

# Health Assessment Workspace Collaborative (HAWC)

## Project Overview

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# Overall project concept

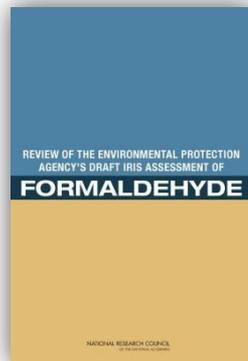
## Web-based workspace to create, store, share, and display data and results and conduct chemical health assessments

- **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

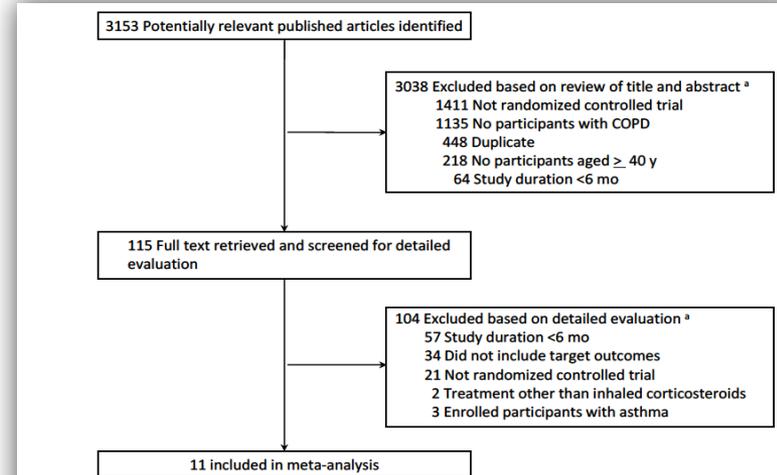


FIGURE 7-3 Example of an article-selection process. <sup>a</sup>Articles could be excluded for more than one reason; therefore, summed exclusions exceed total. Abbreviation: COPD, chronic obstructive pulmonary disease. Source: Drummond et al. 2008.

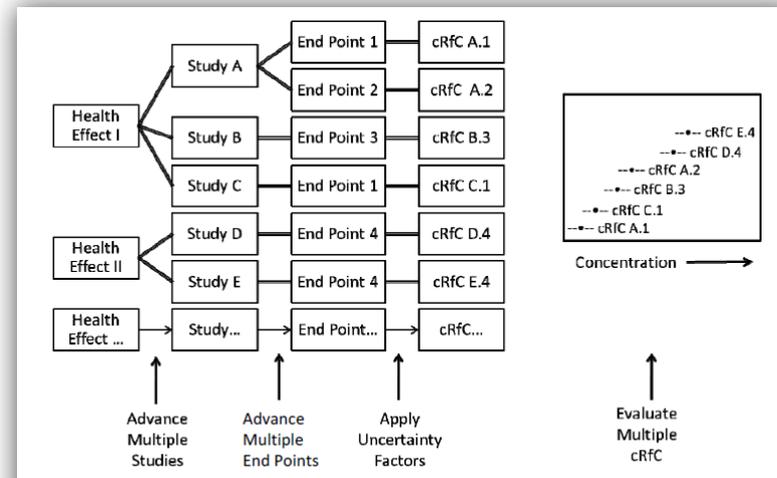
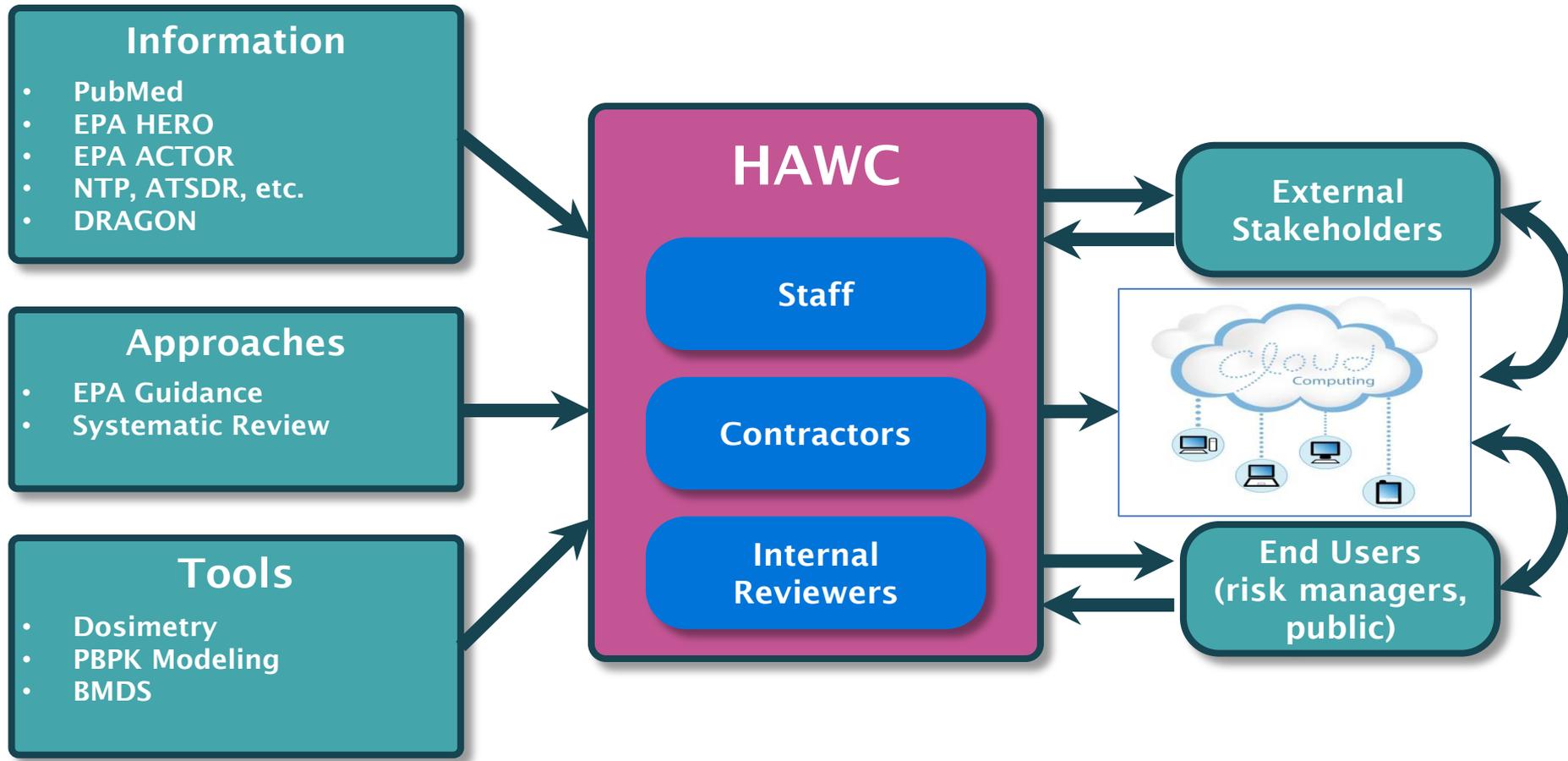
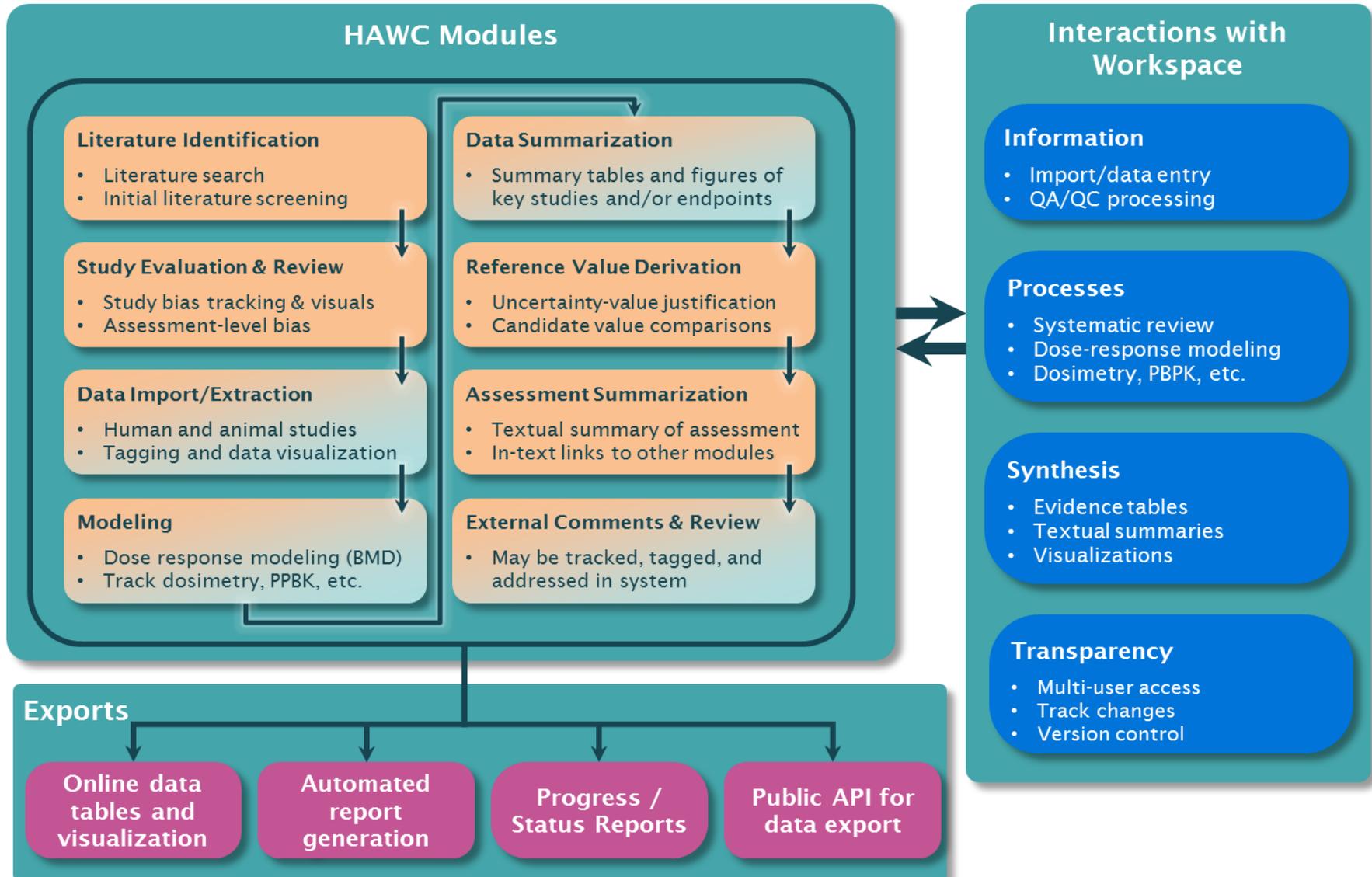


FIGURE S-1 Illustration of potential process for identifying an RfC. Health effects associated with exposure to the chemical are identified.

# 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

HAWC Settings

Home /

Select an Assessment

## Welcome, Paul Bunyan.

Welcome to the HAWC portal screen. Here you're able to create new assessments, or work on existing assessments. Each assessment is a unique risk assessment profile.

### Assessments you're managing:

Name	Year	Latest Version	Date Created
Dihydrogen monoxide (2009)	2009	1	Jan. 31, 2013, 8:08 p.m.

### Assessments you're a team-member on:

Name	Year	Latest Version	Date Created
test_cases (2013)	2013	v2	Jan. 25, 2013, 7:50 p.m.
Nitrofen (2012)	2012	1	Jan. 28, 2013, 12:32 p.m.

Create a New Assessment

## 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)

## Update Nitrofen (2012)

Update an existing assessment to be saved in HAWC. Assessments are the base component, to which additional components can be added.

Assessment Name

Assessment Year

Assessment Version

Project manager   
 rev@rev.com  
 team@team.com  
 ajshapir@email.unc.edu

Have full assessment control, including the ability to add team members, make public, or delete an assessment. Hold down "Control", or "Command" on a Mac, to select more than one.

Team members   
 rev@rev.com  
 team@team.com  
 ajshapir@email.unc.edu

Can view and edit assessment components, when the project is editable. Hold down "Control", or "Command" on a Mac, to select more than one.

Reviewers   
 rev@rev.com  
 team@team.com  
 ajshapir@email.unc.edu

Can view assessment components in read-only mode; can also add comments. Hold down "Control", or "Command" on a Mac, to select more than one.

Editable  Team-members are allowed to edit assessment components.

Public  The assessment and all components are publicly assessable.

Update assessment Cancel

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

<https://hawcproject.org>

Compatible browsers:



## 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

Home / Nitrofen (demo) (2012) / Literature Review / Searches / Nitrofen /

SELECTED ASSESSMENT

**Nitrofen (demo) (2012)**

AVAILABLE MODULES

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

REPORTING

- Manager reports (coming soon)
- Other reports (coming soon)

## Nitrofen

**Description** A simple search here where we only use the keyword nitrofen

**Search Type** PubMed

**Search Text** nitrofen

**Created** Aug. 5, 2013, 5:18 p.m.

**Last Updated** Aug. 19, 2013, 4:12 p.m.

**Results from queries**

Date last executed	Total references found	References added	References removed
Aug. 5, 2013, 5:18 p.m.	424	424	0

[Edit tags](#) [Rerun search](#)

**References**

Tagged

Untagged

**Migliazza L, Xia H, Diez-Pardo JA, and Tovar JA**

Okoye BO et al.

Wilcox DT, Holm BA, Karamanoukian H, and Glick PL

Correia-Pinto J et al.

Ji Y et al.

Nikitin PV et al.

Yu TC et al.

Tuffs A

Liu W et al.

Bleyl DW et al.

**Tags for current reference**

**Inclusion**

[Save and go to next unfagged](#) [Remove all tags](#)

**Reference details:**

J. Pediatr. Surg. 1999; 34 (11):1624-9

**Skeletal malformations associated with congenital diaphragmatic hernia: experimental and human studies.**

Migliazza L, Xia H, Diez-Pardo JA, and Tovar JA

Skeletal malformations are seen occasionally in infants with congenital diaphragmatic hernia (CDH). This study examines whether nitrofen, able to produce CDH in fetal rats, also induces skeletal anomalies and, if so, whether these are similar to those seen in CDH patients.

PubMed link: 10591556

**Available Tags** [Edit Tags](#)

Exclusion

Tier I

not toxicology

test species

Tier II

mechanistic

Tier III

Inclusion

**Taglist**

- Exclusion (30)
  - Tier I (17)
    - not toxicology (5)
    - test species (2)
    - wrong compound (2)
  - Tier II (11)
    - mechanistic (7)
    - treatment deviations (1)
  - Tier III (2)
    - test-exposure used (0)
- Inclusion (13)
  - animal evidence (5)**
  - human evidence (1)

Untagged References: (383)

**References tagged **Inclusion/animal evidence****

National Toxicology Program

**Nitrofen.**

Rep Carcinog 2011; 12 (1):296-7

**Inclusion/animal evidence**

Gray LE et al.

**An evaluation of figure-eight maze activity and general behavioral development following prenatal exposure to forty chemicals: effects of cytosine arabinoside, dinocap, nitrofen, and vitamin A.**

Neurotoxicology 1986; 7 (2):449-62

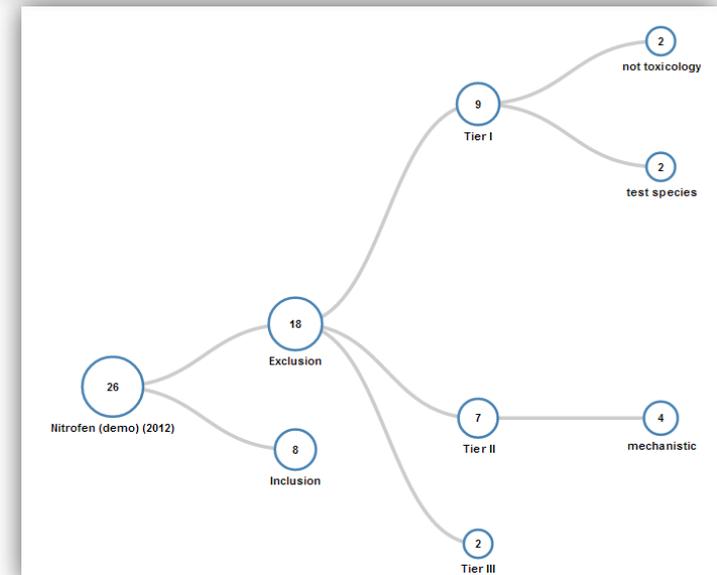
**Inclusion/animal evidence**

Wilcox DT, Holm BA, Karamanoukian H, and Glick PL

**Nitrofen-induced diaphragmatic hernias in rats: an animal model.**

J. Pediatr. Surg. 1993; 28 (5):757

**Inclusion/animal evidence**

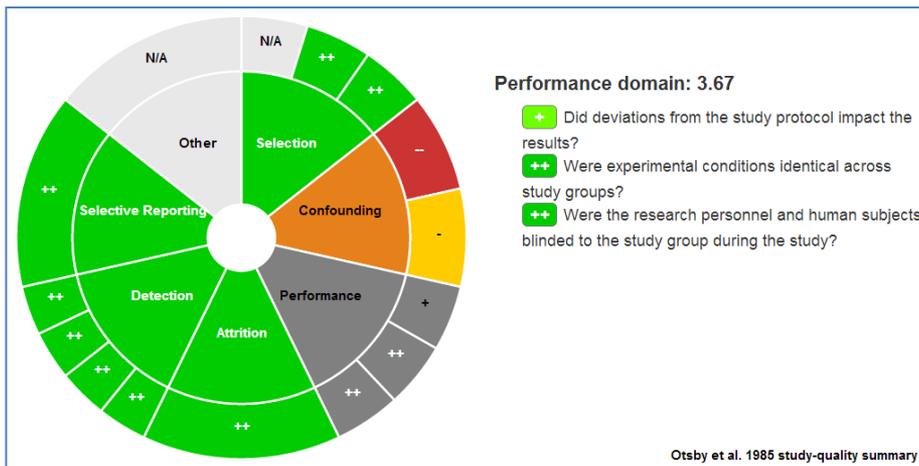


## Demonstration links:

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

# Step 2: Evaluation of the Risk of Bias

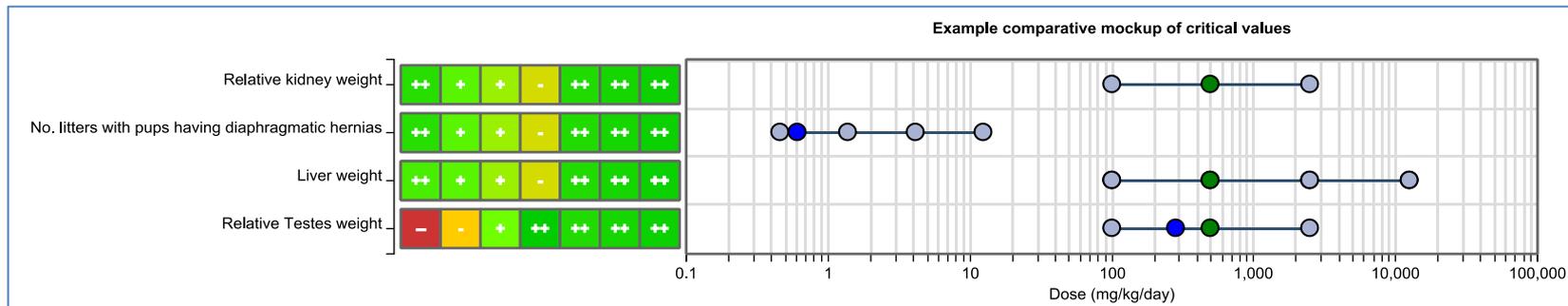
## Individual study summary of bias



## 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



## 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

#### Endpoint Details

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

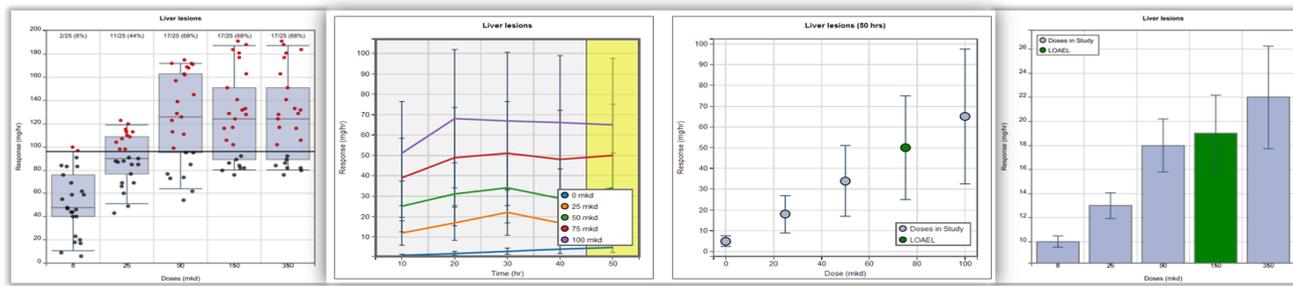
#### Dataset

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

<sup>a</sup> Significantly different from control ( $p < 0.05$ )  
<sup>b</sup> LOAEL (Lowest Observed Adverse Effect Level)

Actions ▾

#### Plot $\alpha$



### 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

<b>Cohort-design</b>	Cross-sectional
<b>Country</b>	United States
<b>State</b>	
<b>Region</b>	
<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>NHANES participants 2003-2008</li> <li>&gt;20 years of age</li> <li>urinary BPA data available</li> </ul>
<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>covariate data missing (education, smoking status, serum glucose levels, systolic/diastolic blood pressure, BMI, cholesterol level)</li> <li>self-reported cardiovascular disease</li> </ul>
<b>Confounding Criteria</b>	

### Demographic information

<b>Starting N</b>	4792
<b>N</b>	3967
<b>Sex</b>	Both
<b>Ethnicities</b>	<ul style="list-style-type: none"> <li>Black or African American</li> <li>Hispanic/Latino</li> <li>White</li> <li>Unknown/Unspecified</li> </ul>
<b>Fraction male</b>	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 X

**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)

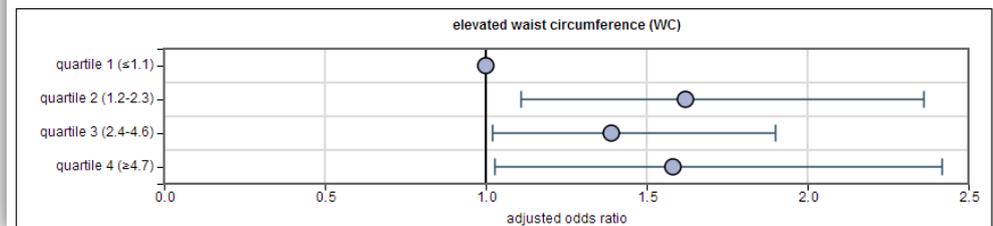
#### Health effect description

<b>Health Effect</b>	elevated waist circumference (WC)
<b>Diagnostic</b>	medical professional or test
<b>Diagnostic Description</b>	≥102 cm in men or ≥88 cm in women
<b>Outcome N</b>	1330
<b>Statistical Metric Presented</b>	adjusted odds ratio
<b>Adjustment factors</b>	<ul style="list-style-type: none"> <li>age</li> <li>education</li> <li>race/ethnicity</li> <li>sex</li> <li>smoking</li> <li>urinary creatinine</li> </ul>

## 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

Home | Nitrofen (2012) | Ostby et al. 1985 | Litters with Diaphragmatic Hernias | BMD modeling

**BMD modeling setup**

**Dose-Response Details**

Dose (mg/kg-d)	Number of Animals	Incidence	Percent Incidence
0	4	0	0%
0.46	2	0	0%
1.39	4	3	75%
4.17	3	2	67%
12.5	5	5	100%

**BMDs Modeling Setup**

HAWC BMDs version 2.40

**Model Options**

Model Name	Non-Default Settings	Modify	Type	Value	Confidence Level	Modify
Exponential-M2		edit	Std Dev	1	0.95	edit
Exponential-M3		edit	Rel Dev	10%	0.95	edit
Exponential-M4		edit	All models will be run using the selected BMRs if appropriate for that particular model type.			

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	<a href="#">View</a>
Logistic	0.1974	42.2346	4.60161	2.81096	2.62356	1.54713	0.222	<a href="#">View</a>
LogLogistic	0.4283	37.9348	1.23831	0.617243	0.58657	0.292378	1.709	<a href="#">View</a>
Probit	0.1974	42.1248	4.26256	2.62289	2.38625	1.42725	0.185	<a href="#">View</a>
LogProbit	0.1432	42.643	4.1219	1.71245	2.86627	1.1908	0.103	<a href="#">View</a>
Weibull	0.1647	40.7611	1.70175	0.930926	0.828472	0.453208	2.04	<a href="#">View</a>
Multistage	0.1648	40.7611	1.70173	0.930926	0.828466	0.453208	2.039	<a href="#">View</a>

Selected model highlighted in yellow

**Target BMR** 10%

**Model** LogLogistic

**Notes**

## Model Selection Recommendations

No. litters with pups having diaphragmatic hernias

Response (%)

**Recommendations to assist BMD Model Selection**

Model Name	AIC	BMD	BMDL	Notes	Warnings	Overall bin	Override
Gamma	40.7611	1.70173	0.930926	12	1	Questionable	N/A
Logistic	42.2346	4.60161	2.81096	13	0	Alternate	N/A
LogLogistic	37.9348	1.23831	0.617243	13	0	Recommended model (lowest BMDL)	N/A
Probit	42.1248	4.26256	2.62289	13	0	Alternate	N/A
LogProbit	42.643	4.1219	1.71245	13	0	Alternate	N/A
Weibull	40.7611	1.70175	0.930926	12	1	Questionable	N/A
Multistage	40.7611	1.70173	0.930926	12	1	Questionable	N/A

**Warnings**

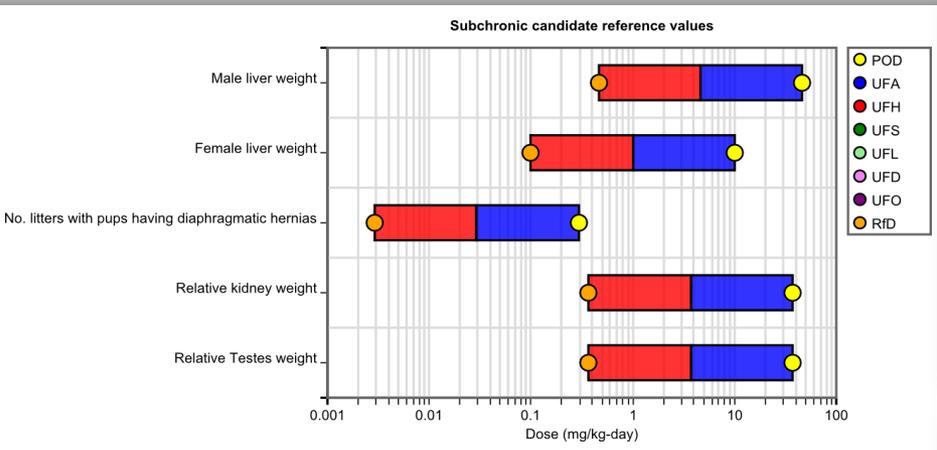
**Questionable Warnings**

FAILED: Residual of Interest is greater than 2.00 (2.040)

**Demonstration links:**  
[BMD Modeling Example](#)

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

## Uncertainty factor derivation



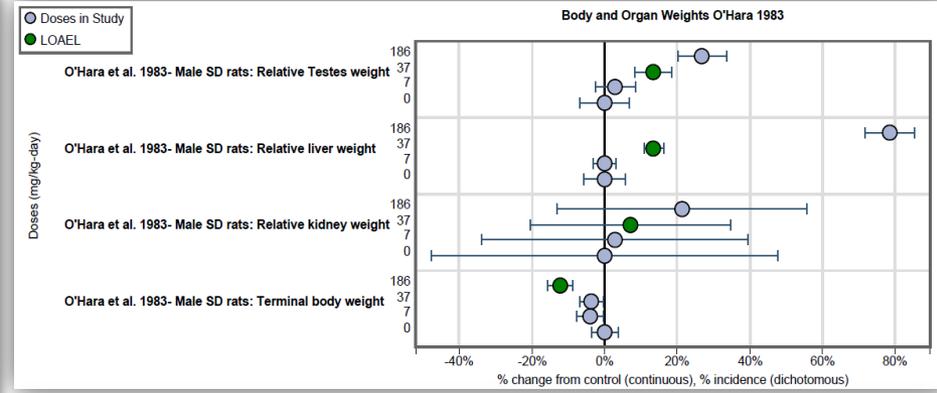
## Uncertainty Factor Values

Animal Group	Endpoint	UF <sub>A</sub>	UF <sub>H</sub>	UF <sub>S</sub>	UF <sub>L</sub>	UF <sub>D</sub>	UF <sub>O</sub>
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	Database incomplete		
Male SD rats	Relative Testes weight	10	10	1	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).		

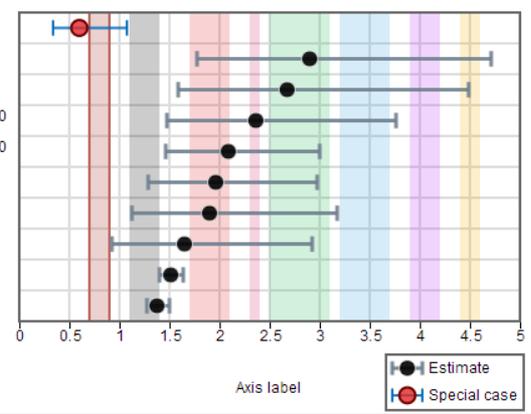
## Summary Text

Although chronic toxicity testing of nitrofen has been conducted, effects in fetal animals occurred at much lower relative doses indicating developmental. Therefore, the critical endpoint is diaphragmatic hernias as indicated by Ostby et al. (1965). This is the same critical effect as the subchronic p-RID. Consistent with the practice of the EPA, the developmental period is recognized as a susceptible life stage with windows is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991b).

## Customizable endpoint comparisons



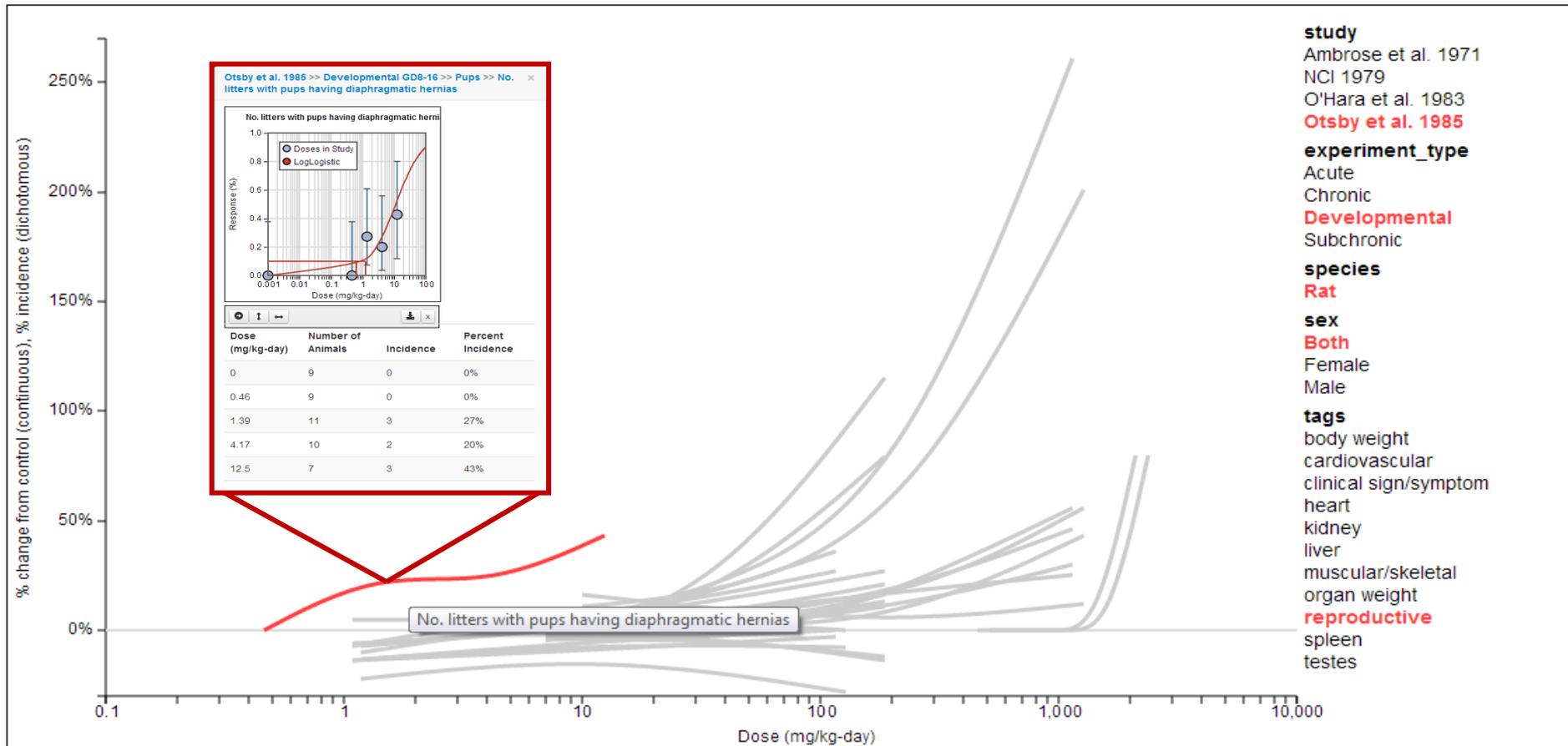
Reference	Sex	N	Title
Author, 2013	♀	400	
Author, 2001	♂	300	
Author, 2002	♀	210	
Author, 2003	♂	30000	
Author, 2004	♀	21000	
Author, 2005	♂	1200	
Author, 2006	♀	800	
Author, 2007	♂	400	
Author, 2000	♀	2100	
Author, 1999	♂	3000	



### 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

- 1. Introduction >
- 2. Data Review >
  - 2.1. Human studies >
  - 2.2. Animal studies >
- 3. Provisional Value Derivation >
  - 3.1. Oral Reference Values >
    - 3.1.1. Chronic p-RfD >
    - 3.1.2. Subchronic p-RfD >
  - 3.2. Inhalation Reference Values >
  - 3.3. Cancer Weight-of-Evidence Descriptor >
  - 3.4. Provisional Cancer Potency Values >
    - 3.4.1. Oral slope factor (p-OSF) >
    - 3.4.2. Inhalation unit risk (p-IUR) >

### 2.2. Animal studies

#### Oral Exposures

The effects of oral exposure of animals to nitrofen have been evaluated in 7 subchronic-duration (Ambrose et al. 1971, NCI 1979, O'Hara et al. 1983), 2 chronic-duration (1971), 44 reproductive and developmental (Otsby et al. 1985), and 4 carcinogenic (NCI 1979) studies.

#### Inhalation Exposures

No studies were identified.

## 3. Provisional Value Derivation

### 3.1. Oral Reference Values

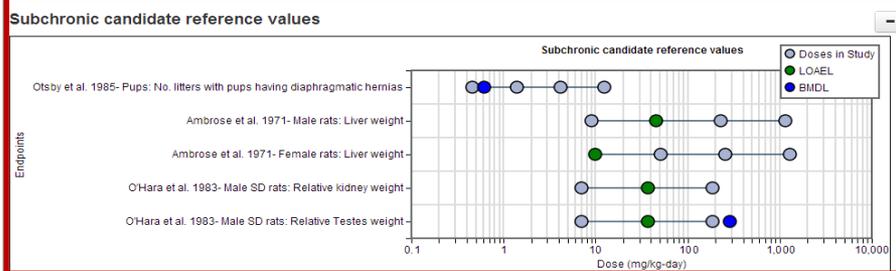
#### 3.1.1. Chronic p-RfD

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. The critical endpoint is **diaphragmatic hernias** as indicated by Otsby et al. 1985. This is the same critical effect used to derive the subchronic p-RfD.

Consistent with the practice of the EPA, the developmental period is recognized as a susceptible life stage where exposure during certain time windows is more relevant to the developmental effects than lifetime exposure (U.S. EPA, 1991b). Therefore, a UF for extrapolation from less-than-chronic results is not used, and the chronic p-RfD is derived.

#### 3.1.2. Subchronic p-RfD

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, the critical endpoint is **diaphragmatic hernias** as indicated by Otsby et al. 1985. This is the same critical effect used to derive the subchronic p-RfD.



Inline endpoint data aggregation

Dose-response details

## Study quality information

Comment

Otsby et al. 1985

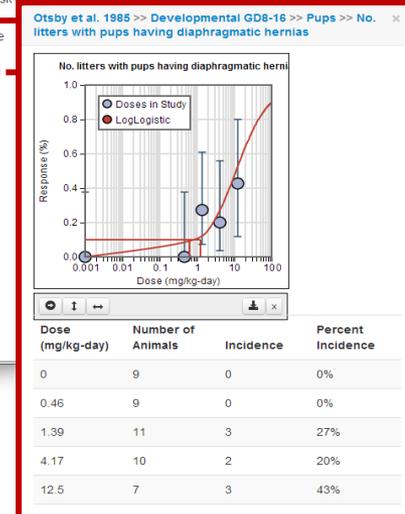
Selection	Confounding	Performance	Attrition	Detection	Selective Reporting	Other
+	++	++	++	++	++	++

**Selection**

**Was administered dose or exposure level adequately randomized?**

Randomization requires that each human subject or animal had an equal chance of being assigned to any study group including controls (e.g., use of random number table or computer generated randomization).

Probably low risk of bias.



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 users 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	<p>Relative kidney weight</p> <p>Relative Testes weight</p> <p>Liver weight</p> <p>Liver weight</p> <p>No. litters with pups having diaphragmatic hernias</p> <p>Relative kidney weight</p>

**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-RID. A full description concerning the selection of this endpoint as the critical effect and calculation of the appropriate BMDL<sub>105</sub> are provided in the section on the derivation of the subchronic p-RID. 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](mailto:iir@unc.edu)