WEB-BASED BENCHMARK DOSE MODELING MODULE AS A PROTOTYPE COMPONENT OF AN INFORMATICS-BASED SYSTEM FOR HUMAN HEALTH ASSESSMENTS OF CHEMICALS

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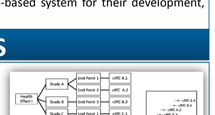
ABSTRACT

We propose developing a modular, cloud-ready, informatics-based system to synthesize multiple data sources into overall human health assessments of chemicals. This system would seamlessly integrate and document the overall workflow from literature search and review, data extraction, and evidence synthesis, to dose-response analysis and uncertainty characterization. Crucial benefits of such a system include improved data integrity, greater transparency, standardization of data presentation, and increased consistency. By including both a web-based workspace for assessment teams, and complementary web-based portal for reviewers and stakeholders, all interested parties would have dynamic access to completed and ongoing assessments. The modular approach will also facilitate rapid prototyping, testing, review, and incorporation of methodological improvements. Here we present a prototype module for benchmark dose (BMD) modeling used to develop points-of-departure, from which toxicity values are derived. Previously-developed BMDS Wizard and DRAGON Excel-based programs were used to develop a web-based tool where assessment teams can view/upload/enter dose-response data sets into the module, perform BMD modeling, and export results. Example summary views and plots are available online, or can be converted to report format. In addition, multiple nested views of the data and analyses enable interested users to rapidly "dive into the details." We conclude that given new data streams, diverse user needs, and multiple stakeholder interests, assuring the utility, integrity, and objectivity of human health assessments will be greatly facilitated by a modular, upgradeable, informatics-based system for their development, review, and dissemination.

OBJECTIVES

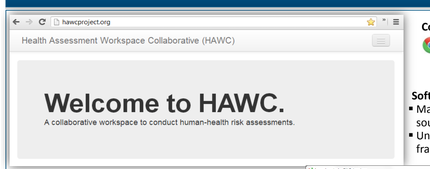
To create a web-based workspace to create, store, share, and display data and results, in order to conduct chemical health assessments

- **Team collaboration** – multiple users can work together on a single assessment
- **Automate** data presentation, and **standardize** the process of building an assessment, based on existing guidance
- **Modular** architecture based on key components in assessment process such as literature search, data-extraction, synthesis, and reference-value
- Facilitates **integration** with existing tools (BMDS) and information (HERO, ACTOR, etc.)
- **Track changes** over the course of the project, including revisions after review
- Enables stakeholders to engage, participate, and **dive into the details**
- Makes the process of developing human health assessments more **transparent**



RfC Identification (NRC, 2011): Designed to assist users in completing the risk-assessment in a step-wise process, similar to the process shown here.

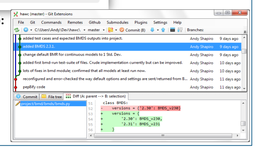
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE (HAWC)



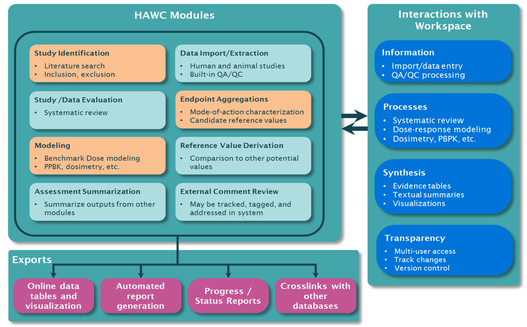
Compatible browsers: Chrome, IE 9+, Firefox

Software Version Control:
- Maintained using open-source ***Git*** software
- Unit-testing development framework

Health Assessment Workspace Collaborative (HAWC):
- Publically accessible website currently under development
- Tested with previously published PPRTV assessments, such as Nitrofen (no new data in prototype website).
- Initially focusing on capturing animal bioassay data for integration into human health assessments of chemicals
- Designed using open-source tools technologies, such as RESTful API for data sharing

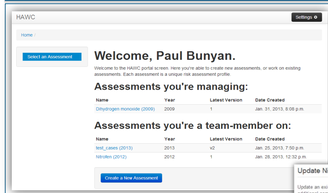


HAWC FRAMEWORK

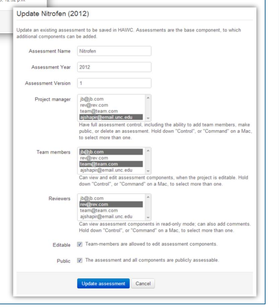


HAWC Framework and Modules: Modules currently under development in orange
- Conceptualization of modules which would be incorporated into HAWC, along with proposed interactions from within the tool and exports to other potential uses
- Should be a holistic process which captures all key steps in conducting an risk analysis
- As methods or guidance changes, modules can be updated, added, or removed to ensure the current best-practices are being followed

ASSESSMENTS AND PERMISSIONS



- **Users** login to personalized login screen, showing all assessments users have permissions to edit or review
- Content is organized by **assessments**. Different *versions* of an assessment can be created to view changes in assessment



Levels of access:

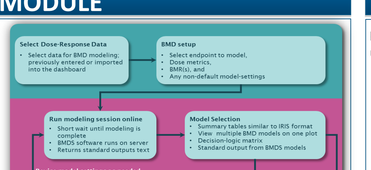
1. Project managers – change permissions settings, including who can edit content for your assessment.
2. Team members – add, edit, and delete assessment information.
3. Reviewers – reviewers can view assessments and add comments, but cannot change content.

Assessments can be **locked**, where content is read-only, and cannot be edited by anyone (even those on the team).

Assessments can also be made **public**, where content can be reviewed (but not changed) by anyone.

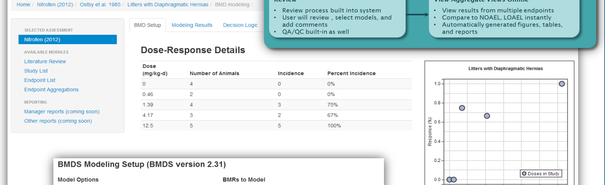
BENCHMARK DOSE MODULE

- ***First module designed for HAWC.*** Enables users to conduct benchmark-dose modeling, using EPA's existing Benchmark Dose Modeling Software (BMDS, version 2.31) and current EPA guidelines for BMD modeling (09/2012)
- Inputs and outputs are seamlessly integrated in a web-interface, so users do not need to download the software or deal with raw inputs or outputs
- After completion of modeling, results can be used in other modules, exported, or reviewed by peer-reviewers online
- Overview diagram of the BMD module workflow is shown to the right



Dataset Inputs:

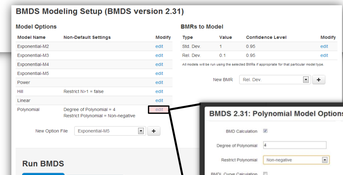
- Data are currently manually entered into HAWC, but in the future may be imported from other data systems
- Allows for continuous or dichotomous datasets



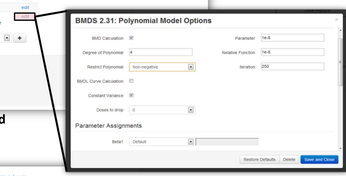
Dose-response dataset to be modeled

BMD Modeling Inputs:

- Load session for default models
- Customize any options, including dropping-doses as needed for a particular model in option file
- Specify which BMRs should be used for all models; results are also formatted so that identical model options with different BMRs are grouped together

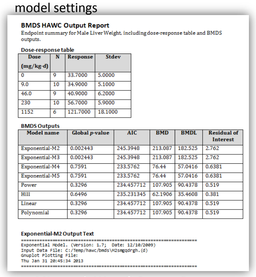


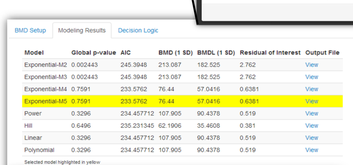
Model setup and configuration



Execution and Model Selection:

- After customization of model inputs, BMD models are executed and results are returned when modeling is complete
- After model-selection results can be used in subsequent models downstream
- Reviewers have detailed access to all model settings





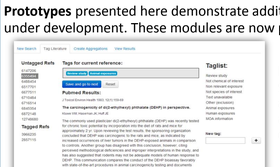
Output Summary Table and Detailed Modeling Results

Model Outputs

- Summary table automatically populated with key fit statistics
- As user hovers over different rows, chart automatically updates showing model fit
- Standard BMDS text outputs and figures be viewed
- Downloadable Microsoft Word® reports

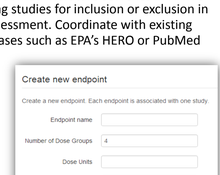
OTHER HAWC MODULES

Prototypes presented here demonstrate additional HAWC modules and functionality under development. These modules are now partially implemented in HAWC.



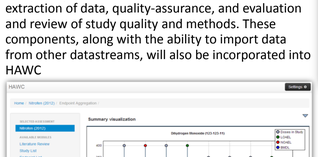
Literature Search Module

Save PubMed literature searches in HAWC and tag studies for inclusion or exclusion in an assessment. Coordinate with existing databases such as EPA's HERO or PubMed



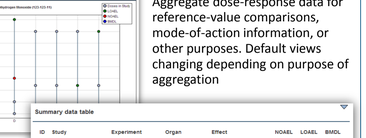
Data Import/Extraction Module

A key component in the risk-assessment process is extraction of data, quality-assurance, and evaluation and review of study quality and methods. These components, along with the ability to import data from other datastreams, will also be incorporated into HAWC



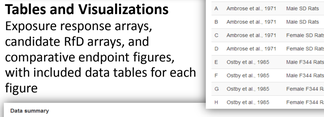
Data Aggregation Module

Aggregate dose-response data for reference-value comparisons, mode-of-action information, or other purposes. Default views changing depending on purpose of aggregation



Tables and Visualizations

Exposure response arrays, candidate RfD arrays, and comparative endpoint figures, with included data tables for each figure

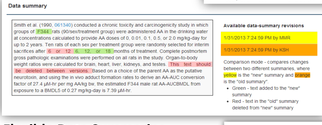


Text Revision Tracking

Demonstration of the ability to track-changes in text summaries, enabling version control across assessments

Flexible Data Summaries

Summary tables demonstrating ability to represent data in many ways. This example shows a study-summary table of various effects



LIVE PROTOTYPE WEBSITE

The website is still under development, but we appreciate feedback. Content and structure will change as the project evolves. Create an account and explore at:

http://www.hawcproject.org

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References available upon request