Health Assessment Workspace Collaborative (HAWC)

Project Overview

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Overall project concept

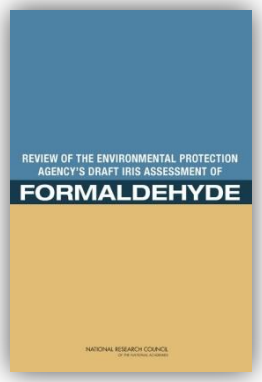
Web-based workspace to create, store, share, and display data and results and conduct chemical health assessments

- **Team collaboration** – multiple users can work on a single assessment
- **Automate** report generation, 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 derivation
- Facilitates **integration** with existing tools (BMDS) and information (HERO, ACTOR, NTP/OHAT, etc.)
- Enables **stakeholders** to engage, participate, and **dive into the details**
- Makes the process more **transparent**

Why is this important?

NRC (2011) Recommendations :

- Standardize the presentation of reviewed studies in **tabular or graphic form** to capture the key dimensions of study characteristics, weight of evidence, and utility as a basis for deriving reference values and unit risks
- Develop templates for **evidence tables, forest-plots, or other displays**
- **Establish protocols for review** of major types of studies, such as epidemiologic and bioassay



NRC (2011): Review of EPA Draft IRIS Assessment of Formaldehyde

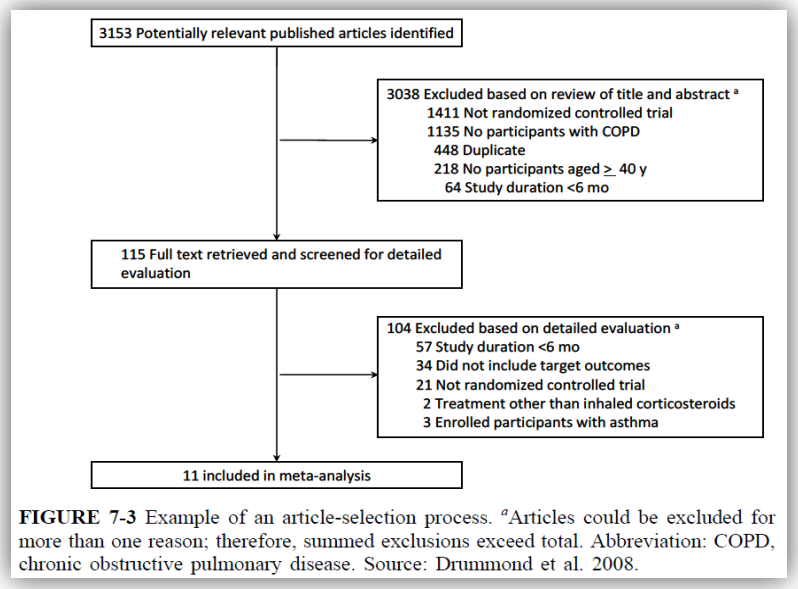


FIGURE 7-3 Example of an article-selection process. [a]Articles could be excluded for more than one reason; therefore, summed exclusions exceed total. Abbreviation: COPD, chronic obstructive pulmonary disease. Source: Drummond et al. 2008.

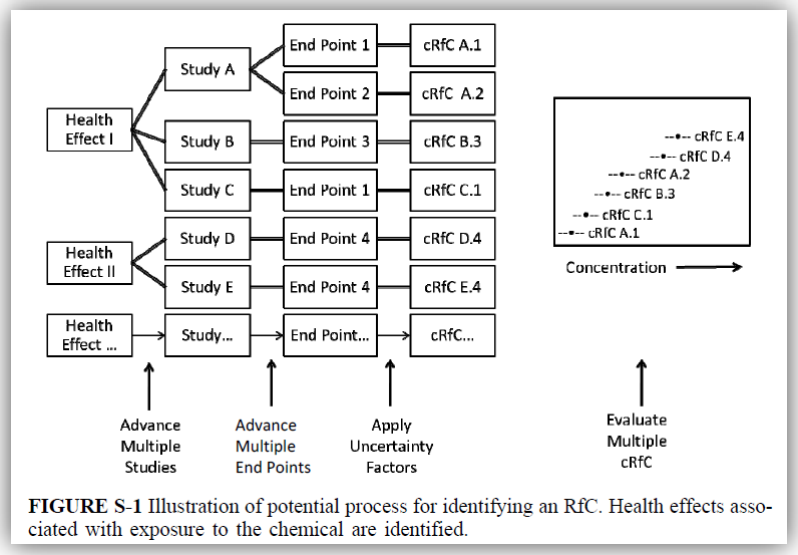
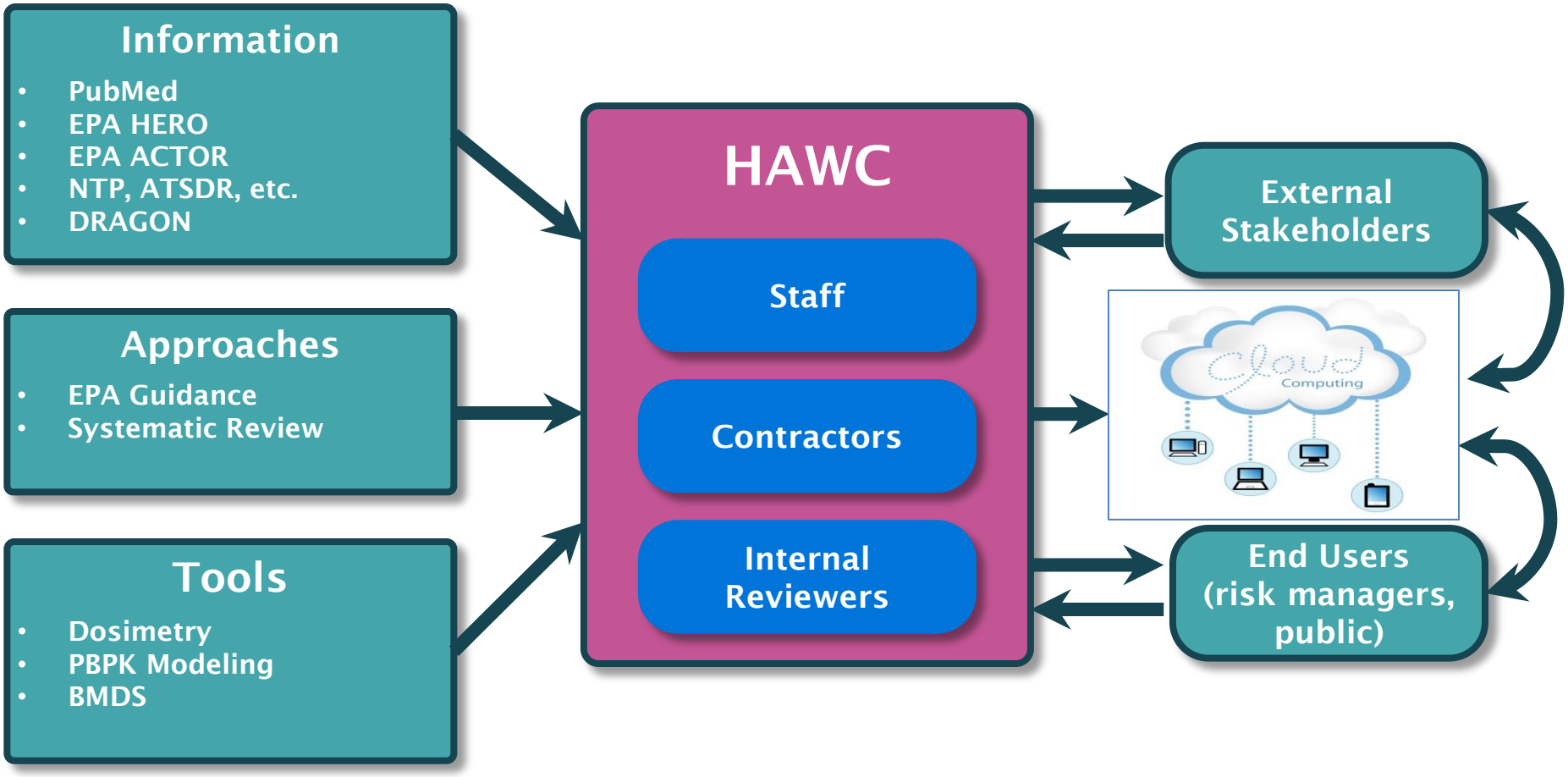
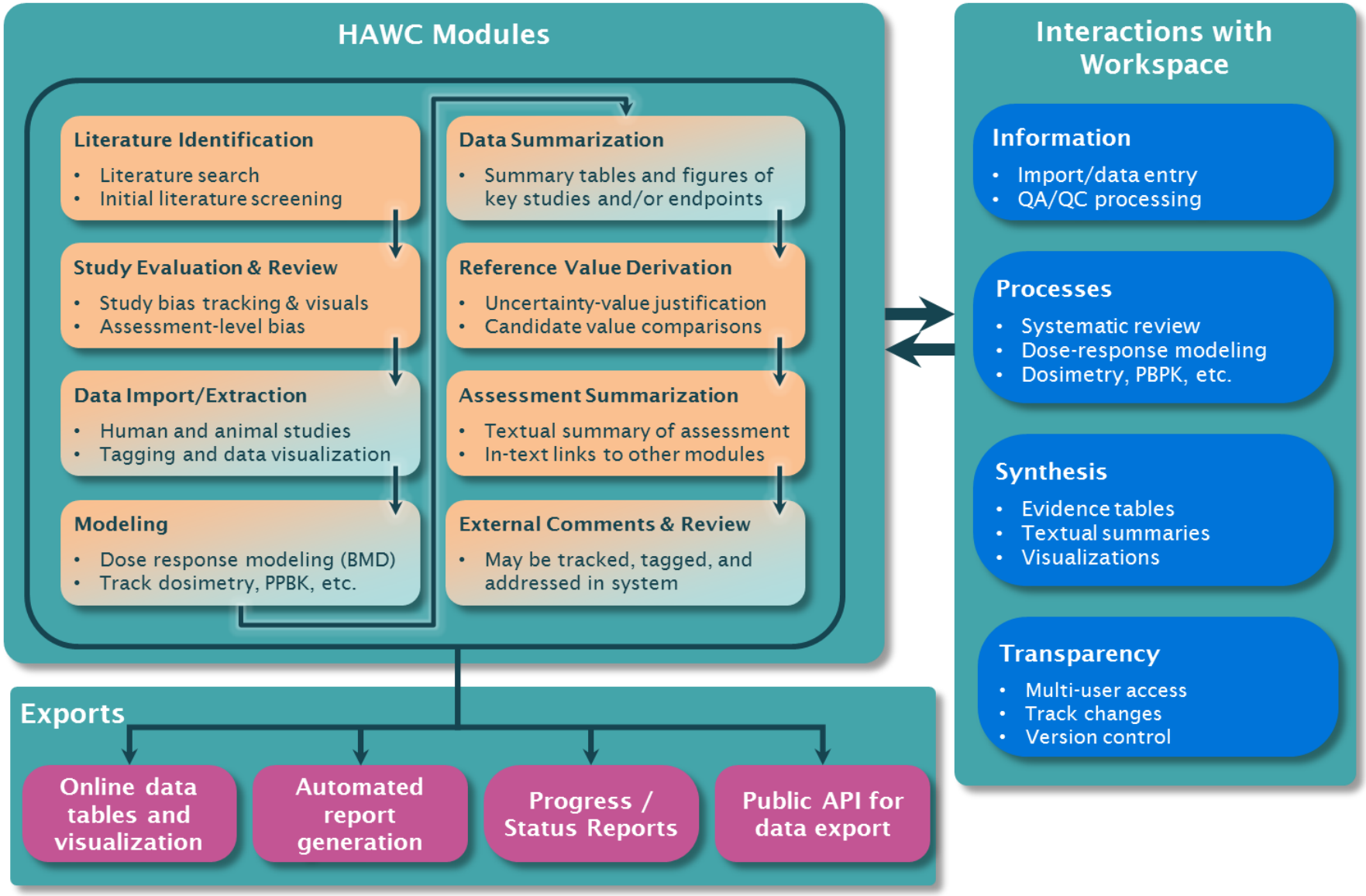


FIGURE S-1 Illustration of potential process for identifying an RfC. Health effects associated with exposure to the chemical are identified.

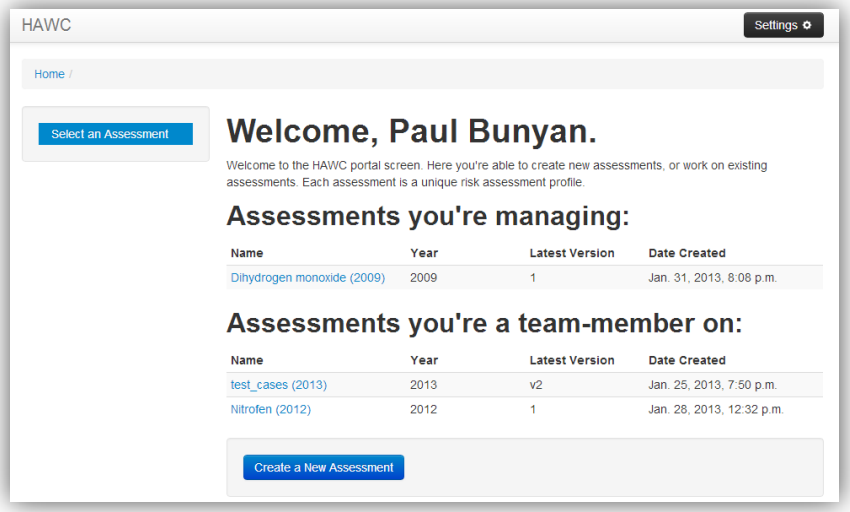
Where does HAWC fit in the human health assessment process?

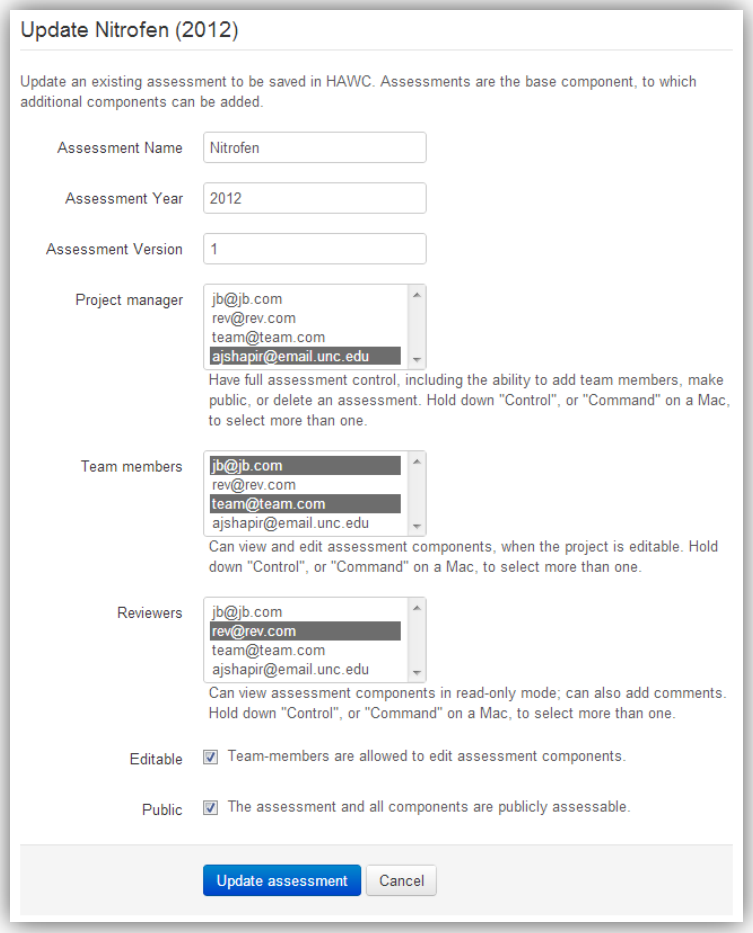


A complex assessment process simplified through modules



Web-based workspace enables sharing and tiered access





Levels of access:

- ***Project managers:*** change permissions settings, including who can edit assessment content and which modules are enabled
- ***Team-members:*** add, edit, and delete content
- ***Reviewers:*** view assessment and potentially add comments before assessment is public
- ***Public:*** if an assessment is made public, the general-public can view and potentially add comments (if commenting is enabled)

HAWC is a prototype website actively under development, feedback is appreciated. Create an account at:

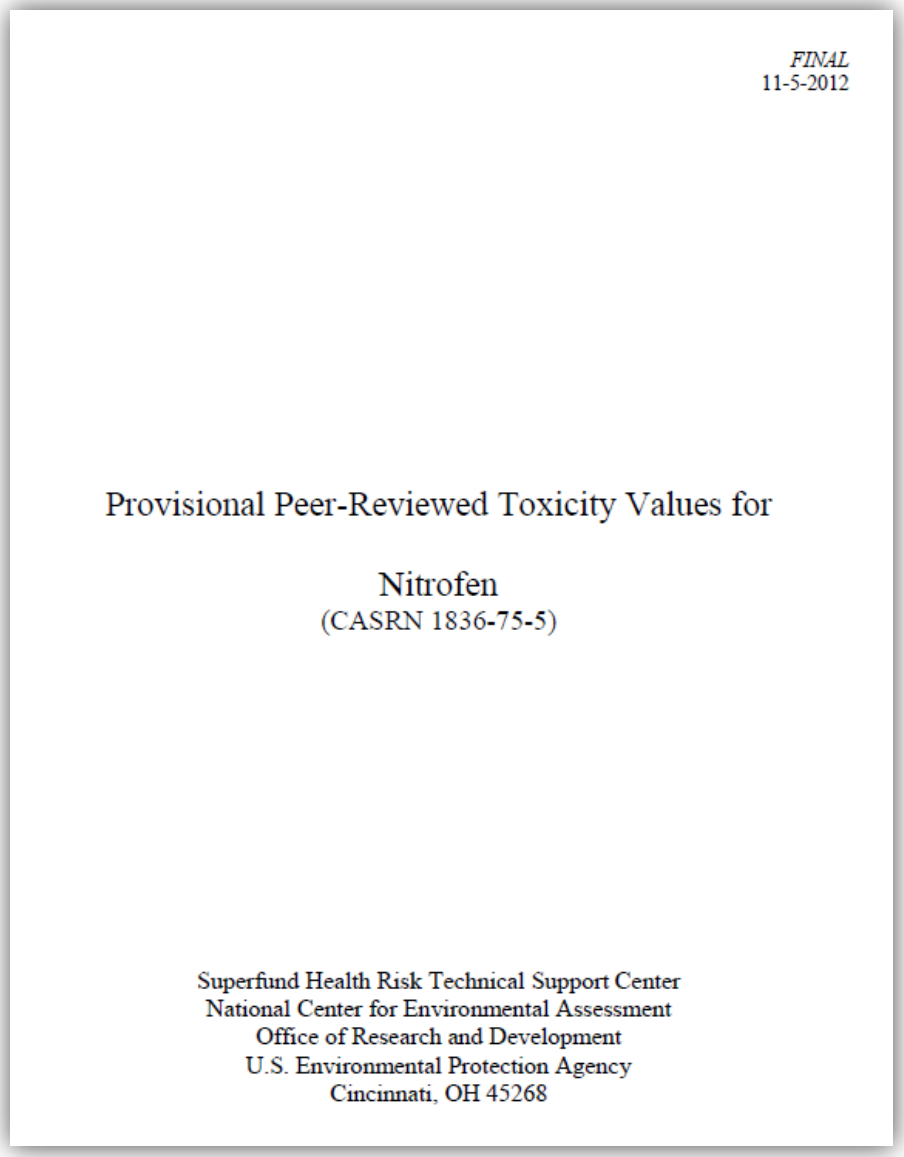
https://hawcproject.org

Compatible browsers:

Chrome IE 9+ Safari Firefox

Case Study: Nitrofen (EPA, 2012)

- Data-rich PPRTV
- Herbicide; currently banned in US but still of interest at some Superfund sites
- Little human data, but animal chronic, subchronic, reproductive, developmental, and cancer data
- Derived Provisional RfD (p-RfD) and Provisional Oral Slope Factor (p-OSF)
- 71-page document (including summary tables, appendices, and supplementary tables)



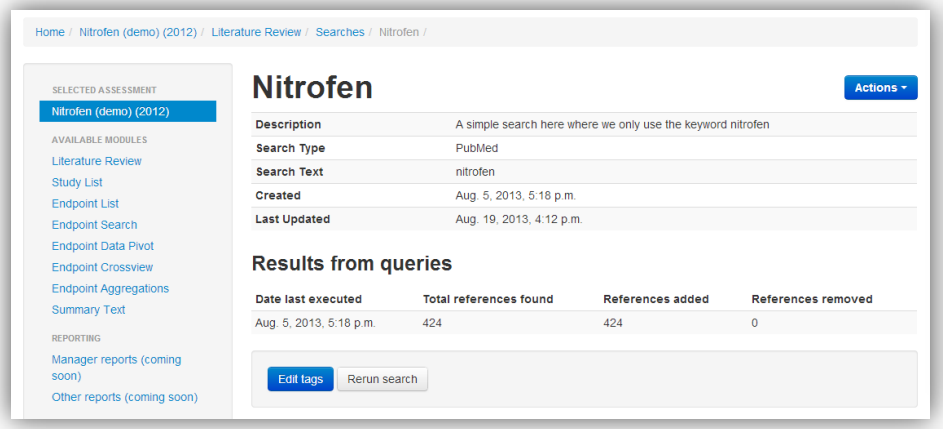
FINAL
11-5-2012

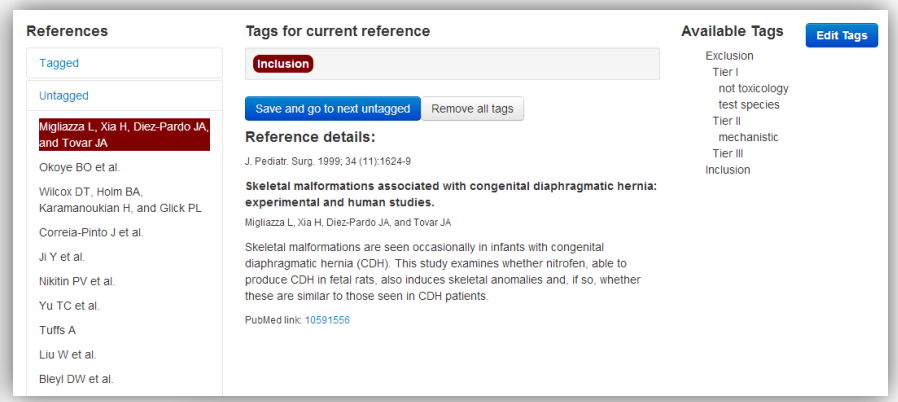
Provisional Peer-Reviewed Toxicity Values for

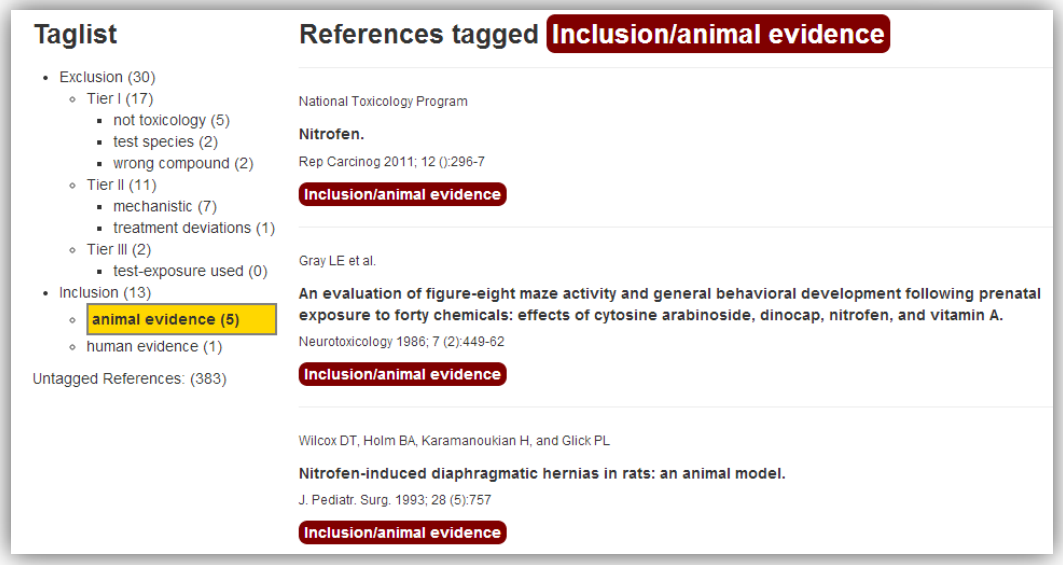
Nitrofen
(CASRN 1836-75-5)

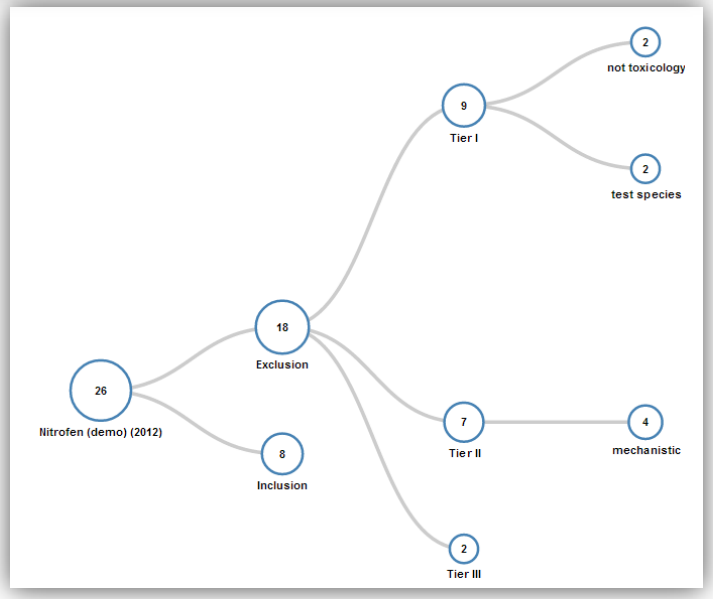
Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Step 1: Literature Search and Initial Screening





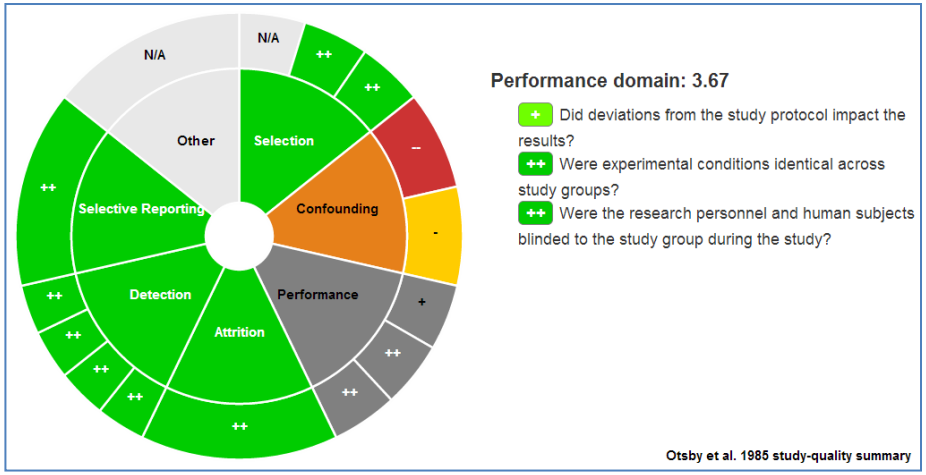




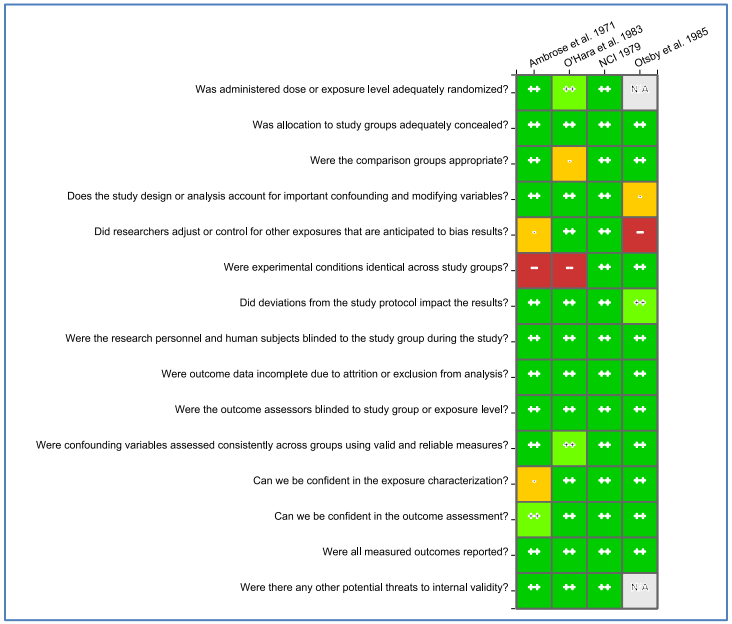
Demonstration links:
[Pubmed Search](#) | [Tagging (login required)](#) | [Tagged Reference (tabular)](#) | [Tagged References (visualization)](#)

Step 2: Evaluation of the Risk of Bias

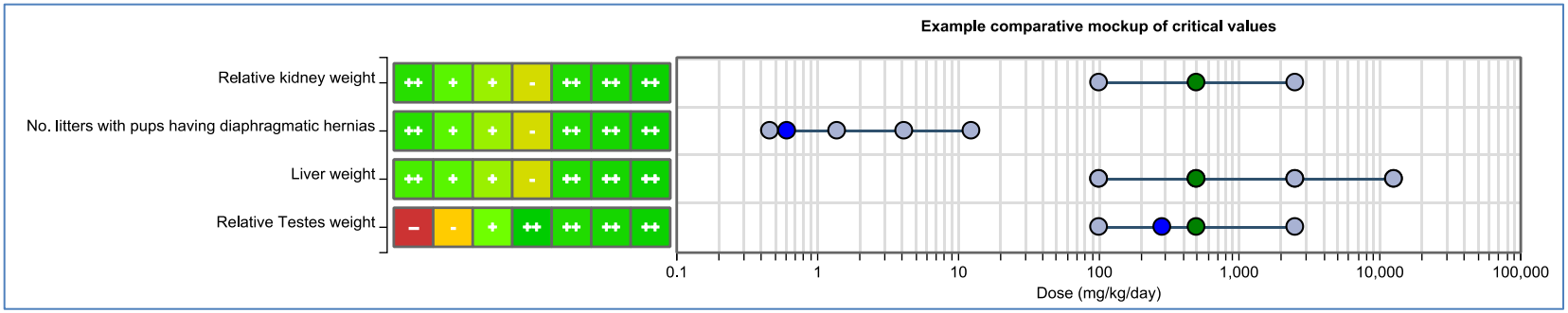
Individual study summary of bias



Cross-study summary of bias



Study/endpoint bias + dose-response



Demonstration links:
Individual Study Bias | Cross-Study Bias | Study Bias + Dose-Response (under development)

Step 3a: Adding and Visualizing Animal Bioassay Data

HAWC Database†

Two methods for loading assessment content:

1. Import from existing database (in-development)
2. Manually enter data from HAWC interface

Female rats

Name	Female rats
Species	Rat
Strain	Wistar
Sex	Female
Dose Groups	5
Siblings	Male rats

Dosing Regime

Dosed Animals	Female rats
Route of Exposure	Oral Diet

Doses	ppm	mg/kg-day
	0.0	0.0
	100.0	10.0
	500.0	51.0
	2500.0	256.0
	12500.0	1282.0

Liver weight

Actions

Endpoint Details

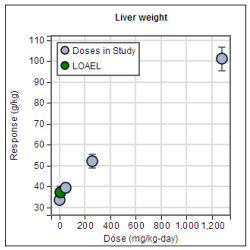
Response Units	g/kg
Data Type	Continuous
Individual Animal Data	False
Endpoint tags	organ weight, liver

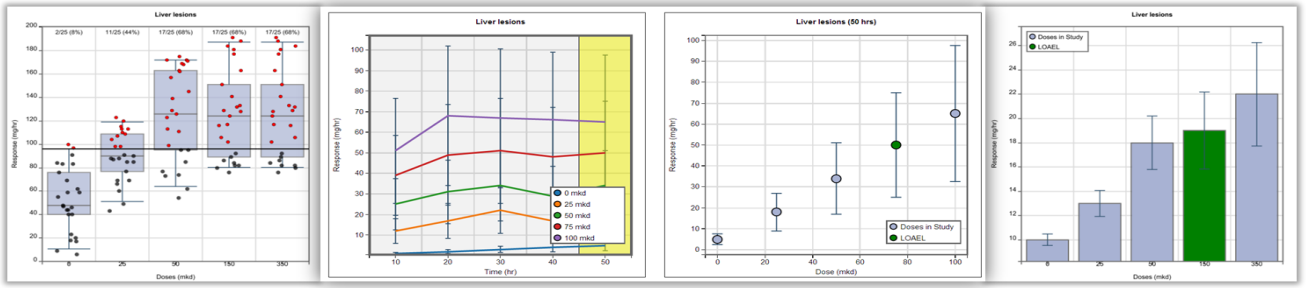
Dataset

Dose (mg/kg-day)	Number of Animals	Response	Std. Dev.
0	9	33.5	2.4
10[a,b]	10	37.3	3.9
51[a]	9	39.5	2.9
256[a]	10	52.1	4.5
1282[a]	6	101	5.4

[a] Significantly different from control ($p < 0.05$)
[b] LOAEL (Lowest Observed Adverse Effect Level)

Plot





Demonstration links:
Animal Group | Endpoint | Dose+Response+Time Plots | Dose-Response Plot | Dose-Response Barchart

Step 3b: Adding and Visualizing Epidemiology Data

Study-population level information

NHANES (2003-2008); adults without cardiovascular disease

Cohort-design	Cross-sectional
Country	United States
State	
Region	
Inclusion Criteria	• NHANES participants 2003-2008 • >20 years of age • urinary BPA data available
Exclusion Criteria	• covariate data missing (education, smoking status, serum glucose levels, systolic/diastolic blood pressure, BMI, cholesterol level) • self-reported cardiovascular disease
Confounding Criteria	

Demographic information

Starting N	4792
N	3967
Sex	Both
Ethnicities	• Black or African American • Hispanic/Latino • White • Unknown/Unspecified
Fraction male	0.474

Available exposures

- urinary BPA concentration (females)
- urinary BPA concentration (males)

Assessed outcome details

Home / bpa (2013) / Epidemiology studies / Carwile and Michels 2011 / NHANES participants 2003-2006 / urinary BPA concentrations / elevated waist circumference (WC) /

SELECTED ASSESSMENT
bpa (2013)

AVAILABLE MODULES
Literature Review
Study List
Endpoint List
Endpoint Search
Endpoint Data Pivot
Endpoint Crossview
Endpoint Aggregations
Summary Text
Comment Summary

EPIDEMIOLOGY
Study List

elevated waist circumference (WC)

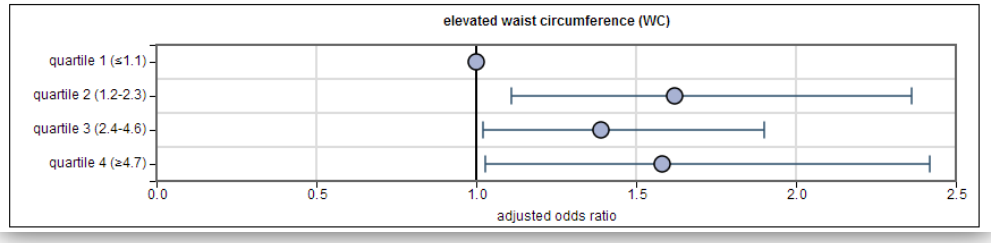
Health effect description

Health Effect	elevated waist circumference (WC)
Diagnostic	medical professional or test
Diagnostic Description	≥102 cm in men or ≥88 cm in women
Outcome N	1330
Statistical Metric Presented	adjusted odds ratio
Adjustment factors	• age • education • race/ethnicity • sex • smoking • urinary creatinine

Results summary and visualizations

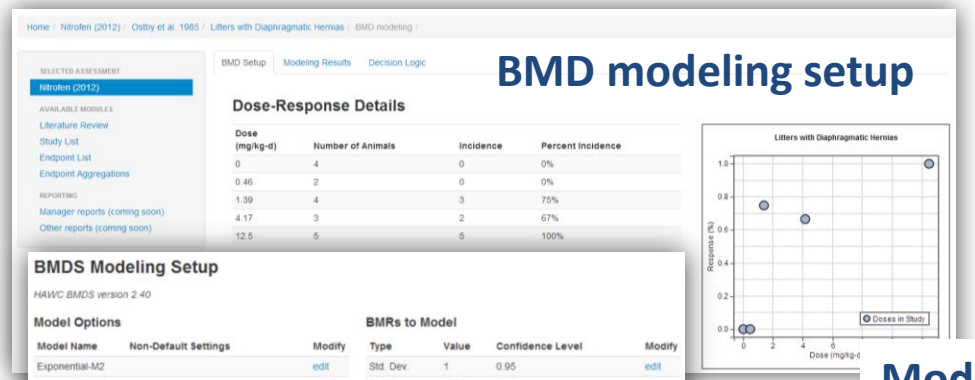
Health results by exposure-group

Exposure-group	N	Estimate	SE	(low, high)	*p*-value
quartile 1 (≤1.1)	658	1	-	(-,-)	-
quartile 2 (1.2-2.3)	680	1.62	-	(1.11,2.36)	-
quartile 3 (2.4-4.6)	657	1.39	-	(1.02,1.9)	-
quartile 4 (≥4.7)	665	1.58	-	(1.03,2.42)	-



Step 4: Conduct Benchmark Dose Modeling

BMD modeling setup



EPA/100/R-12/001
June 2012

Benchmark Dose Technical Guidance

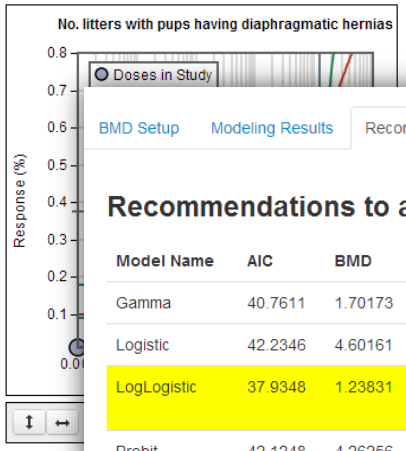
Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

Modeling Results

Model	Global *p*-value	AIC	BMD (10%)	BMDL (10%)	BMD (5%)	BMDL (5%)	Residual of Interest	Output File
Gamma	0.1648	40.7611	1.70173	0.930926	0.828466	0.453208	2.039	View
Logistic	0.1974	42.2346	4.60161	2.81096	2.62356	1.54713	0.222	View
LogLogistic	0.4283	37.9348	1.23831	0.617243	0.58657	0.292378	1.709	View
Probit	0.1974	42.1248	4.26256	2.62289	2.38625	1.42725	0.185	View
LogProbit	0.1432	42.643	4.1219	1.71245	2.86627	1.1908	0.103	View
Weibull	0.1647	40.7611	1.70175	0.930926	0.828472	0.453208	2.04	View
Multistage	0.1648	40.7611	1.70173	0.930926	0.828466	0.453208	2.039	View

Selected model highlighted in yellow

Target BMR	10%
Model	LogLogistic
Notes	

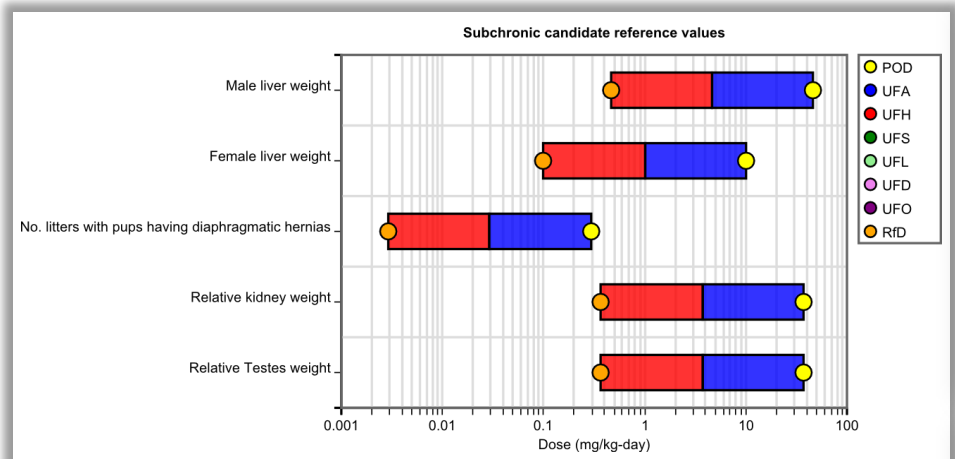


Model Selection Recommendations

Demonstration links:
[BMD Modeling Example]

Step 5a: Data Summary Options: Uncertainty Values and Data Pivots

Uncertainty factor derivation



Uncertainty Factor Values

Animal Group	Endpoint	UF_A	UF_H	UF_S	UF_L	UF_D	UF_O
Male rats	Liver weight	10	10	1	1	1	1
Female rats	Liver weight	10	10	1	1	1	1
Pups	No. litters with pups having diaphragmatic hernias	10	10	1	1	1	1
Male SD rats	Relative kidney weight	10	10	1			
Male SD rats	Relative Testes weight	10	10	1			

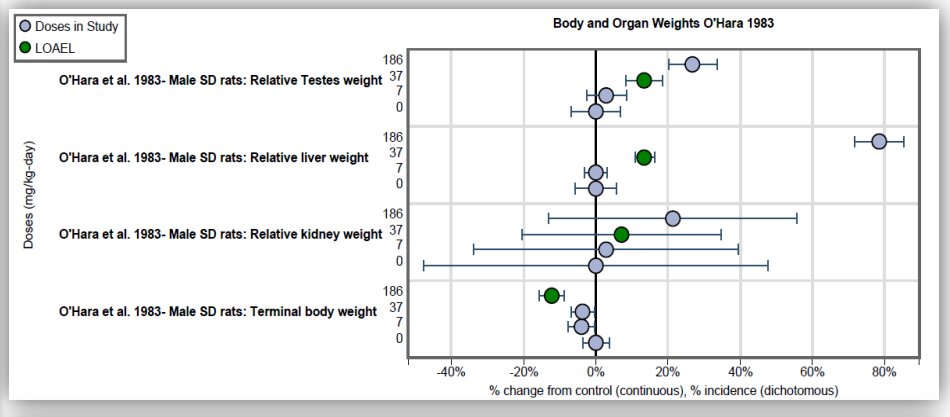
Database incomplete

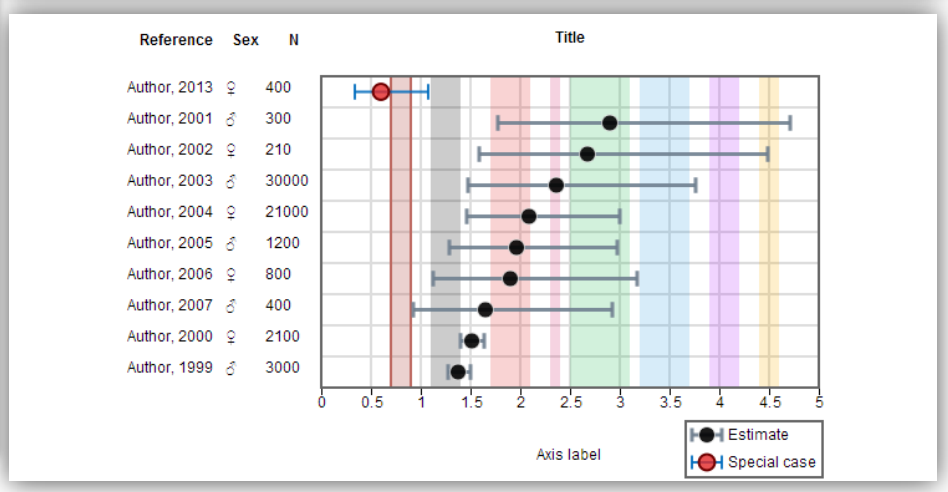
A UFD of 1 is applied because the database includes 1 acceptable 2-generation reproduction study in rats (Kimbrough et al., 1974), 1 acceptable 3-generation reproduction studies in rats (Ambrose et al., 1971e), and multiple developmental studies across 4 species (rat, mouse, rabbit, hamster).

Summary Text

Although chronic toxicity testing of nitrofen has been conducted, effects in fetal animals occurred at much lower relative doses indicati
developmental. Therefore, the critical endpoint is diaphragmatic hernias as indicated by Ostby et al. (1985). This is the same critical e
RfD. A full description concerning the selection of this endpoint as the critical effect and calculation of the appropriate BMDL05 are pr
of the subchronic p-RfD. Consistent with the practice of the EPA, the developmental period is recognized as a susceptible lifestage wh
windows is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991b).

Customizable endpoint comparisons

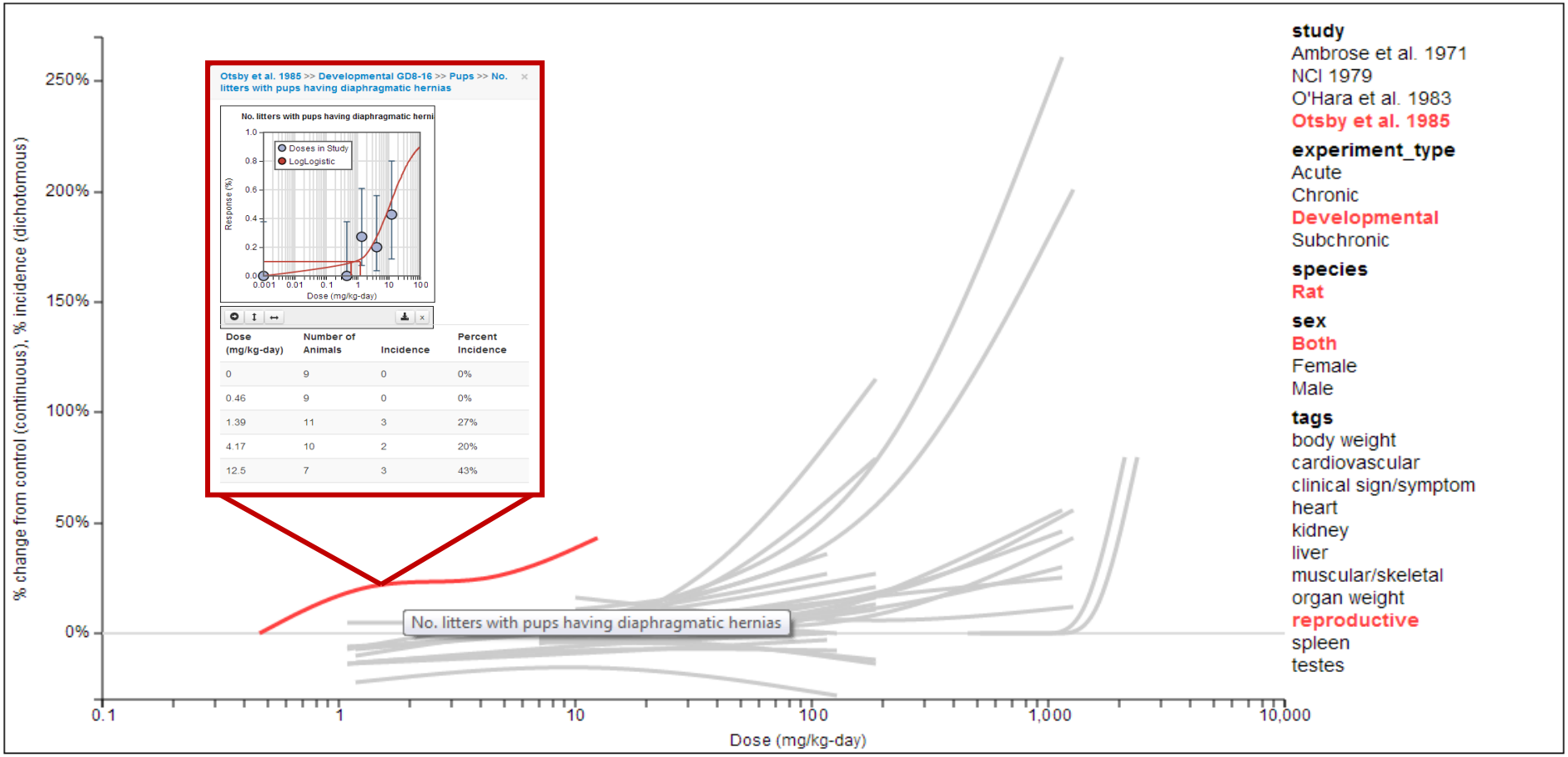




Demonstration links:

Uncertainty Values (left) | Forest-plot (top-right) | Data Pivot Example #1 (bottom-right) | Data Pivot Example #2

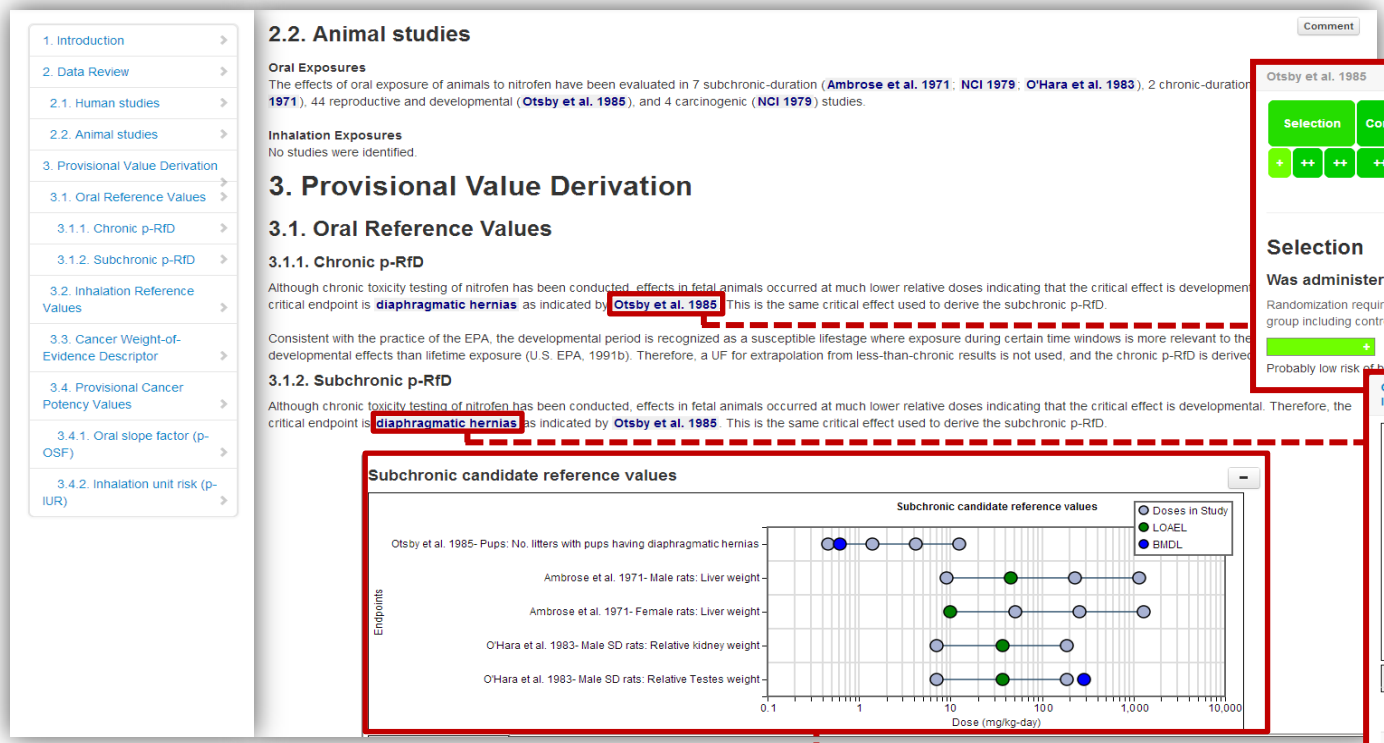
Step 5b: Data Summary Options: Crossview Plot



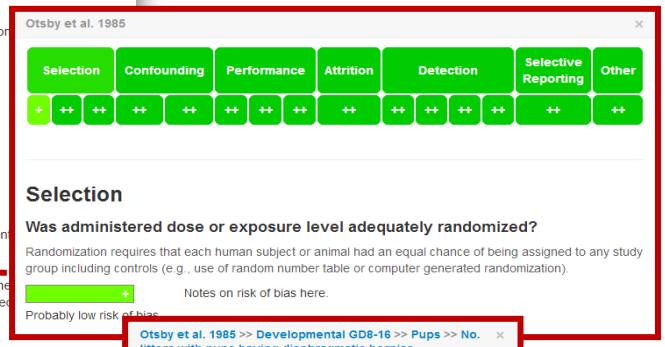
Crossview plot: All animal bioassay dose-response datasets available in a HAWC assessment for a given dose-unit, with response normalized to percent change from control using spline interpolation. Interactive – clicking on any line displays dose-response details and relevant metadata in red. **Live link**

Step 6: Summary Report

Document tree and summary report section

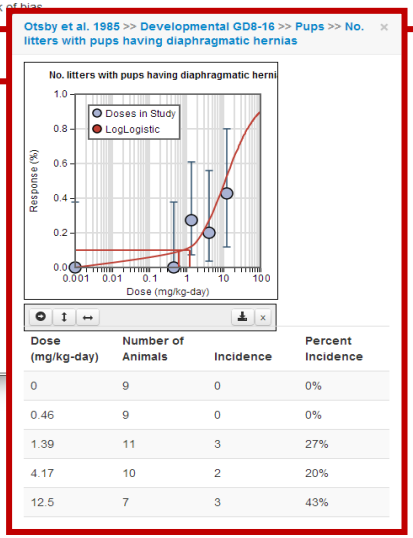


Study quality information



Inline endpoint data aggregation

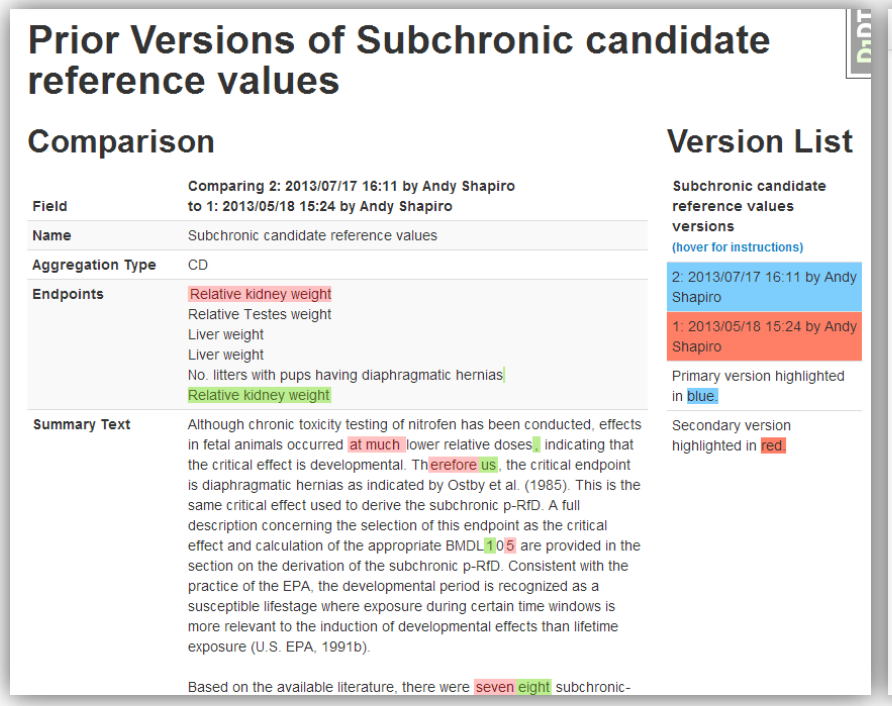
Dose-response details



A web-report with headers and sub-headers, similar to a standard report; however, "smart-tags" dynamically link to other HAWC components. The result is a data-driven summary of the key findings, but allows uses to view details easily, instead of referring to appendices. Live link

Step 7: Public Commenting and Component Versioning

Endpoint aggregation versioning



Prior Versions of Subchronic candidate reference values

Comparison

Field	Comparing 2: 2013/07/17 16:11 by Andy Shapiro to 1: 2013/05/18 15:24 by Andy Shapiro
Name	Subchronic candidate reference values
Aggregation Type	CD
Endpoints	Relative kidney weight Relative Testes weight Liver weight Liver weight No. litters with pups having diaphragmatic hernias Relative kidney weight
Summary Text	Although chronic toxicity testing of nitrofen has been conducted, effects in fetal animals occurred at much lower relative doses, indicating that the critical effect is developmental. Therefore us, the critical endpoint is diaphragmatic hernias as indicated by Ostby et al. (1985). This is the same critical effect used to derive the subchronic p-RfD. A full description concerning the selection of this endpoint as the critical effect and calculation of the appropriate BMDL 10 5 are provided in the section on the derivation of the subchronic p-RfD. Consistent with the practice of the EPA, the developmental period is recognized as a susceptible lifestage where exposure during certain time windows is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991b). Based on the available literature, there were seven eight subchronic-

Version List

Subchronic candidate reference values versions
(hover for instructions)

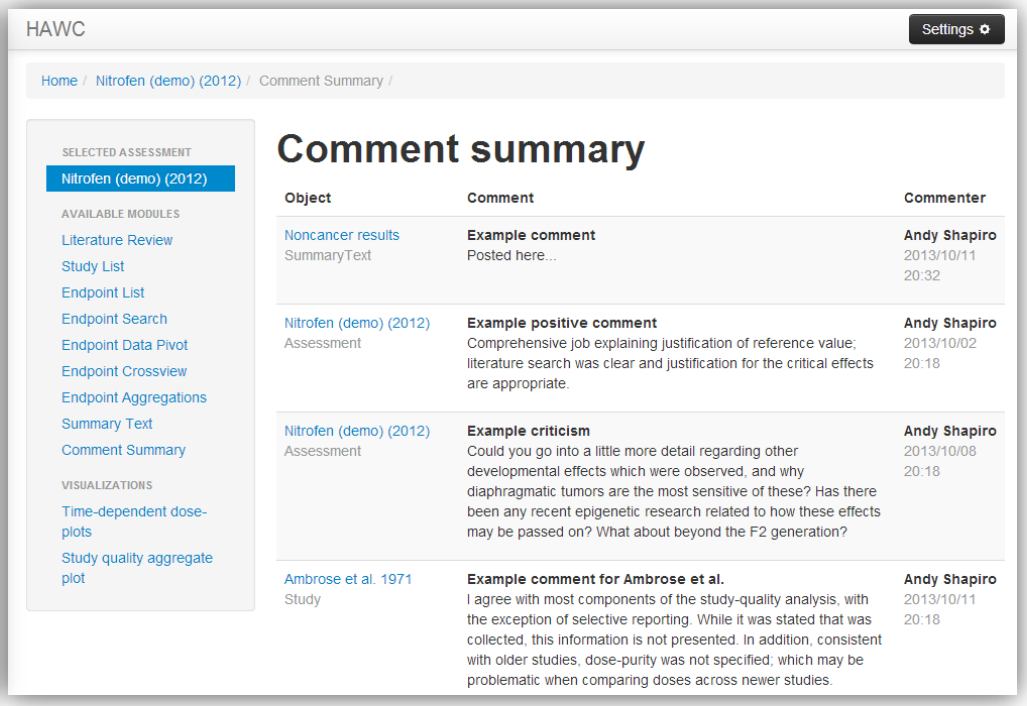
2: 2013/07/17 16:11 by Andy Shapiro

1: 2013/05/18 15:24 by Andy Shapiro

Primary version highlighted in blue.

Secondary version highlighted in red

Peer review comments



HAWC

Settings

Home / Nitrofen (demo) (2012) / Comment Summary /

SELECTED ASSESSMENT
Nitrofen (demo) (2012)

AVAILABLE MODULES
- Literature Review
- Study List
- Endpoint List
- Endpoint Search
- Endpoint Data Pivot
- Endpoint Crossview
- Endpoint Aggregations
- Summary Text
- Comment Summary

VISUALIZATIONS
- Time-dependent dose-plots
- Study quality aggregate plot

Comment summary

Object	Comment	Commenter
Noncancer results SummaryText	**Example comment** Posted here...	**Andy Shapiro** 2013/10/11 20:32
Nitrofen (demo) (2012) Assessment	**Example positive comment** Comprehensive job explaining justification of reference value; literature search was clear and justification for the critical effects are appropriate.	**Andy Shapiro** 2013/10/02 20:18
Nitrofen (demo) (2012) Assessment	**Example criticism** Could you go into a little more detail regarding other developmental effects which were observed, and why diaphragmatic tumors are the most sensitive of these? Has there been any recent epigenetic research related to how these effects may be passed on? What about beyond the F2 generation?	**Andy Shapiro** 2013/10/08 20:18
Ambrose et al. 1971 Study	**Example comment for Ambrose et al.** I agree with most components of the study-quality analysis, with the exception of selective reporting. While it was stated that was collected, this information is not presented. In addition, consistent with older studies, dose-purity was not specified; which may be problematic when comparing doses across newer studies.	**Andy Shapiro** 2013/10/11 20:18

Demonstration links:
Object Versioning (login-required) | Comments Report | Study Comment

Important Considerations

- We appreciate the interest to HAWC and other tools developed by the Carolina Center for Computational Toxicology
- These projects are supported by funding from US EPA (STAR cooperative agreement), NTP/NIEHS (contract), and UNC
- Software license: "…permission to use, copy, and modify the software in source and binary forms, with or without modification ***for non-profit purposes only*** provided that certain criteria are met…"
- **HAWC is a project under active development; therefore, please bear with us as we work to improve the functionalities**
- Please send questions and/or inquiries to: iir@unc.edu