Quality Assurance Project Plan (QAPP) for:

Chemical Information Quality Review and Physicochemical Property Calculations for Hydraulic Fracturing Chemical Lists

Hydraulic Fracturing (HF) Study

National Center for Computational Toxicology (NCCT)
Office of Research and Development (ORD)
United States Environmental Protection Agency (USEPA)
Research Triangle Park, NC 27711

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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 **Chemical Mixing Stage Projects** and **Flowback and Produced Water Stage Projects** of the HF water cycle as found in Figure 1 of the HF QMP and as described in 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.

REVISION HISTORY:

Revision Number	Date	Revision
0	February, 2012	New document
1	October, 2012	Added REVISION HISTORY page 2
		Signature Page 3: Changed MANAGEMENT REVIEW AND APPROVAL from "David Dix, Deputy Director" to "Rebecca Clausen, Associate Director for Management". Abbreviations and Acronyms: page 4 – Deleted reference to NCCT QMP.
		Section A.1– removed reference to NCCT QMP and ORD QMP and retained reference to HF QMP.
		Section A.2 – paragraph 1 and 2 – removed sentences referring to ToxCast assays and other "second phase" activities in FY13.
		Section A.3 - removed reference to NCCT QMP. Updated names for NCCT Director from Robert Kavlock to David Dix and NCCT Deputy Director David Dix to Associate Director for Management Rebecca Clausen in the org. chart and in A.4 roles and responsibilities.
		Section A.6 – Remove reference to PPM 13.2, an internal policy manual document.
		B. – remove reference to FY2013 ToxCast assays in project plan.
		C. – remove reference to NCCT QMP.
		Distribution list – updated Director and Deputy Director names as in A3 and updated PQAM
		Added 3 appendices as supporting information or documents referenced in the QAPP.

PREPARED BY

Name: Keith Houck, Ph.D.   Phone: (919) 541-5519
Title: HF Project Co-Lead for NCCT

Signature: /s/   Keith Houck   Date: 08Nov2012

QUALITY ASSURANCE APPROVAL

Name: Stephen Little   Phone: (919) 541-0963
Title: Quality Assurance Manager, NCCT

Signature: /s/   Stephen Little   Date: 08Nov2012

MANAGEMENT REVIEW AND APPROVAL

Name: Rebecca Clausen   Phone   (919) 541-3002
Title: Associate Director for Management, NCCT

Signature: /s/   Rebecca Clausen   Date: 08Nov2012

Acronyms and References:
See corresponding section of the EPA HF Quality Management Plan (QMP).

A. Project Management - project objectives, and roles and responsibilities of the participants.

A.1.   Quality Assurance for NCCT HF activities are managed according to EPA quality standards and reinforced by the guidelines in the <u>HF QMP</u> for a QA category I project.

A.2   Project objectives -

This Quality Assurance Project Plan (QAPP shall serve as the quality assurance plan for the National Center for Computational Toxicology (NCCT) portion of the Health and Toxicity (H&T) Theme's work in the Hydraulic Fracturing Study. This QAPP addresses the creation of a list of chemicals of concern for hydraulic fracturing by NCCT scientists using chemical lists received from the Office of Science Policy (OSP) contractor Environmental Research Group (ERG), chemical QC of chemical list identifiers, preparation of a structure annotated chemical list and the generation of chemical properties for the list of chemical structures in FY12.

The products to be delivered to NCEA in FY12 will include a final list of chemicals of concern which can be evaluated for toxicological information based on confirmed chemical structure and 3 sets of chemical properties derived from the chemical structures. Various software packages (EpiSuite, LeadScope and QikProp) will be used to generate the physicochemical properties by NCCT.

Project summary and tasks:
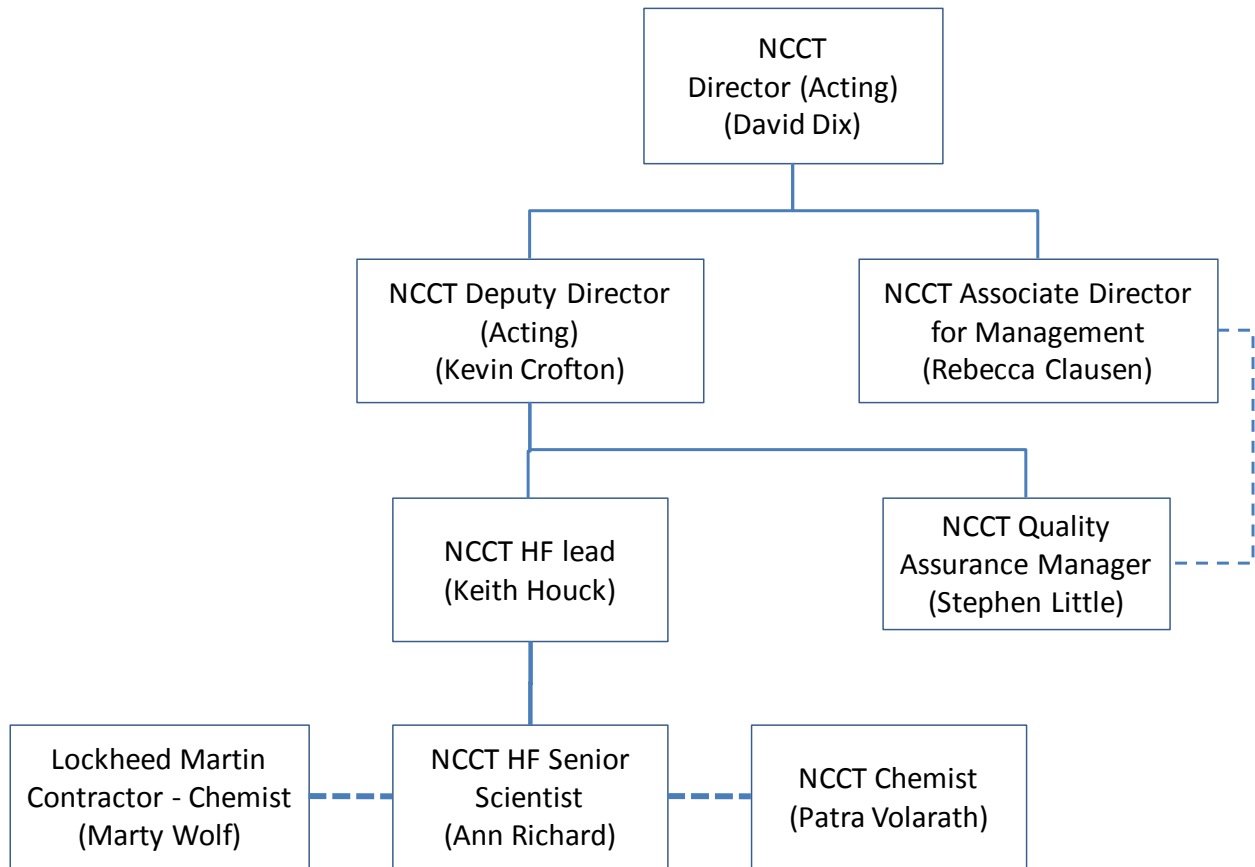This QAPP shall cover the following tasks performed by NCCT:.
1. Generate a list of chemicals with structures based on the HF chemical list received from ERG.
2. Generate the corresponding physicochemical properties for the list of chemical in 1 using the software packages EpiSuite, QikProp and LeadScope.

A.3   Project Organization

The Office of Research and Development Hydraulic Fracturing Study Research Team is managed by the Interim National Program Director (iNPD) for the Safe and Sustainable Water Resources Research Program (SSWR). The work products covered by this QAPP will be generated by the NCCT members of the HF Health and Toxicity Team (listed as "Toxicity Assessment" in the May 18, 2011 draft Hydraulic Fracturing Study Research Team Organizational Chart). The H&T Team is co-lead by Lyle Burgoon (NCEA) and Keith Houck (NCCT). The H&T Co-Leads report to the Technical Research Lead on research items, and to the Study Coordinator for all other items.

Quality assurance activities for the NCCT HF team are managed by the NCCT Quality Assurance Manager as delegated by the NCCT Associate Director for Management. For this study, the NCCT QAM 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.

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                         │       NCCT       │
                         │ Director (Acting) │
                         │   (David Dix)     │
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              ┌──────────────────┐        ┌──────────────────┐
              │ NCCT Deputy Director │     │ NCCT Associate Director │
              │     (Acting)      │        │  for Management   │
              │  (Kevin Crofton)  │        │ (Rebecca Clausen) │
              └──────────────────┘        └──────────────────┘
                    ┌──────────────────┐   ┌──────────────────┐
                    │   NCCT HF lead   │   │   NCCT Quality    │
                    │  (Keith Houck)   │   │ Assurance Manager │
                    │                  │   │  (Stephen Little) │
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  ┌──────────────────┐  ┌──────────────────┐  ┌──────────────────┐
  │  Lockheed Martin │  │   NCCT HF Senior │  │   NCCT Chemist   │
  │ Contractor - Chemist │  Scientist     │  │ (Patra Volarath) │
  │   (Marty Wolf)   │  │  (Ann Richard)   │  │                  │
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NCCT QA and project organization for Hydraulic Fracture Health and Toxicity

A.4   Roles and Responsibilities

This section shall describe each of the roles and delegated responsibilities in the NCCT H&T Team.

NCCT Deputy Director (Acting) (Kevin Crofton)
 Supervises NCCT science staff, responsible for NCCT science.

NCCT Associate Director for Management – Rebecca Clausen
Responsible for NCCT QA.

NCCT HF Health and Toxicity theme co-lead (Keith Houck)
The NCCT HF Health and Toxicity Lead shares accountability and responsibility for the overall performance of the tasks covered by this QAPP.

NCCT Senior Scientist – Chemistry and Cheminformatics (Ann Richard)
The Senior Scientist for chemistry and cheminformatics has the primary responsibility for the oversight of the generation of the structure annotated chemical list and the chemicals property generation.

Lockheed-Martin contractor, Chemist (Marty Wolf)
This individual is the chemical curator for all DSSTox chemical lists and expert in chemical list QC.

NCCT Research Chemist (Patra Volarath)
This individual will generate the physicochemical properties using QikProp and LeadScope and EpiSuite.

NCCT Quality Assurance Manager (Stephen Little)
The NCCT Quality Assurance Manager with assess and document the activities for this project following the HF QMP guidelines.

A.5   Special Training and Certification

The NCCT HF HT team members who work on this project have extensive knowledge and training within their area of expertise. Technical background of NCCT staff can be found on the NCCT website www.epa.gov/ncct/staff_profiles.html. The NCCT HF HT team is using procedures set forth under the Toxic Substances Control Act (TSCA) to handle all CBI-designated materials. To maintain approval to access this data, all personnel who work with or view CBI designated materials will receive training and will follow the procedures described in the TSCA CBI Security Manual.

A.6   Documentation and records

Paper records shall adhere to EPA records policy. The majority of records will require permanent retention under EPA Records Schedule 501, "Applied and Directed Scientific Research." TSCA CBI records and data-handling will be conducted using TSCA CBI procedures in the TSCA CBI Security Manual. Final deliverables will be transferred via the local DCO following TSCA CBI guidelines. All CBI data, when not in use, is stored in an approved storage container.

B. Project plan for data generation activities -

NCCT will receive a disk containing a consolidated chemical list file generated by Environmental Research Group (ERG), which will be a consolidated list of chemical names and other identifiers of chemical identity, but free of information that could link a chemical to a specific company. This final consolidated list will be annotated with chemical structures from DSSTox, wherever a current overlap exists, and from public sources for the remainder of the list. Physicochemical properties, also known as

chemical descriptors, for EpiSuite, QuickProp, and Leadscope will be computed for the portion of the final consolidated list having assigned structures that can be processed. These final consolidated files (final chemical list, structure file, property file) will then be transfered to NCEA for compilation of toxicity values via the RTP DCO following TSCA CBI guidelines.

C. Project Assessment and QC activities –

Project activities will be documented and subject to periodic assessment of documentation and records as appropriate for a QA category I project as documented in the HF QMP guidelines. Periodic research meetings are held both to plan and monitor research activities, but also to discuss ongoing QA monitoring activities. A technical systems audit and product quality review will be performed prior to final release of products.

D. Data Validation and Usability –

These QAPP elements cover the QA activities that occur after the data collection phase of the project is completed. Implementation of these elements ensures that the data conform to the specified criteria, thus achieving the project objectives.

The chemicals from ERG, will have been validated by ERG prior to receipt by NCCT, using the chemical QA guidelines provided by NCCT (Appendix A) and corresponding to the chemical QA/QC procedures documented in the DSSTox Chemical Information Quality Review Procedures webpage.
The ERG datafile chemicals that match chemicals in the DSSTox structure searchable toxicity database will have curated identities and structures verified using the DSSTox chemical quality procedures.. ERG chemicals that are not in DSSTox will be manually curated to remove duplicates, generic substances and individual unique chemicals will have identities and structures assigned from public sources such as PubChem and ChemSpider when possible. This subset of chemicals will have a review process that is by necessity less rigorous than the DSSTox curation process. These methods are consistent with the approaches for QA and research as detailed in the DSSTox Chemical Information Quality Review Procedures webpage: http://www.epa.gov/ncct/dsstox/ChemicalInfQAProcedures.html. The DSSTox public website contains additional information on standard chemical fields and field name definitions. http://www.epa.gov/ncct/dsstox/MoreonStandardChemFields.html Details on methodology specific to particular work in this HF project will be provided with all deliverables as well as sufficient documentation or metadata describing the dataset, to document data review and facilitate data usability.

The generation of the data produced by the software EpiSuite, LeadScope and QikProp are described in the SOPs for each method that are found in Appendix B – NCCT HF Structure-Property (Phys-Chem) Calc Procedures.. The validations and ranges of applicability are described in the software manuals and in the literature. Data Quality Assessment on a subset of these data will be performed to verify consistent calculated values compared to previous calculated property values (Appendix C). Details on methodology specific to particular work in this HF project will be provided with all deliverables.

Distribution List :

Kevin Crofton
NCCT Acting Deputy Director
crofton.kevin@epa.gov

Rebecca Clausen
NCCT Associate Director for Management
Clausen.rebecca@epa.gov

Keith Houck
HF Health and Toxicity co-lead for NCCT with NCEA
houck.keith@epa.gov

Ann Richard
HF Health and Toxicity Senior Scientist – Chemistry
richard.ann@epa.gov

Stephen Little
NCCT Quality Assurance Manager
little.stephen@epa.gov

Lyle Burgoon
HF Health and Toxicity co-lead for NCEA with NCCT
Burgoon.lyle@epa.gov

Cheryl Itkins
NCEA Director of Quality Assurance
Itkins.cheryl@epa.gov

Michelle Henderson
NERL QAM and HF Project Quality Assurance Manager
Henderson.Michelle@epa.gov

QMP and QAPPs referenced in this QAPP:

HF QMP   Dec 2011

References:

TSCA CBI manual: http://www.epa.gov/oppt/pubs/tsca-cbi-protection-manual.pdf

DSSTox: http://www.epa.gov/ncct/dsstox/

Richard, A. M. AND C. R. Williams. Distributed Structure-Searchable Toxicity (Dsstox) Public Database Network: A Proposal. MUTATION RESEARCH NEW FRONTIERS ISSUE 499(1):27-52, (2001).

Software references for chemical property calculation software:

MOE 2011.10   Chemical Computing Group   http://www.chemcomp.com/

QikProp 3.4   Schrodinger, Inc   https://www.schrodinger.com/

Leadscope Enterprise v3.0.6-3   Leadscope, Inc   http://www.leadscope.com/

EpiSuite EPIWEB4.10   US EPA, OPPTS   http://www.epa.gov/oppt/exposure/pubs/episuite.htm

ACD/ Chemfolder (Windows version 12.00)   http://www.acdlabs.com/products/km/ackm/chemfolder/

Appendix A – ERG HF Chemical List QC Procedure

Original procedure passed along from Ann Richard (NCCT) to Jeanne Briscow (OSP) to provide ERG on June 6, 2011:

ERG will work to develop two lists of chemicals (one public, one CBI) that will be used as the basis for collecting physical and toxicological properties. These lists require further CAS numbers and chemical name verification. EPA (via NCCT) will provide ERG with a copy of the DSSTox Master Inventory, containing over 13K unique structures and 15K unique substance records. ERG will compare the CAS numbers (and chemical names, where CAS are not primary from the Source) from both chemical lists with the DSSTox database to determine where records overlap, extracting the CAS (or name) matching DSSTox records. The DSSTox records will contain QC'd chemical identifiers with structures and accurate substance descriptions -- for more information on DSSTox Standard Chemical Fields, see:
http://www.epa.gov/ncct/dsstox/MoreonStandardChemFields.html
http://www.epa.gov/ncct/dsstox/StandardChemFieldDefTable.html
For the CAS numbers and chemical names that do not appear in the DSSTox database overlap file, ERG will use Internet searches to determine consensus for a consistent and accurate chemical name assignment for each CAS number (ChemFinder, ChemSpider, manufacturer or chemical supplier websites, etc.). The DSSTox Chemical Information Quality Review Procedures webpage may be consulted for guidance in these procedures: http://www.epa.gov/ncct/dsstox/ChemicalInfQAProcedures.html

Next steps will include:
1. After performing further QC of CAS and names NOT corresponding to DSSTox records, ERG creates a listing of QC'd CAS + Names (from the QC process above), and communicates to EPA separate smaller listings of problem cases where CAS and name cannot be confidently reconciled by use of public Internet sources -- with separate listings of CBI and non-CBI cases communicated through appropriate procedures.
2. The small lists of problem cases remaining, after DSSTox matching records and QC'd records are removed (no more than 50), will undergo further QC review at EPA, including possible consultation of the commercial SciFinder resource for definitive CAS information. These results will be provided to ERG to consolidate with the larger lists.
3. Any listing in the final revised HF list (CBI and non-CBI) not containing DSSTox corresponding records will be submitted to EPA for further structure-annotation (using a name-to-structure conversion program). The final structure-annotated records will be provided to ERG. These will include mol file structures, SMILES (parent and tested chemical), and InChI representations of structure.
4. ERG will use the EPA-provided SMILES and mol file structure representations to generate phys-chem and persistence/bioavailability predictions from the publicly available EpiSuite program (results also available by CAS or structure search from ChemSpider: http://www.chemspider.com/) and the on-line PBT Profiler (http://www.pbtprofiler.net/). Bill Waugh (waugh.bill@epa.gov) should be consulted as to whether the PBT properties are all included in EpiSuite as well (I do not believe so). ChemSpider also includes predicted phys-chem properties from ACD/Labs and ChemAxon, as well as Experimental properties from users. ChemID also contains experimental phys-chem properties, but these are likely the same as those listed in EpiSuite (both are from a database built by SRC for EPA). Links to chemical spectra and other types of analytical standard information can be found on the NIST Webbook webpage: http://webbook.nist.gov/ (URLs could be gathered for these).

Appendix B – NCCT HF chemicals Structure-Property (Phys-Chem) Calculation Procedures

02Feb2012 (P. Volarath)

*Documentation of procedures for generating calculated properties from structure SD file:
NCEAHS_397_v1a_02Feb2012.sdf*

I. Procedures for Generating Leadscope Properties

The input 2D (non-desalted) SD file was input into Leadscope Enterprise v3.0.6-3. The import process was carried out automatically using the default settings. All chemical salts or complexes are automatically converted into the parent form of the chemical. All Leadscope descriptors (Parent Molecular Weight, ALogP, Hydrogen Bond Acceptors, Hydrogen Bond Donors, Lipinski Score, Molecular Weight, Parent Atom Acount, Polar Surface Area, and Rotatable Bonds) were selected and calculated automatically. For more information, refer to Leadscope Enterprise User Manual Version 2.2).

### II. Procedures for Generating EPISuite Properties

1.   The input 2D file was desalted using ACD Chemfolder:

The input SD file was, first, desalted using the *Desalt Batch* option in ChemFolder (ACD/Labs Windows version 12.00). The following desalt options were chosen:
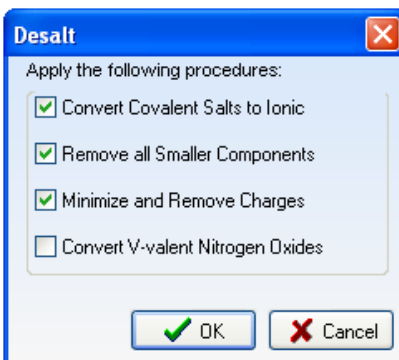
The output SD file contains the DSSTox_CID and the ChemFolder generated SD fields: ID, Formula, and formula weight (FW).

2.   . Both the non-desalted and desalted 2D SD files were input into EPIWEB4.10 (http://www.epa.gov/oppt/exposure/pubs/episuite.htm). The files were input using Batch Mode (Batch File Input Using MDL SDFile). The files were processed using the following options:
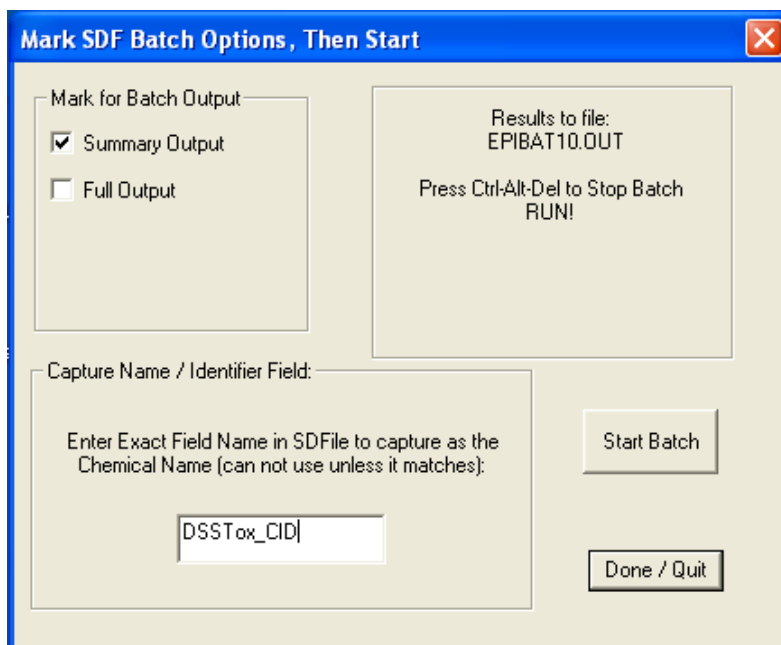
The calculated results are stored in the EPIBATxx.OUT file. A Perl script called EPI_Suite_SMILES_Batch_Parser.pl (author: J. Wambaugh 2/2/2012) was used to extract the data from the .OUT file. The script output is stored in output.xls. The script assumes that the chemical IDs are CAS numbers. Hence, the title of the column labeled "cas" needs to be changed to the ID in the input SD files (in this case it is "DSSTox_CID").
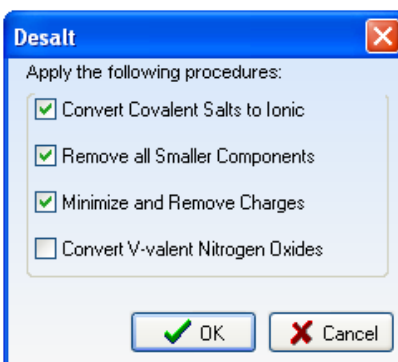
III. Procedures for Generating QikProp Properties

     1.   Input SD File Description:

The input SD file contains 2D structures of 397 chemicals with DSSTox_CIDs as their SD field.

     2.   Preparing SD File for QikProp:

The input SD file was, first, desalted using the *Desalt Batch* option in ChemFolder (ACD/Labs Windows version 12.00). The following desalt options were chosen:

The output SD file contains the DSSTox_CID and the ChemFolder generated SD fields: ID, Formula, and formula weight (FW).

The desalted .sd file was then imported into Linux version MOE 2011.10 (Chemical Computing Group's Molecular Operating Environment software) using the file open option. All SD fields were imported into MOE. The 2D input structures were converted to 3D using the *Rebuild3D* function (Compute > Molecule > Energy Minimize) with the following options (where 'mol' represents the column in the MOE Database Viewer that holds the 2D structures and '3D Forms' is a new column that will be created in the viewer to hold the 3D structures):
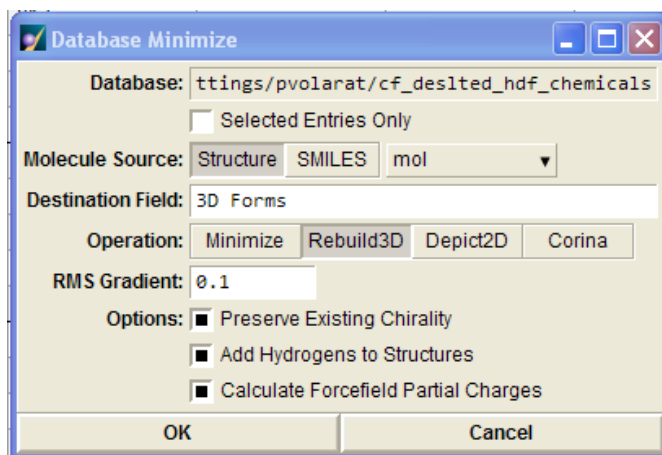
The newly created 3D structures were then minimized following the same procedure to build the 3D structures. Here, the 'Molecule Source' was reset to '3D Forms', the 'Destination Field' was reset to '3D Minimization' to hold the minimized 3D structures, and the option 'Minimize' was chosen:

From the Database Viewer window, the columns 'DSSTox_CID' and '3D Minimization' were selected and output into a new .sdf using the 'Save As' option.

3. QikProp Processing:

The output SD file from MOE was input into Linux QikProp v3.4 program. The program was executed using the fast mode (see QikProp 3.4 User Manual). The QikProp properties are contained in .csv file. The molecules that were rejected or not processed are listed in the .warning file.

Revision: 07Nov2012 – reordered the listing of the 3 chemical property calculation software procedures to better follow the flow of chemical list preparation -- LeadScope with unprocessed 2D structures, EPISuite with desalted 2D structures and QikProp with desalted 2D structures transformed to 3D optimized structures prior to calculations.

Appendix C – Data Quality Assessment for NCCT HF chemicals phys-chem calculations

Stephen Little, Chemist, NCCT QAM   29Feb2012

Historically at NCCT the physical-chemical calculations have been subject to less stringent QC than the ToxCast experimental data for various reasons. The primary reasons are that the data is generated by simple chemical structure inputs that are validated by DSSTox QC, property calculations have no variation in the output for the same version of software and input parameters and the software is validated by the manufacturer. The data derived from phys-chem calculation are modeled estimates that can vary in accuracy for different chemical classes. The single most important QC activity for phys-chem generation is the verification of the chemical identity by some means and removal of known problem chemicals. For EpiSuite and LeadScope software, the input is SMILES two-dimensional (2D) chemical structure code that can be obtained directly from DSSTox and the chemical QC is covered in the DSSTox QAPP. For QikProp the input is three-dimensional (3D) chemical structures which are modeled from the 2D SMILES structure code using either Schrodinger LigPrep if the software is available (as it has in the past) or using a general molecular modeling package such as MOE (Molecular Operating Environment) which is currently available via a floating license at EPA. MOE was used for the HF chemical 3D structures that were used as input to calculate the QikProp phys-chem properties.

Data Quality Assessment – to verify that the change in procedure from the historical use of LigPrep for 3D geometries to using MOE 3D geometries did not contribute to a significant change in the calculation results, the phys-chem descriptor known as the logPow (log of the octanol-water partition coefficient) was compared for the two methods for the 290 chemicals that had matching DSSTox CIDs in the two sets of chemicals. The resulting correlation between current and previous QikProp logPow looks like this:
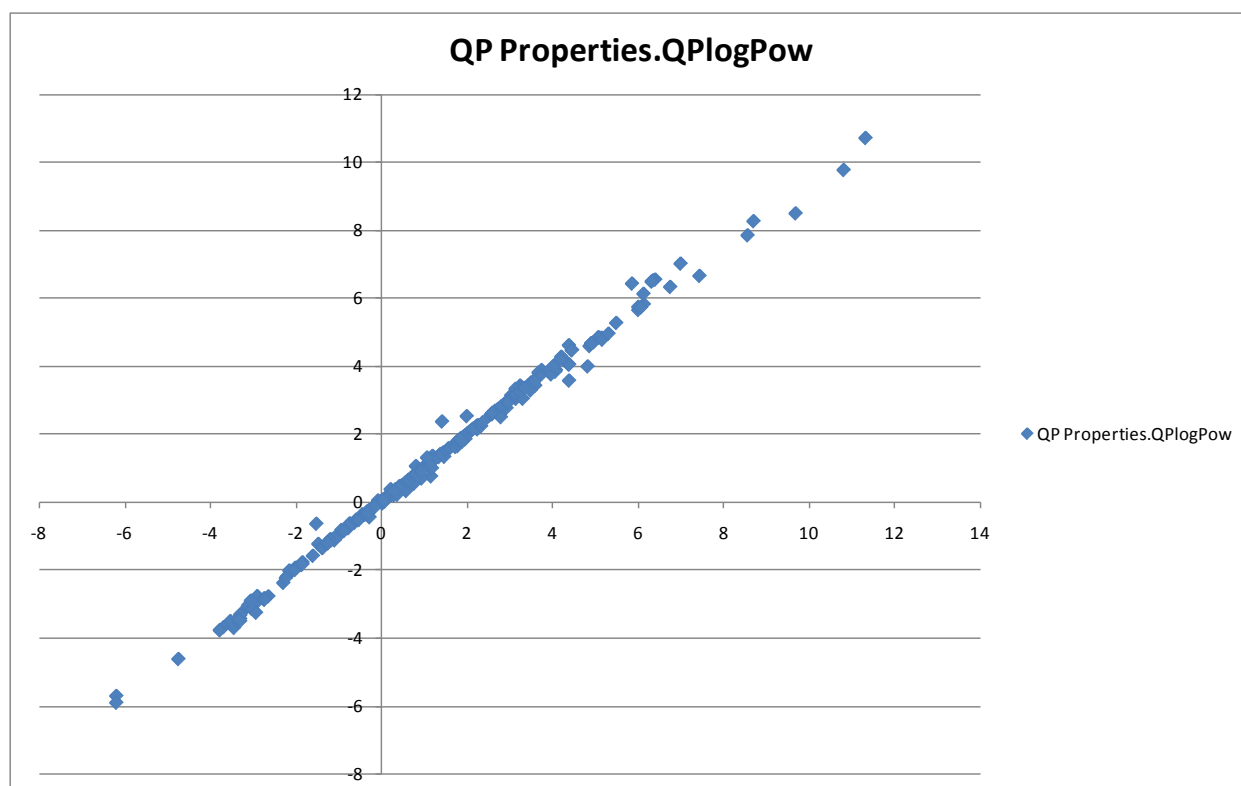
If simple standard statistics are done for this comparison of QikProp calculations, (ie. between the older DSSTox defined organic chemicals with LigPrep 3D geometries and a slower, but slight more accurate QikProp algorithm (which fails for more chemicals) and the current HF chemicals MOE 3D geometry and faster QikProp algorithm) the results are

:

The range in logPow values for the two sets of data are

(-6.174,11.306) for older DSSTox chemicals QikProp calculations used as reference dataset for this QC
(-5.908, 10.695) for current HF QikProp calculations

The average of the absolute value of the difference between the two datasets is 0.103.
The variance for the absolute differences is 0.032
The Standard deviation of the absolute differences is 0.178

The accuracy of the QikProp chemical calculations or the ability of QikProp data to model real experimental values is documented in the QikProp manual n pages 27 – 38 of the QikProp User Manual. As an example some of the QikProp logPow comparisons from the page 29 table are shown:

QikProp User Manual partial Table 4.3. Log Po/w results for a test set of molecules.

Molecule	MW	exp log Po/w	QPlogPo/w1	QPlogPo/w2
Isoniazid	137.1	–0.70	–0.24	–0.04
Nicotinamide	122.1	–0.37	–0.13	–0.20
Sulfadiazine	250.3	–0.09	–0.06	0.02
Pyrazole	68.1	0.26	0.21	0.20
Sulfamethiazole	270.3	0.54	–0.40	–0.39
Minoxidil	209.3	1.24	1.00	1.13
Heptabarbital	250.3	2.03	0.82	0.86
2,4-D	221.0	2.81	2.03	2.27
Ethisterone	312.5	3.11	3.78	4.35
Pericyazine	365.5	3.52	3.19	3.34
Terbutyrne	241.4	3.74	2.52	2.82
Captafol	349.1	3.80	2.83	3.13

1. Using structures from SciFinder.
2. Using optimized structures.

The main thing to take away from this vendor data on QikProp accuracy is that the differences in calculated QPlogPow due to differences in geometry (method reproducibility or robustness, which is validated in the previous plot) are usually less than the differences between calculated values and the experimental value (predictive accuracy). This table was created using a relatively well behaved set of organics. The errors in predicted values would be expected to be greater for inorganics and organometallics.