-led by Lyle Burgoon (NCEA) and Keith Houck (NCCT). The Toxicity Assessment Co-Leads report to the Hydraulic Fracturing Study Technical Research Lead on research items, and to the Study Coordinator for all other items.

Lyle Burgoon leads the hydraulic fracturing efforts within NCEA. Dr. Burgoon reports organizationally to the Deputy Division Director and Division Director of the RTP Division of NCEA. This effort operates in a matrix management structure, where NCEA staff assigned to hydraulic fracturing efforts report programmatically to Dr. Burgoon, while also reporting to their respective line management.

Quality assurance activities for the NCEA Toxicity Assessment Team are managed by the NCEA Director of Quality Assurance (DQA). The NCEA DQA is responsible to the Program Quality Assurance Manager (PQAM) for overall Study QA. The PQAM is responsible and accountable to the ORD Director of Quality Assurance and accountable to the Study Coordinator.

ROLES AND RESPONSIBILITIES

This section shall describe each of the roles and delegated responsibilities in the NCEA Toxicity Assessment Team.

NCEA Toxicity Assessment LEAD (LYLE D. BURGOON)
The NCEA Toxicity Assessment Lead is accountable and responsible for the performance of the NCEA Toxicity Assessment Team. The Toxicity Assessment Co-Leads are responsible for the creation of any and all Toxicity Assessment Quality Assurance documents for their specific Center. The NCEA Toxicity Assessment Lead shall have the authority to delegate responsibility for preparing sections of the NCEA-specific QAPP to members of the NCEA Toxicity Assessment Team. The NCEA Toxicity Assessment Lead will advise the NCEA Director, the Human Health Risk Assessment (HHRA) National Program Director, or their designees, on the most appropriate scientific and analytical strategies proposed by the Toxicity Assessment Team for final decision.

The Lead is responsible for:

- review and approval of this QAPP;
- identification, review, and assessment of data relevant to the research questions posed in the report *Plan to Study the Potential Impacts of Hydraulic Fracturing on Drinking Water Resources* (Study Plan) (US EPA, 2011);
- tracking and recording data associated with the toxicity task for the HF project; and
- oversight of the verification and validation checks described in Section D.

The NCEA HF Lead is responsible for keeping the NCEA QA Manager and HF Study Coordinator apprised of any quality problems that arise during this project. The NCEA Project Lead is responsible for maintaining the QAPP throughout the course of this project.

NCEA Toxicity Assessment SCIENTISTS (ILA COTE, ROB DEWOSKIN, LYLE BURGOON)
NCEA Toxicity Assessment Scientists are experts in the field of chemical risk assessment. They will obtain toxicity reference values from authoritative sources, including Federal and State agencies. They will also perform Quantitative Structure Activity Relationship (QSAR) analyses.

NCEA HF QUALITY ASSURANCE MANAGER (CHERYL ITKIN) AND ALTERNATE NCEA HF QUALITY ASSURANCE MANAGER (VICKI SOTO) AND ESTIMATED QA/QC RESOURCES
NCEA's Director of Quality Assurance (DQA) also serves as an NCEA Quality Assurance Manager (QAM) and will perform the responsibilities outlined in the HF Study QMP and the NCEA QMP. Given the potential national significance of the results of this study, NCEA has assigned an alternate HF QA Manager to serve as QA backup. The NCEA HF QA Manager is responsible for the review and approval of all HF QA/QC documents generated by or for NCEA. The HF QA Manager will submit NCEA HF Quality Assurance Project Plans (QAPPs) to the HF PQAM for concurrence that they meet HF Research Program requirements and will be responsible for the review and approval of NCEA HF QAPPs. An essential part of the QA system is an assessment/audit and the NCEA HF QA Manager or designee, will perform QA Technical System Audits (TSAs), as required by the HF QMP and NCEA HF QAPPs. It is the responsibility of the NCEA HF QA Manager to ensure that audits are conducted without conflict of interest. The NCEA HF QA Manager will also review NCEA Toxicity Assessment Quarterly Reports of problems and corrective actions, shall audit these corrections, and shall report any corrective action to the PQAM. The NCEA HF QA Manager will participate in meetings (e.g., teleconferences) organized by the HF NCEA Team and the HF PQAM. The NCEA HF QA Manager will be part of the review of all technical work products produced by the Toxicity Assessment Team such as reports, journal articles, models, and data summaries. The NCEA HF QA Manager and the alternate NCEA HF QA Manager are independent from the Toxicity Assessment Team of scientists generating the data.

It is estimated that NCEA Toxicity Assessment Scientists will spend approximately 10-30% of their time performing QA/QC activities in support of the HF Study. This includes QAPP development and review, training, and quality control activities. The HF QMP and study plan describe the required QA activities for this study. NCEA's task is focused on the stage of chemical mixing in the HF process.

The organization chart for this project is depicted in Figure 1, below.

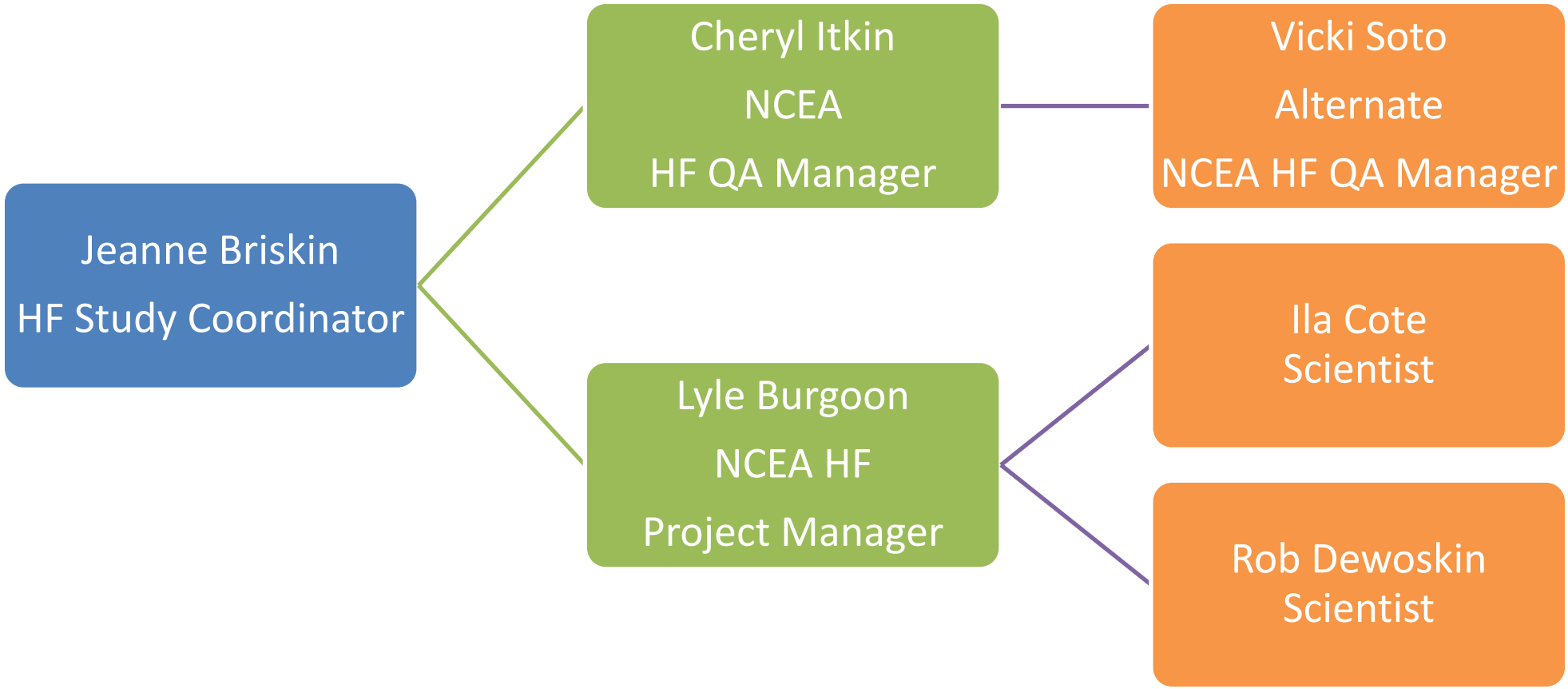

Figure 1. Organization chart for the NCEA health and toxicity project.

A5. PROBLEM DEFINITION AND BACKGROUND

The objective of this project is to identify and determine the toxicity reference values for the chemicals relevant to the research questions outlined in the HF Study Plan (US EPA, 2011).

The needs and capabilities for the HF toxicity work have changed; therefore, there is no need to fulfill the original toxicity QAPPs. There have been personnel and management changes in NCEA which directly impacted the toxicity task of the HF study. This QAPP replaces all previous toxicity QAPPs generated by NCEA. The toxicity work NCEA is doing for the HF study has changed to the work described in this document.

The toxicity assessment will be conducted by NCEA due to NCEA's expertise with hazard assessment and dose-response assessments based on quantitative structure activity relationship (QSAR) data.

A6.PROJECT DESCRIPTION AND OBJECTIVES

The objectives of this project are to:

- Identify existing toxicity reference values from authoritative sources for chemicals identified as being used or produced as a result of hydraulic fracturing operations
- Estimate toxicity reference values using QSAR for chemicals where a reference value from an authoritative source does not exist

This Quality Assurance Project Plan (QAPP) shall serve as the primary quality assurance plan for the National Center for Environmental Assessment (NCEA) portion of the Toxicity Assessment work in the Hydraulic Fracturing Study (HFS). NCEA Scientists will not use CBI data or CBI chemical lists in this project

Given the potential national significance of the results of this study, the EPA researchers will need to apply a consistent, defensible approach to deciding when to include or exclude data obtained and analyzed for inclusion in the EPA report.

The goals of this project are to:

1) Identify existing authoritative toxicity reference values for chemicals identified as being part of, or produced as a result of, hydraulic fracturing operations.
2) Use commercial off-the-shelf Quantitative Structure Activity Relationship (QSAR) software (Accelrys TOPKAT) to estimate a rat chronic lowest observed adverse effect level (LOAEL).

NCEA Scientists on the Toxicity Assessment Team will obtain existing authoritative toxicity reference values from the following data sources:

- Integrated Risk Information System Database (IRIS)
- Provisional Peer-Reviewed Toxicity Value Database (PPRTV)
- Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels for Hazardous Substances Database (MRL)
- State Agencies (e.g., California EPA)

A master spreadsheet of authoritative toxicity reference values will be generated for every chemical in each of these data sources. This master spreadsheet will be generated by an NCEA Toxicity Assessment Scientist. Once the master spreadsheet has been completed, each value will be verified against the original data source using a physical record. A second NCEA Toxicity Assessment Scientist will further verify and validate at least 10% of the records, chosen at random, within each spreadsheet.

Current Best Practices for writing Excel automation functions/equations/scripts will be used. Specifically, the "write once, copy and paste" philosophy will be used for functions/equations entered into cells. This means that a function/equation will be entered into a single cell, and that function/equation will be copied into all other cells, as appropriate. This is a commonly used practice when calculating values to go into a column of a spreadsheet. The initial function will be checked in all cases. When a function/equation has been copied across a column or row, at least 10% of the cell functions/equations will be verified and validated by a second NCEA Toxicity Assessment Scientist.

NCEA Scientists will use Accelrys TOPKAT (in Accelrys Discovery Studio version 3.5) to identify rat chronic LOAELs. TOPKAT will take as input the SDF file that contains the chemical structure information for the non-CBI chemicals generated by NCCT, and issued to NCEA by the ORD Office of Science Policy (OSP). The LOAEL module compares LOAEL values from the open literature, National Cancer Institute/National Toxicology Program technical reports, and EPA databases to estimate rat oral LD_{50} values, and then compares the octanol-water partition coefficient (log P) from the chemical structure data file to the range of log P in the training set.

The estimated LOAEL values will be compared to the authoritative toxicity reference values (for the chemicals with these authoritative values) to provide an estimate of how similar these values are. It is important to note that there may be significant deviation between the estimated LOAEL and the authoritative toxicity reference value for any given chemical due to the use of uncertainty factors in calculating the reference value, the fact that the reference value is not based on a rat chronic assay, and whether the reference value is calculated using the benchmark dose, a no observed adverse effect level (NOAEL), or a LOAEL. However, there is evidence that the estimated LOAEL is generally within 100× of the actual rat chronic LOAEL (Rupp, Appel, and Gundert-Remy, 2010).

PROJECT TIMELINE

July 31, 2013 Deliverable 1: The spreadsheet containing the existing authoritative toxicity reference values for chemicals identified as being part of, or produced as a result of, hydraulic fracturing operations.

July 31, 2013 Deliverable 2: A spreadsheet of the TOPKAT estimated rat chronic LOAEL and an analysis of how similar the rat chronic LOAEL estimates are to the authoritative toxicity reference values (for those chemicals with authoritative values).

A7. QUALITY OBJECTIVES AND CRITERIA

Authoritative toxicity reference values are the only data that will be used for Deliverable 1 as these sources are well known to NCEA scientists and their values are peer-reviewed and authoritative.

The quality objective of our TOPKAT LOAEL estimation is to ensure the estimates are reasonable and meet the model acceptance criteria (listed below). All Accelrys TOPKAT LOAEL estimates will be reported, along with whether or not they meet the acceptance criteria.

TOPKAT Acceptance Criteria 1: Chemical with Optimum Prediction Space (OPS)

Optimum Prediction Space (OPS) of the LOAEL model. Because the model descriptor space is multivariate, a simple univariate examination of a query structure is not sufficient to determine the acceptability of the assessment. T he query structure is checked to ensure that it is within the OPS of a model. The OPS is unique multivariate descriptor space in which the model is applicable. In TOPKAT, assessment of a chemical structure inside a model's OPS may be accepted with confidence, subject to the results obtained from hypothesis testing. Chemical structures must be within the OPS for the LOAEL to be considered acceptable.

TOPKAT Acceptance Criteria 2: Chemical with log P within training set range

The VLOGP Model of the TOPKAT package is a statistically significant and cross-validated quantitative structure-property relationship (QSAR) model. This model assesses log P - the logarithm of the partition coefficient - of a chemical in the n-octanol/water system. Molecular structure is the only input required to conduct a VLOGP assessment. Chemicals must be within the log P range of the training set to have an acceptable LOAEL estimate.

TOPKAT Acceptance Criteria 3: Chemical with LD_{50} greater than the LOAEL

The LD_{50} module of the TOPKAT package comprises 19 statistically significant and cross-validated quantitative structure-activity relationship (QSAR) models, and the data from which these models are derived. These models are derived from experimental LD_{50} values of approximately 4,000 chemicals from open literature. Each QSAR model assesses oral acute median lethal dose, LD_{50}, in the rat of a specific class of chemicals. Molecular structure is the only input required to conduct an LD_{50} assessment. Acceptable LOAEL estimates must be lower than the chemical's estimated LD_{50}.

TOPKAT Acceptance Criteria 4: Chemical fragments not present in the training set

Query molecules are checked for substructures not considered during the model development process. TOPKAT performs this by comparing all 1- and 2-atom fragments in the query structure with the list of fragments from the model's training set. Chemicals must have fragments represented within the training set to have an acceptable LOAEL estimate.

A8. SPECIAL TRAINING/CERTIFICATION

All NCEA Toxicity Assessment Scientists who will use special software will obtain training and support in the proper use of the software prior to using it. Training and support may include access to manuals, technical support, and support by other knowledgeable scientists. Scientists maintain their own certification and other training documents.

A9. DOCUMENTATION, RECORDS, AND DATA MANAGEMENT

Existing data, including the master spreadsheet, will be saved on the EPA intranet, on ORD managed hardware, to the HF project folders on the O:\ drive when work is completed. This hardware is secured

from improper release, and appropriate disaster mitigation methods are in place to prevent data loss. Reference documents could be either record or non-record material, depending on how they are utilized. Items cited or referenced that support a decision/conclusion should be retained as records, and also placed in the O:\ drive, as part of the Project File. Informational copies of references or data sources are, by agency definition (EPA Schedule 008), "non-records." They will also be moved to the HF project folders when the report is completed; however, as non-records they will be retained only through project completion and then destroyed.

We will follow all policies outlined in the QMP for the Study.

B. DATA ACQUISITION AND DATA MANAGEMENT

This section addresses data acquisition, analysis, and management activities.

B9. DATA SOURCES NON-DIRECT MEASUREMENTS

The data needed for this project fall under the category of non-direct measurements and may include data from more than six government databases. See Section A6 for the list of database sources. These databases will be viewed as containing the most reliable information. Supporting information is often available online. Government agencies are known to follow extensive quality assurance and review procedures for documents they produce.

B10. DATA MANAGEMENT

Leads should use a file naming convention. File names should be kept as short as possible to prevent violating file name lengths when placed on the O:\ drive.

C. ASSESSMENT AND OVERSIGHT

This section describes the audits and other assessments needed to determine whether this QAPP is being implemented as approved and to increase confidence in the data and information obtained and produced as a result of this project.

C1. ASSESSMENTS AND RESPONSE ACTIONS

An NCEA QA Manager will conduct a Technical Systems Audit (TSA) of the project and evaluate how the project plan is carried out and to ensure that the Project Lead is adhering to the practices outlined in the QAPP. In particular, the QA manager will evaluate the use of TOPKAT and how the results were documented. At various times during the project lifecycle, the QA Manager may inspect the files, the records and non-records stored on the project's O:\ drive, and the data sources. Problems will be discussed with the team and reported to the Study Coordinator. Any necessary corrective actions will be monitored by the QA Manager. Also, as required by the HF QMP, the ORD Director of Quality Assurance will conduct a Quality System Audit (QSA) of this project.

C2. REPORTS TO MANAGEMENT

The NCEA Toxicity Assessment Co-Lead will provide updates and reports to NCEA management as requested, and will provide a final report at the conclusion of the study. The final report will detail any problems encountered, quality assurance activities performed, any deviation from the QAPP, and any corrective actions. In addition, an NCEA QA Manager will conduct a Technical Systems Audit (TSA) of the project and evaluate how the project plan is carried out and to ensure that the Project Lead is adhering to the practices outlined in the QAPP. The TSA report will be provided to management.

Progress will be discussed during project conference calls. The Project Lead will ensure that project criteria are applied in a consistent manner. Any inconsistencies in applying quality criteria that develop will be discussed with the Project Lead and reported to the Study Coordinator.

D. DATA VALIDATION AND USABILITY

This section addresses the quality of the completed final dataset. This product will conform to the objectives outlined in this QAPP. As required by the HF QMP, a QA statement will be included with the delivery of the final product and also included in EPA HF Reports. Project results will be subjected to ORD QA product review and approval. This project is required to be reviewed by a NCEA QA manager.

D1. DATA REVIEW, VERIFICATION, AND VALIDATION

A master spreadsheet of toxicity values will be generated for every chemical in each of these data sources by consulting the specific database. This master spreadsheet (where each data source's values will be entered onto its own worksheet) will be generated by an NCEA Toxicity Assessment Scientist. Once the master spreadsheet has been completed, each value will be verified against the original data source using a physical record. A second NCEA Toxicity Assessment Scientist will further verify and validate at least 10% of the records, chosen at random, within each spreadsheet.

The Project Lead will ensure that all data included in the report have been reviewed according to the criteria listed in Section A7.

D3. RECONCILIATION WITH USER REQUIREMENTS

Data sources that do not strictly meet the criteria listed in Section A7 may still be included at the discretion of the Project Lead.

REFERENCE DOCUMENTS

1. EPA Order C10 2106.0, 2008, EPA Office of Environmental Information (OEI), Washington, D.C.

2. ANSI/ASQC E4-2004, *Specifications and Guidelines for Quality Systems for Environmental Data Collection and Environmental Technology Programs,* American National Standards Institute/American Society for Quality Control, 2004.

3. U.S. Environmental Protection Agency, *Guidance for Quality Assurance Project Plans*, EPA QA/G-5, Office of Environmental Information, Washington D.C., December, 2002.

4. Toxic Substances Control Act (TSCA) Good Laboratory Practice Standards, 54 CFR 34034, August 17, 1989 [40 CFR 791].

5. U.S. Environmental Protection Agency, *Guidance on Technical Audits and Related Assessments for Environmental Data Operations*, EPA QA/G-7, Office of Environmental Information, Washington, D.C., January, 2000.

6. U.S. Environmental Protection Agency, *Data Quality Assessment: A Reviewer's Guide*, EPA QA/G-9R Office of Environmental Information, Washington, D.C., May, 2000.

7. U.S. Environmental Protection Agency, *ORD Policies and Procedures Manual, Section 13.2 and Section 13.4*, Washington, D.C., December 2006, http://dcordhqapps1.epa.gov:9876/orma/policies.nsf/webPolicy

8. U.S. Environmental Protection Agency, EPA Records Schedules, Office of Environmental Information, National Records Management Program, Washington, D.C. http://www.epa.gov/records/policy/2155/rm_policy_cio_2155_1_2.pdf

9. U.S. Environmental Protection Agency, Information Resource Management Policy Manual, Directive Number 2100, Office of Environmental Information, Washington D.C., July, 1987.

10. U.S. Environmental Protection Agency, *EPA Good Automated Laboratory Practices: Principles and Guidance to Regulations for Ensuring Data Integrity in Automated Laboratory Operations with Implementation Assistance*, 1995 Edition, Office of Information Resource Management, Research Triangle Park, NC, August, 1995.

11. U.S. Environmental Protection Agency, *ORD Policies and Procedures Manual, Section 13.2: Paper Laboratory Records*, Washington, D.C., December 2006, http://dcordhqapps1.epa.gov:9876/orma/policies.nsf/f536fba05d681a598525702600653e9c/c820ee1b2ec5289385257218006abf91?OpenDocument

14. Rupp, Bernd, Klaus E Appel, and Ursula Gundert-Remy. 2010. "Chronic Oral LOAEL Prediction by Using a Commercially Available Computational QSAR Tool." *Archives of Toxicology* 84 (9) (September): 681–688. doi:10.1007/s00204-010-0532-x.

QAPP Change Procedure and History

The QAPP is a living document. NCEA Team Members may request changes be made to the QAPP by contacting the NCEA Toxicity Assessment Lead. The NCEA Toxicity Assessment Lead will have the final decision as to whether to change the document, and how. The NCEA Toxicity Assessment Lead may delegate this responsibility as necessary to others. Any changes to the document will be noted in the following table:

Date of Change	Name of Personnel Editing Document	Nature of Change (include description and current page number(s) if applicable)
11-2-12	Lyle D. Burgoon	Initial Write.
12-4-12	Cheryl Itkin	Review and Comments/Suggested edits
12-5-12	Vicki Soto	Review and Comments/Suggested edits
4-10-13	Lyle D. Burgoon	Edited and reviewed.