NTP
National Toxicology Program

HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

Andy Shapiro, MSPH
Program Operations Branch
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 16, 2015

HAWC: Presentation Outline

- Overview
  - Project need and design requirements
  - Software structure and permissions schema
- Current capabilities
  - Literature search and initial screening
  - Risk of bias evaluation
  - Animal bioassay data extraction and visualization
  - Epidemiological data extraction and visualization
  - *In vitro* data extraction and visualization
- Future Development

Contributors and collaborators

HAWC was originally my graduate-school master's thesis; now an open-source development project with a steering committee/support from multiple organizations.

- NIEHS/NTP
  - Office of Health Assessment and Translation (OHAT)
  - Program Operations Branch (POB)
- WHO/IARC Monographs Program
- US EPA National Center for Computational Toxicology

- Graduate committee
  - Ivan Rusyn (advisor; Texas A&M University)
  - Rebecca Fry (UNC Chapel-Hill)
  - Fred Wright (NC State University)

Support provided by:

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Grant # RD83574701 RD83516601

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

TEXAS A&M UNIVERSITY

NTP National Toxicology Program
U.S. Department of Health and Human Services

International Agency for Research on Cancer
World Health Organization

Literature based human health assessments are hard

1. **Multiple increasingly complex datastreams and areas of expertise**
2. **No database currently exists which contains data used in the production of these assessments**
3. **Best practices to improve transparency are more data driven and are difficult to manage using conventional approaches**

HAWC software goal:

Web-based content management system to create, store, share, and display data and results in order to conduct human health assessments

Overall HAWC project requirements

- **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, and synthesis
- Facilitates **integration** with existing tools and information
- Enables **stakeholders** to engage, participate, and **dive into the details**
- Makes the process more **transparent**
- **Open source**; should be free to use, and easy to collaborative with

Create a HAWC account or view public-assessments:

https://hawcproject.org

Actively under development; feedback is appreciated.

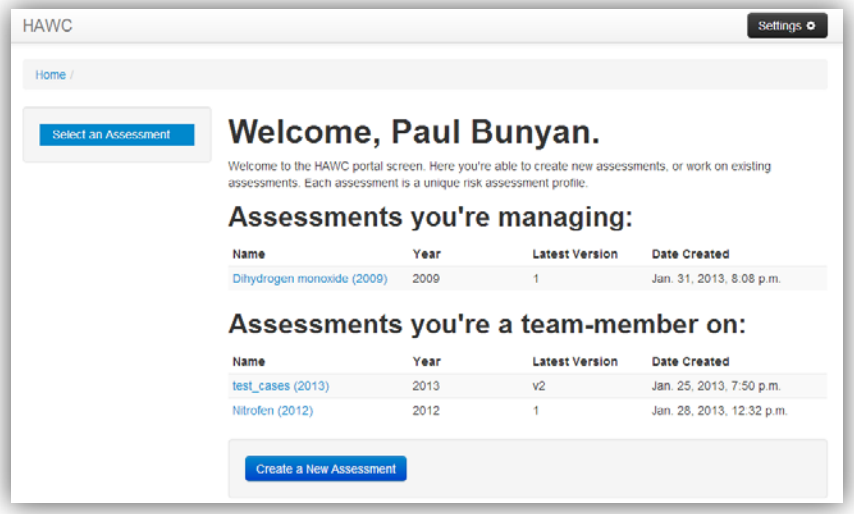
Compatible browsers:

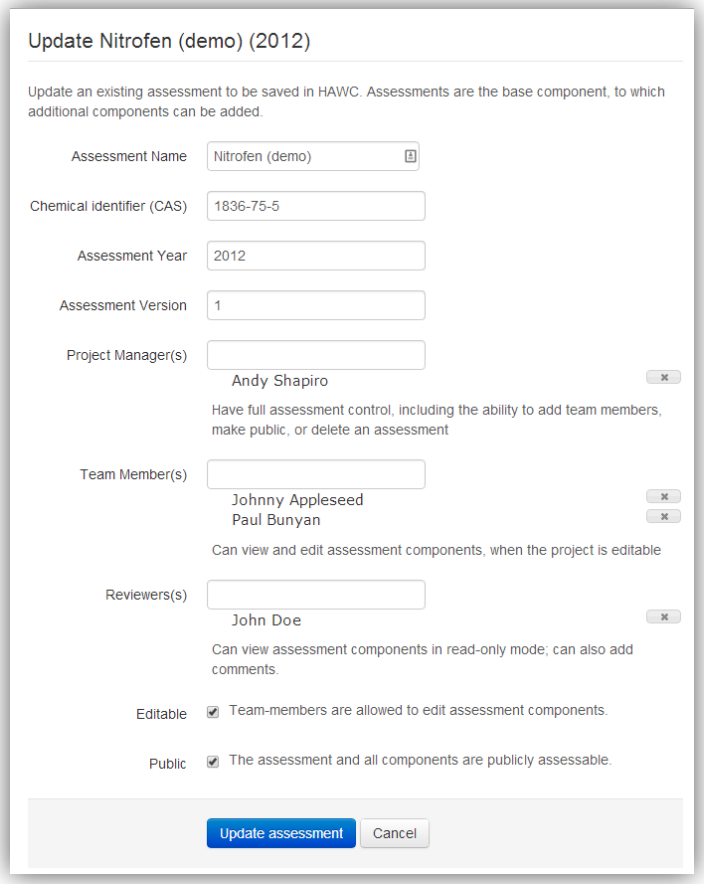
Chrome* IE 9+

Safari Firefox

*Recommended browser

Content management system with tiered access



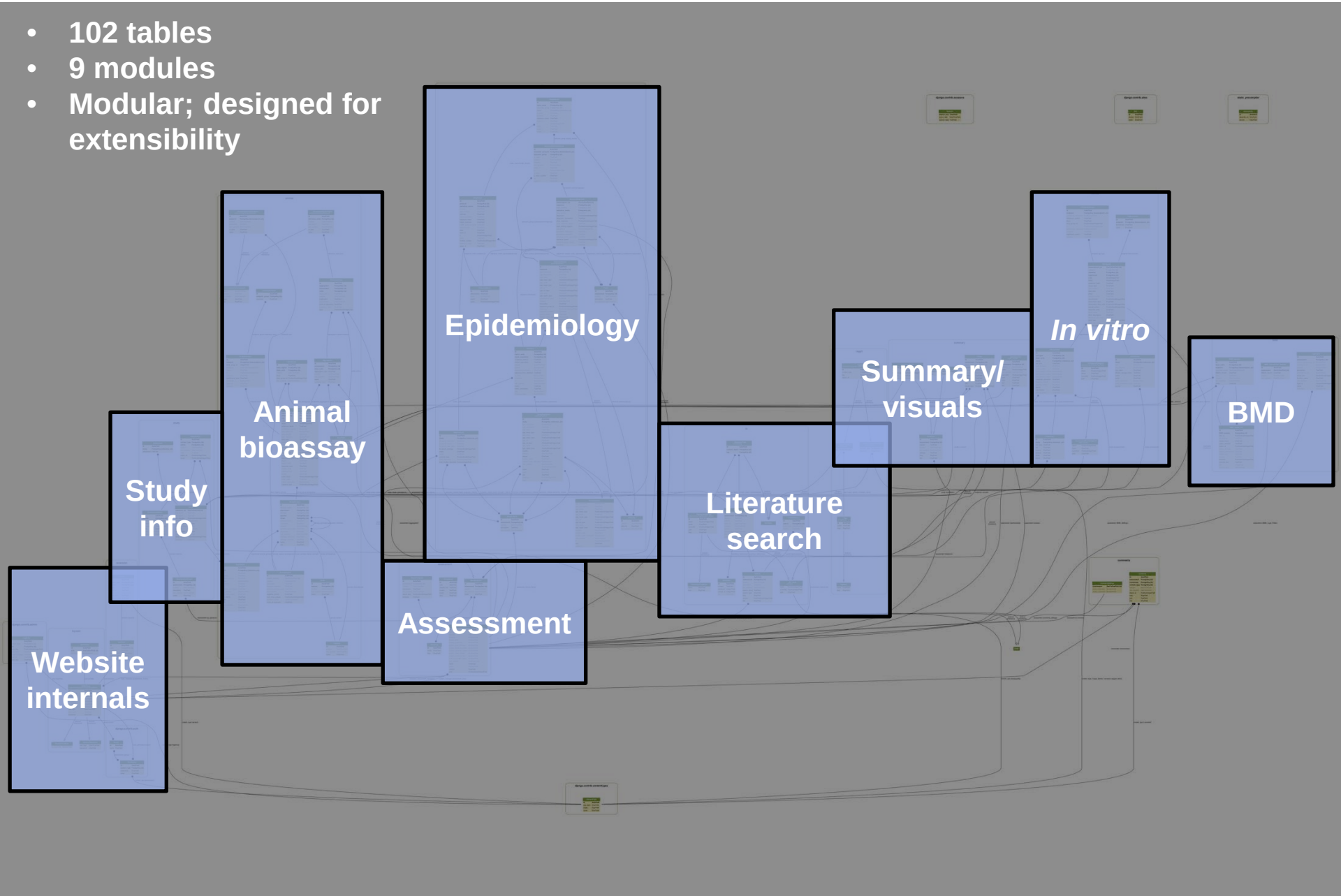


Levels of access:

- **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 database schema

- 102 tables
- 9 modules
- Modular; designed for extensibility



Different assessments demonstrate HAWC features

- WHO/IARC Monograph 112: Parathion
  - **Literature search and initial screening**
- NTP/OHAT Fluoride assessment
  - **Risk of bias evaluation**
  - **Animal bioassay data extraction**
- NTP/OHAT Folic Acid assessment
  - **Epidemiological data extraction**
- NTP/OHAT BPA analogues (ongoing)
  - ***In vitro* data extraction**

Literature search and initial screening

Section 4.2.4- Parathion epigenetics

Actions

Description	Section 4.2.4 Epigenetics
Search Type	Search
Search Database	PubMed
Search Text	("parathion"[MeSH Terms] OR "parathion"[All Fields]) OR ("paraoxon"[MeSH Terms] OR "paraoxon"[All Fields]) NOT ("methyl parathion"[MeSH Terms] OR "methyl parathion"[All Fields]) AND ("rna"[MeSH Terms] OR "rna"[All Fields] OR "rna, messenger"[MeSH Terms] OR "rna"[All Fields] OR "messenger rna"[All Fields] OR "mrna"[All Fields] OR "histones"[MeSH Terms] OR "histones"[All Fields] OR "epigenetic"[All Fields] OR "miRNA"[All Fields] OR "methylation"[All Fields])
Created	Sept. 29, 2014, 7:43 a.m.
Last Updated	June 8, 2015, 8:52 a.m.

Literature Tagging Statistics

Total References	62
Total Tagged	62
Total Untagged	0
Reference details	View by tag Visualization

Results from queries

Date last executed	Total references found	References added	References removed
March 2, 2015, 3:16 a.m.	62	0	0
Feb. 11, 2015, 4:02 a.m.	62	0	0
Sept. 29, 2014, 7:43 a.m.	62	62	0

Literature search and initial screening

Home / IARC Vol 112- Mono 2- Parathion (2015) / Literature Review / Searches & Imports / Section 4.2.4- Parathion epigenetics / Edit Tags /

References

Tagged

Abo-Amer A 2011

Aviram M and Rosenblat M 2008

Ben-Shaul Y et al. 2006

Benke GM and Murphy SD 1974

Boesch-Saadatmandi C et al. 2010

Brophy VH et al. 2000

Bustos-Obregón E, Díaz O, and Sobarzo C 2001

Chang PA, Chen R, and Wu YJ 2005

Chang PA, Long DX, and Wu YJ 2007

Charoenying T et al. 2011

Corbett MD et al. 1988

Damiri B et al. 2012

Dombrowski T et al. 1966

Geyer BC et al. 2012

Gudmundson C and Semb H 1971

Hatcher JF and Swaminathan S 1992

Tags for current reference

Section 4/Inclusion/Toxicokinetics/Metabolism/Human

Save and go to next untagged | Remove all tags

Reference details:

Methods Mol. Biol. 2008; 477 ():259-76

Paraoxonases (PON1, PON2, PON3) analyses in vitro and in vivo in relation to cardiovascular diseases.

Aviram M and Rosenblat M

Mammalian paraoxonases (PON1, PON2, PON3) are a unique family of calcium-dependent hydrolases, with enzymatic activities toward a broad range of substrates (lactones, thiolactones, carbonates, esters, phosphotriesters). Although PONs physiological substrates were not yet identified, some studies suggest that they could be some lactones, or some specific oxidized phospholipids, or products of both enzymatic and nonenzymatic oxidation of arachidonic and docosahexaenoic acid, as well as N-acyl-homoserine lactones (which are quorum-sensing signals of pathogenic bacteria). Since no endogenous substrates for PONs activity determination are available yet, synthetic substrates such as paraoxon, phenyl acetate, and several lactones are used for PONs activity assays. All three members of the PON family (PON 1/2/3) were shown to protect from atherosclerosis development. Their anti-atherogenic biological activities were studied in vitro using serum or cell cultures, and also in vivo, using PON 1/2/3 knockout or transgenic mice, as well as humans - healthy volunteers and atherosclerotic patients (diabetics, hypercholesterolemics, and hypertensives).

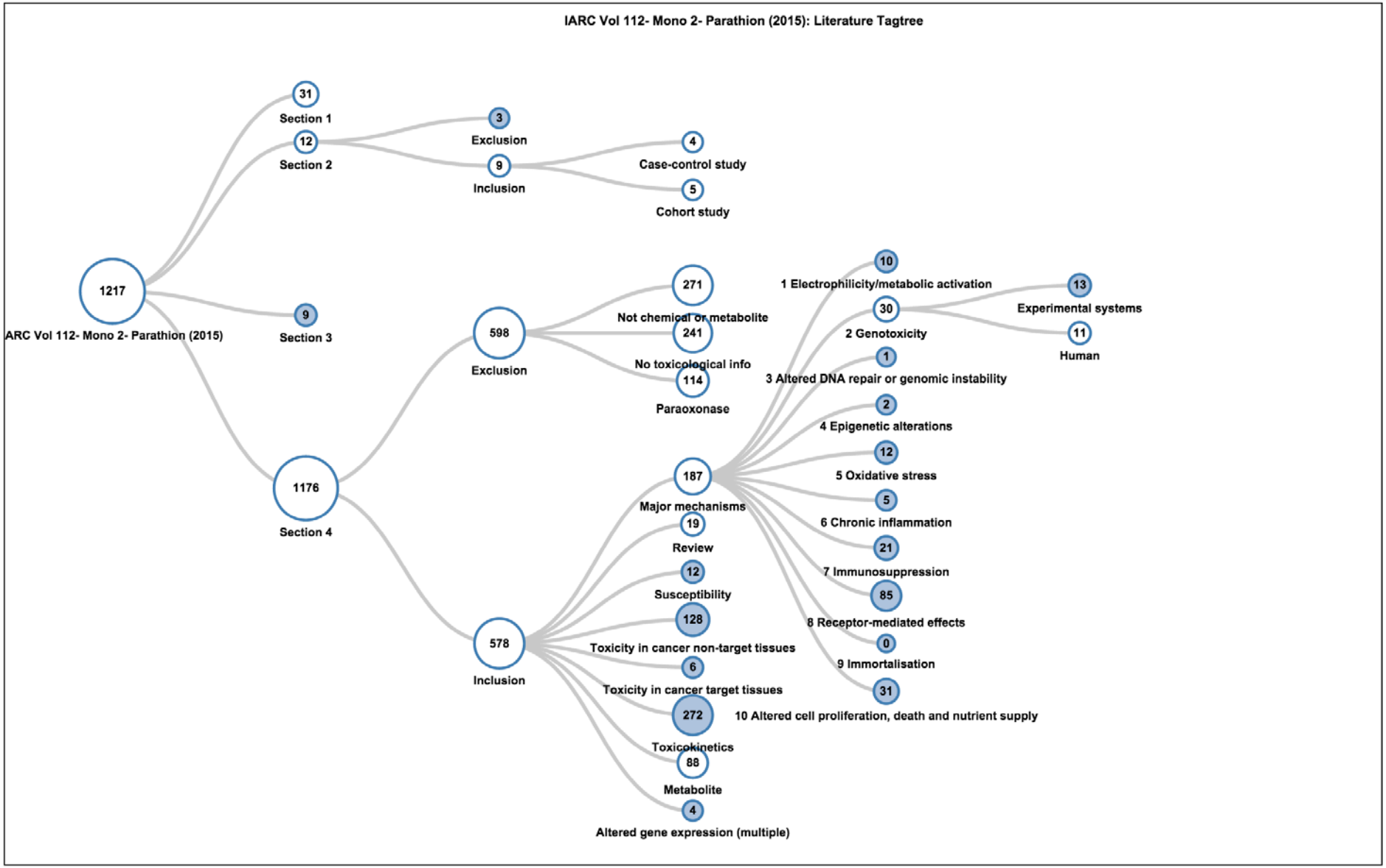
PubMed link: 19082953

Available Tags

Edit Tags

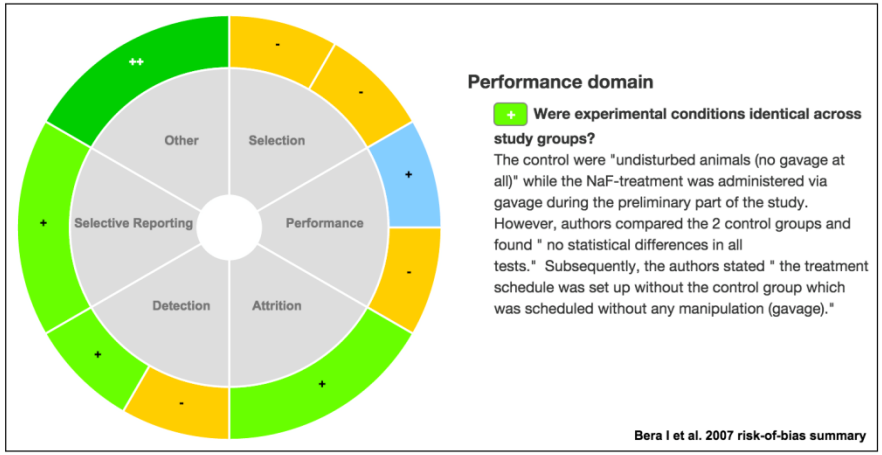
- Section 1
- + Section 2
- + Section 3
- − Section 4
  - − Exclusion
    - Not chemical or metabolite
    - No toxicological info
    - Paraoxonase
  - − Inclusion
    - − Major mechanisms
      - − 1 Electrophilicity/metabolic activation
        - Human
      - − 2 Genotoxicity
        - − Experimental systems
          - Bacteria
          - Drosophila
          - Fish and marine organism
          - Mouse
          - Non-human primates
          - Other
          - Plant
          - Rat
        - Human
      - − 3 Altered DNA repair or genomic instabili
        - Human
      - − 4 Epigenetic alterations
        - Human

Literature search and initial screening

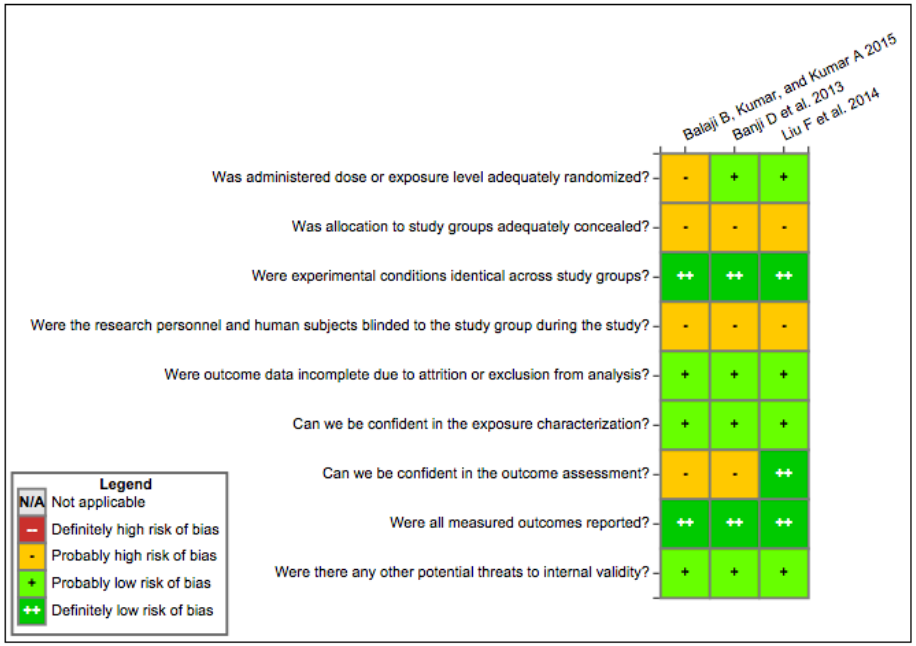


Risk of bias evaluation

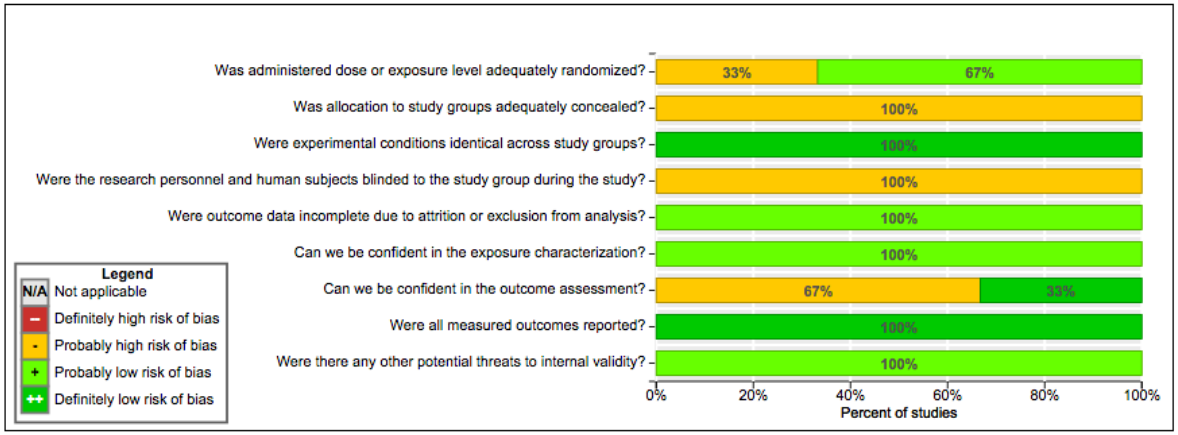
Individual study risk of bias



Heatmap risk of bias for study collection



Summary of risk of bias by metric



Animal bioassay data extraction

Experimental protocol and dose regime

male Kunming mice

Name	male Kunming mice
Species	Mouse
Strain	Kunming
Sex	Male
Duration of observation	180 days
Source	Experimental Animal Center of Shanxi Medical Universit
Lifestage exposed	adult
Lifestage assessed	8 months
Description	Lifestage assessed: approximate values that represents

Dosing regime

Route of exposure	Oral drinking water
Exposure duration	180 days
Number of dose-groups	4
Positive control	No
Negative control	Vehicle-treated

Doses

ppm	mg/kg-day
0	0
11	2.82
22	5.63
45	11.52

Description	Sixty sexually matured male Kunming mice divided rand exposed to distilled water (control group), low F (25 mg/ mg/L F-), medium F (50 mg/L NaF, corresponding to 22 NaF, corresponding to 45 mg/L F-) for 180 days; dose o basis of LD50 values in the mice.

Endpoint summary

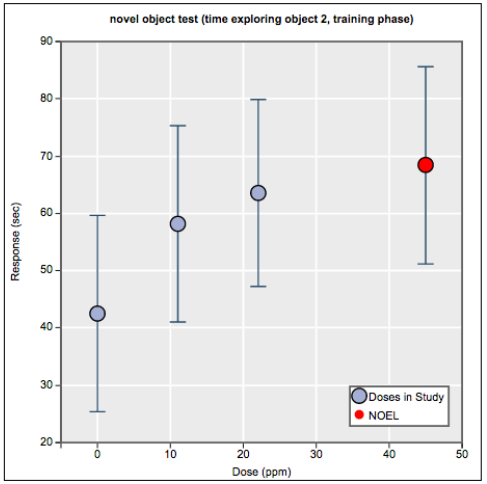
novel object test (time exploring object 2, training phase)

Actions

Endpoint Details

Endpoint name	novel object test (time exploring object 2, training phase)
System	nervous system and special sense organs
Effect	learning and memory: exploration
Diagnostic description	NOR test
Observation time	180 days
Additional tags	memory
Data reported?	☑
Data extracted?	☑
Values estimated?	☑
Location in literature	Figure 2
NOEL	45 ppm
Monotonicity	not-reported
Statistical test description	one-way ANOVA followed by Bonferroni's post hoc test
Trend result	not reported
Power notes	appears underpowered (sample size is ≤50% required), requires approximately 213 animals to detect a 20% change from control
Results notes	not significant
General notes/methodology	There were 15 animals assessed in each group, and all actions were recorded by digital video. The novel object recognition (NOR) test was conducted as described below. First, the mice in each group were allowed to freely explore the open field apparatus (polyvinyl chloride plastic apparatus composed of four 40L×40W×40H cm chambers, floor was divided into a 5×5 grid, and each portion of the grid was equivalent to an 8×8 cm section) for 5 min.

Plot



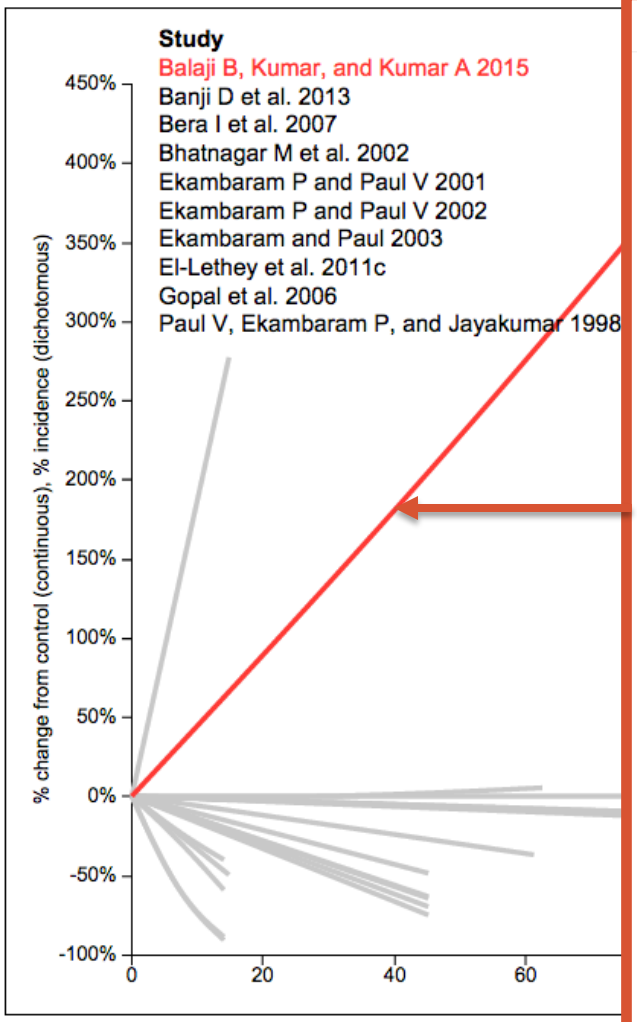
Dataset

Dose (ppm)	Number of Animals	Response	Standard Error
0	15	42.5	8
11	15	58.2	8
22	15	63.5	7.6
45[a]	15	68.4	8

[a] NOEL (No Observed Effect Level)

Animal bioassay visualization

Motor and Sensory Function: Movement Coordination



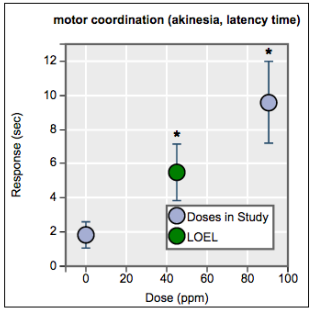
Balaji B, Kumar, and Kumar A 2015 / 30-day study / female Swiss albino mice / motor coordination (akinesia, latency time)

Study | Experiment | Animal Group | Endpoint

Endpoint name	motor coordination (akinesia, latency time)
System	central nervous system
Effect	motor and sensory function: movement coordination
Diagnostic description	Akinesia
Observation time	30 days
Additional tags	motor activity and sensory development
Data reported?	☑
Data extracted?	☑
Values estimated?	☒
Location in literature	Table 1
LOEL	45.25 ppm
Monotonicity	not-reported
Statistical test description	one-way ANOVA and Dunnett's t-test
Trend result	not reported
Power notes	appears underpowered (sample size is ≤50% required), requires approximately 119 animals to detect a 20% change from control
General notes/methodology	Akinesia was measured by observing the latency to move all the four limbs and the test was terminated if the latency exceeded 120 s. Each mouse was initially acclimatized for 5 min on a wooden elevated (30 cm) platform (40 x 40 cm2). Using a stopwatch, the time taken by the mice to move all the four limbs was recorded. Three trials were conducted in each mouse at 5 min intervals. The experiment was performed on the 30th day of the study period.

Dose (ppm)	Number of Animals	Response	Standard Error
0	6	1.83	0.3
45.25[a,b]	6	5.5	0.65
90.49[c]	6	9.6	0.93

[a] Significantly different from control ($p < 0.01$)
[b] LOEL (Lowest Observed Effect Level)
[c] Significantly different from control ($p < 0.001$)



Animal bioassay visualization

Social: Territorial Aggression

study	animal description	route	treatment period	endpoint	units	age at assessment	dose (ppm)
Bataineh and Nusier 2006	Rat, Sprague-Dawley (♂ 16-20)	oral drinking water	chronic (12 weeks)	territorial aggression (boxing bouts with stud male)		not-reported	0.54
							45.25

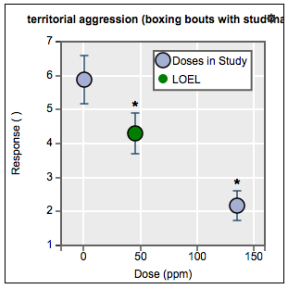
Bataineh and Nusier 2006 / 12 week study / Male Sprague-Dawley rat / territorial aggression (boxing bouts with stud male)

Study | Experiment | Animal Group | Endpoint

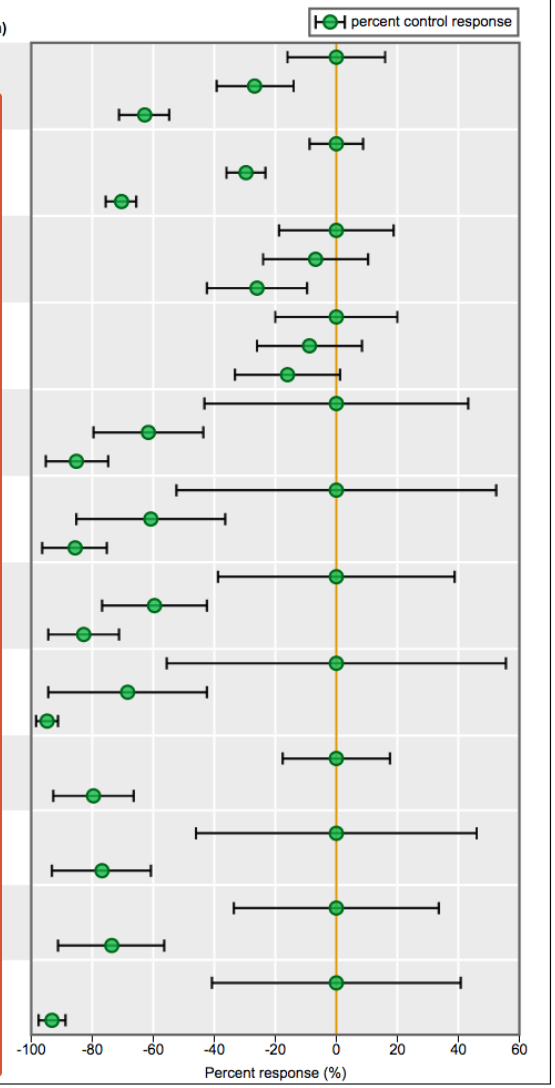
Endpoint name	territorial aggression (boxing bouts with stud male)
System	nervous system and special sense organs
Effect	social: territorial aggression
Additional tags	general behavior
Data reported?	☑
Data extracted?	☑
Values estimated?	☒
Location in literature	Table 1
LOEL	45.25 ppm
Monotonicity	not-reported
Statistical test description	Chi-square test or student t test
Trend result	not reported
Power notes	appears underpowered to detect a change of 10% control (sample size <50% of recommended) [calculated n=194; mean required-N calculation from all dose-groups] appears underpowered to detect a change of 20% control (sample size <50% of recommended) [calculated n=50; mean required-N calculation from all dose-groups]
Results notes	significantly different from control at both doses
General notes/methodology	A rectangular observation cage with a plexiglass front (45x27x40 cm: length x breadth x height) was used for aggression assessment. A stud male rat was placed in the testing arena for 10 days.

Dose (ppm)	Number of Animals	Response	Standard Deviation
0.54	20	5.88	1.52
45.25[a,b]	20	4.31	1.28
135.74[c]	16	2.18	0.83

[a] Significantly different from control ($p < 0.05$)
[b] LOEL (Lowest Observed Effect Level)
[c] Significantly different from control ($p < 0.001$)



Close



Epidemiology data extraction

Study population description

Preschool Children in Southern Nepal: Nepal Nutrition Intervention Project

Study design	Controlled trial
Country	Nepal
Region	Southern Nepal
Inclusion criteria	• All children aged 1-35 months and living in study area during baseline enrollment • Eligible once 1 month old if primary residence in study area
N	22,841
Sex	Male and Female
Ethnicities	• Asian
Fraction male	[0.51]
Age description	children aged 1 to 36 months

Exposure description

Vitamin Supplementation, <36 months

Known exposure routes	• Oral
Measurement metric	intervention
Measurement description	one tablet daily (or half a tablet if 1 year old), containing: iron (12.5 mg) and folic acid (50 ug), iron and folic acid plus zinc, (or placebo) plus as part of a national program: those aged 12 months or older were given 200 000 IU of vitamin A every 6 months and those aged 6–12 months were given 100 000 IU
Measurement metric units	ug/day
Analytical method	"To confirm that the supplements used were active, we selected and tested the iron and zinc status of a sample of children aged 24 months or older after 12 months of follow-up" via blood sample, but NOT done for folate...
Control description	placebo

Assessed outcome

Acute lower respiratory infection (ALRI)

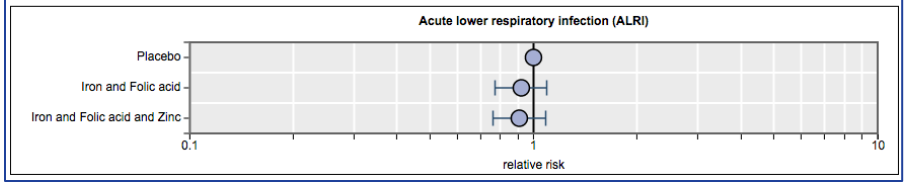
Assessed outcome description

Assessed outcome	Acute lower respiratory infection (ALRI)
Location in literature	Table 5
Population description	Preschool Children in Nepal, 2001-2003
Diagnostic	self-reported
Diagnostic description	Diagnosed acute respiratory infection as one or more consecutive days of fever, cough, and difficulty breathing (all three symptoms had to be present on at least 1 day during the episode) with a minimum of 7 days between episodes
Main finding supported?	inconclusive
Statistical metric presented	relative risk
Statistical metric description	We compared treatment groups by baseline household, maternal, and child characteristics to assess imbalance after randomisation. We adjusted estimates of standard error to account for the clustered randomisation, using the generalised estimating equations approach.
Statistical power sufficient?	not reported or calculated
Dose response trend?	not-applicable
Effect tags	immunological, infections, respiratory
Adjustment factors	• cluster randomization

Results by exposure-group

Exposure-group	N	Relative risk	*p*-value
Placebo	-	1.0 (1.0, 1.0)	n.s.
Iron and Folic acid[a]	-	0.92 (0.77, 1.09)	n.s.
Iron and Folic acid and Zinc	-	0.91 (0.76, 1.08)	n.s.

[a] Main finding as selected by HAWC assessment authors.



Epidemiology data visualization

Draft: Eczema, Prospective Studies

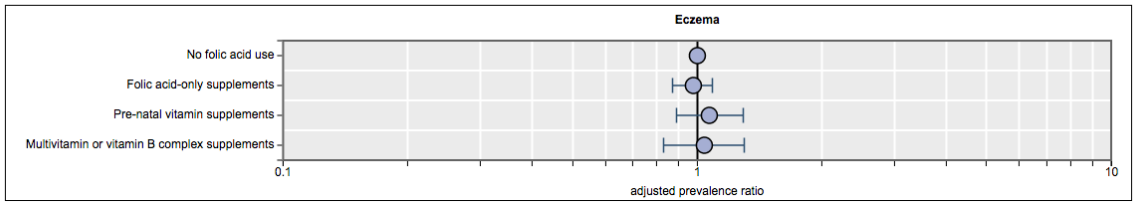
Study	Population Name	Assessed Outcome Name	Exposure Measure	Exposure Comparison	Statistical Metric Abbreviation	Eczema
Bekkers, 2012	PIAMA birth cohort, 1996-1997	Eczema				
Dunstan, 2012	Pregnant women in Western Australia	Eczema				
Dunstan, 2012	Pregnant women in Western Australia	Eczema				
Dunstan, 2012	Pregnant women in Western Australia	Eczema				
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema un				
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema un				
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema un				

Bekkers, 2012 / PIAMA birth cohort, 1996-1997 / Folic acid containing supplements during pregnancy / Eczema

Assessed outcome	Eczema
Population description	PIAMA birth cohort, 1996-1997
Diagnostic	self-reported
Diagnostic description	an itchy rash that came and went on typical eczema sites (the folds of the elbows or behind the knees, around ears or eyes or in front of the ankles)
Main finding supported?	inconclusive
Prevalence Incidence	0.180 - 0.142, reported by age (Table 2)
Statistical metric presented	adjusted prevalence ratio
Statistical metric description	Longitudinally, generalised estimating equations (GEEs) with a log link function were used to obtain prevalence ratios (PRs). GEEs take into account the correlation between repeated measurements in the same individual. An m-dependent correlation structure was used: m=7 for the other outcome measures. An interaction term with age was included in the GEE model to allow the association between maternal use of supplements and the outcomes to vary with age.
Statistical power sufficient?	not reported or calculated
Dose response trend?	not-applicable
Effect tags	dermal, hypersensitivity, immunological
Adjustment factors	• maternal allergy • maternal education • maternal smoking during pregnancy • number older siblings

Exposure-group	N	Adjusted prevalence ratio	*p*-value
No folic acid use	1302	1.0	n.s.
Folic acid-only supplements[a]	1998	0.98 (0.87, 1.09)	n.s.
Pre-natal vitamin supplements	287	1.07 (0.89, 1.29)	n.s.
Multivitamin or vitamin B complex supplements	199	1.04 (0.83, 1.3)	n.s.

[a] Main finding as selected by HAWC assessment authors.

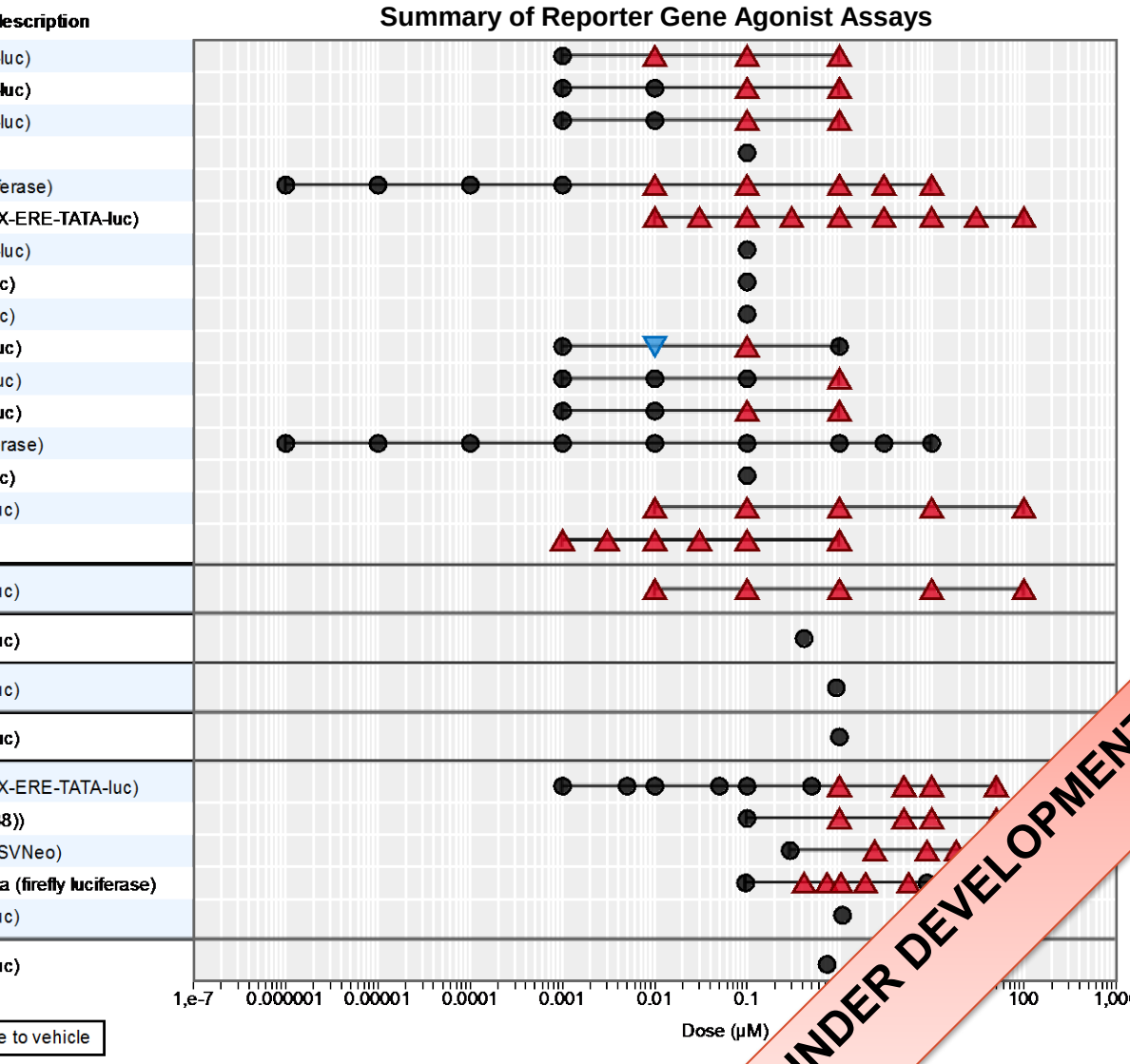


Intake
te Measure
10

NTP/OHAT BPA analogues

In vitro data extraction and visualization

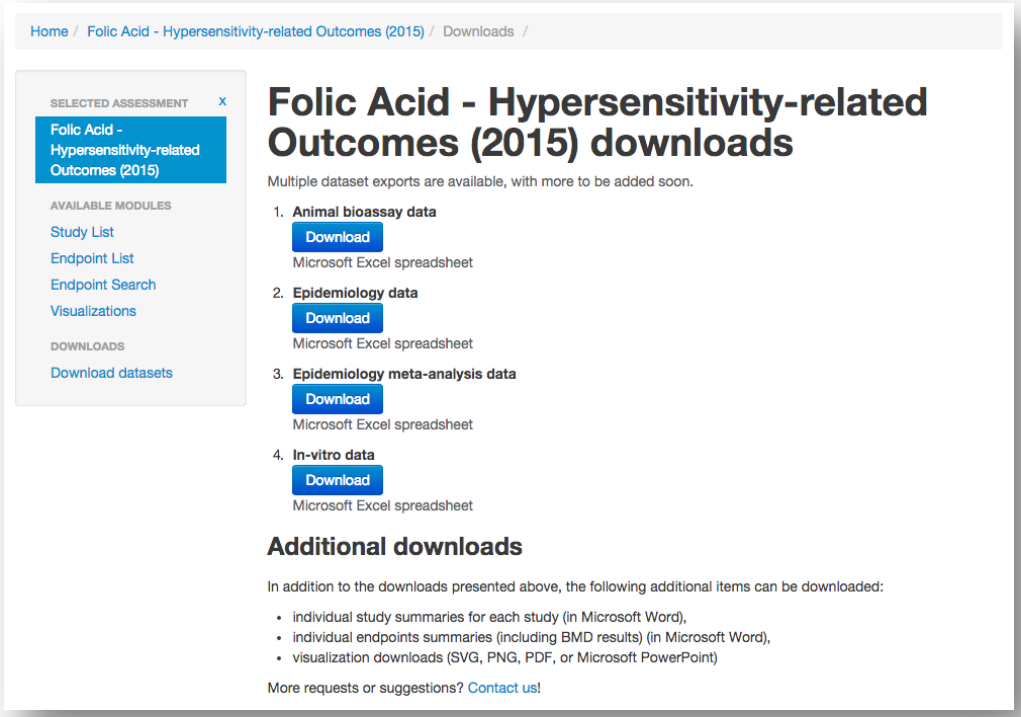
Reference	Chemical	Endpoint description
Li et al. 2012	Bisphenol AF	WT ER-alpha (ERE-luc)
Li et al. 2012	Bisphenol AF	WT ER-alpha (ERE-luc)
Li et al. 2012	Bisphenol AF	WT ER-alpha (ERE-luc)
Li et al. 2012	Bisphenol AF	ER-alpha (ERE-luc)
Matsushima et al. 2010	Bisphenol AF	ER-alpha (ERE-luciferase)
Teng et al. 2013	Bisphenol AF	pRST7-ER-alpha (3X-ERE-TATA-luc)
Li et al. 2012	Bisphenol AF	WT ER-alpha (ERE-luc)
Li et al. 2013b	Bisphenol AF	ER-alpha (3xERE luc)
Li et al. 2013b	Bisphenol AF	ER-alpha (3xERE luc)
Li et al. 2012	Bisphenol AF	WT ER-beta (ERE-luc)
Li et al. 2012	Bisphenol AF	WT ER-beta (ERE-luc)
Li et al. 2012	Bisphenol AF	WT ER-beta (ERE-luc)
Matsushima et al. 2010	Bisphenol AF	ER-beta (ERE-luciferase)
Li et al. 2013b	Bisphenol AF	ER-beta (3XERE Luc)
Kitamura et al. 2005b	Bisphenol AF	ER ((ERE)3-SV40-luc)
Bermudez et al. 2010	Bisphenol AF	ER (luciferase)
Kitamura et al. 2005b	Bisphenol B	ER ((ERE)3-SV40-luc)
Kitamura et al. 2005b	Bisphenol C	ER ((ERE)3-SV40-luc)
Kitamura et al. 2005b	Bisphenol E	ER ((ERE)3-SV40-luc)
Kitamura et al. 2005b	bisphenol F (4,4' isomer)	ER ((ERE)3-SV40-luc)
Teng et al. 2013	Bisphenol S	pRST7-ER-alpha (3X-ERE-TATA-luc)
Kuruto-Niwa et al. 2005	Bisphenol S	ER (EGFP-3(EREc38))
Grignard et al. 2012	Bisphenol S	ER (ERE-Glob-Luc-SVNeo)
Grignard et al. 2012	Bisphenol S	hER-alpha, hER-beta (firefly luciferase)
Kitamura et al. 2005b	Bisphenol S	ER ((ERE)3-SV40-luc)
Kitamura et al. 2005b	TMBPA	ER ((ERE)3-SV40-luc)

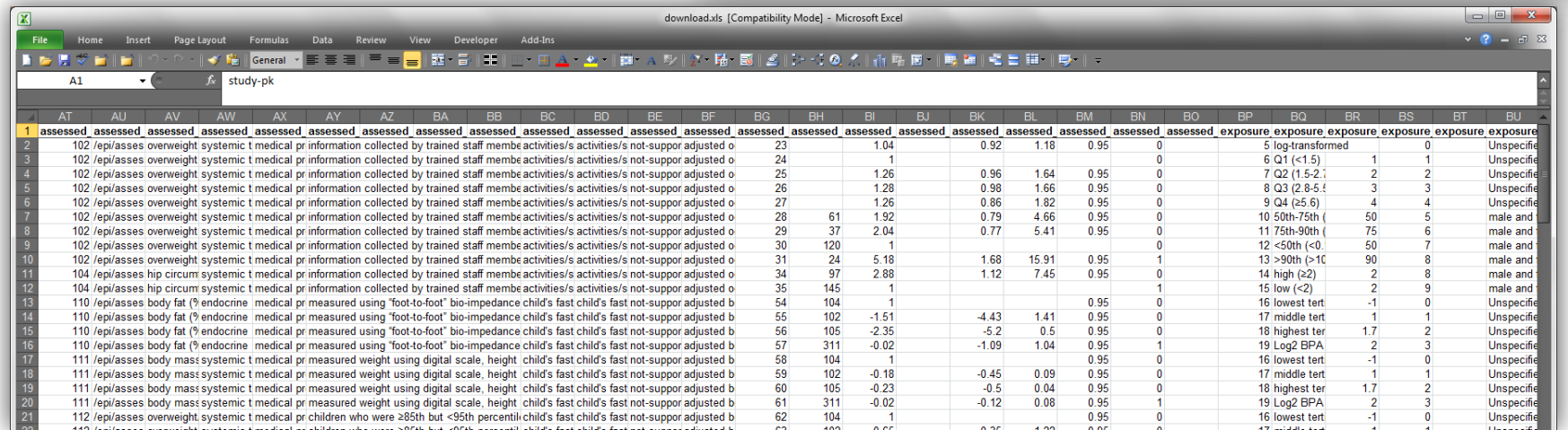


Additional Features

Data exporting

- Entire database for an assessment can be downloaded in Microsoft Excel exports
- Microsoft Word reports can be generated with user-defined templates
- Data accessible using an application programming interface (API)

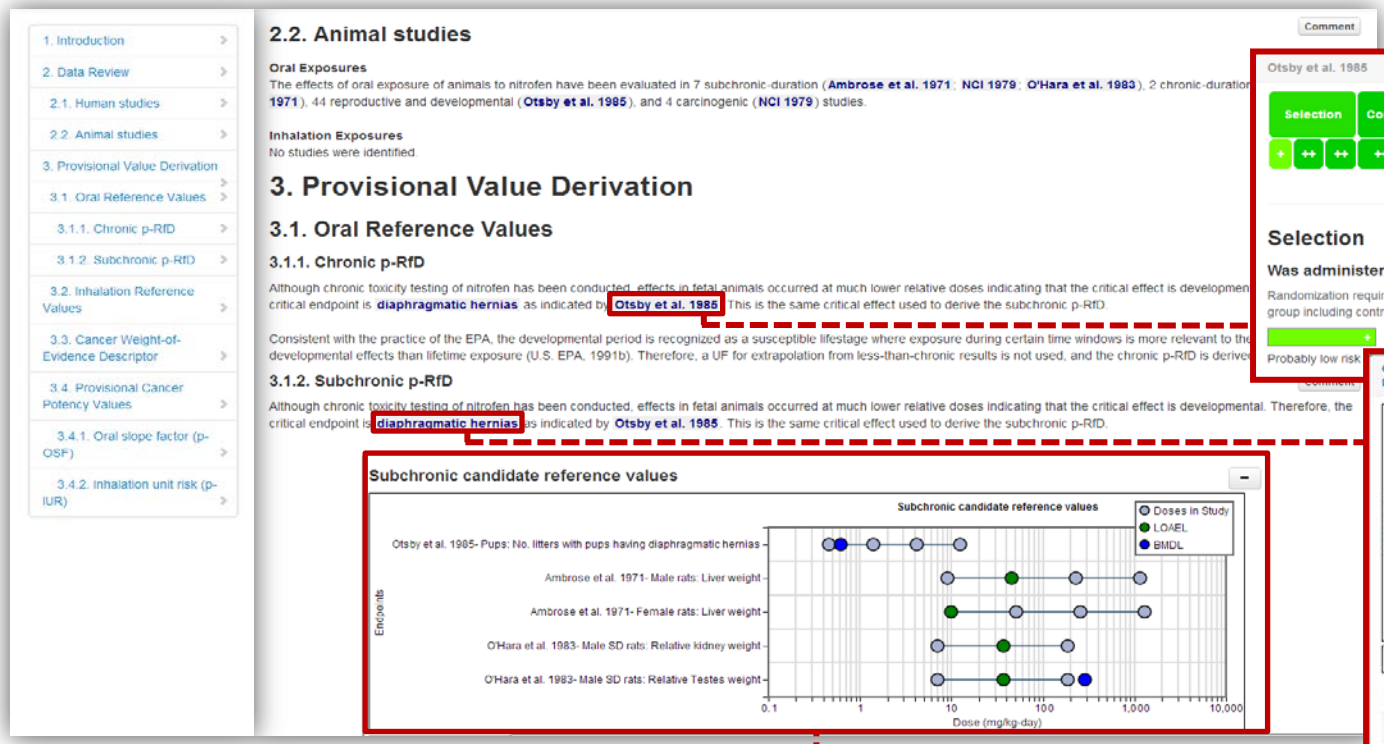




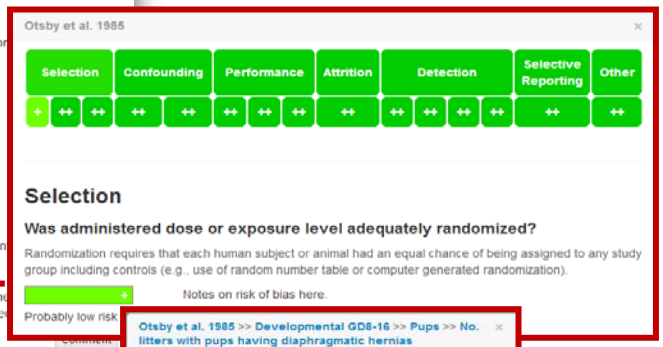
Additional Features

Web-based interactive reports

Document tree and summary report section

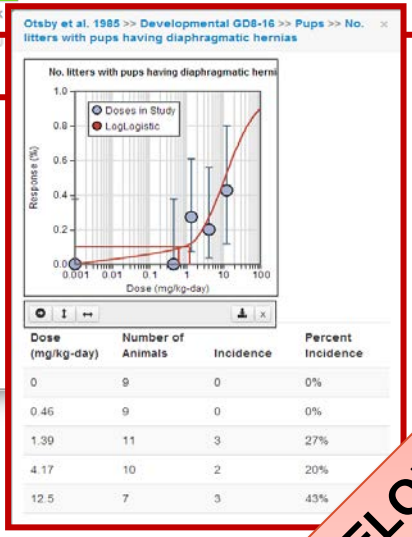


Risk of bias information



Inline visualizations

Endpoint and dose-response details



A web-report with headers and customizable text, similar to a standard report; however, "smart-tags" link to other HAWC components. The result is a summary of key findings written by assessment authors, which allows users to interactively dive into details instead of referring to appendices.

UNDER DEVELOPMENT

Future development

- Continued development of visualizations and tables for summarizing data findings
- Pair review and conflict resolution for literature review and risk of bias
- Specification of assessment-specific data extraction fields
- Improved QA/QC tracking and data extraction management
- Future integrations with SWIFT or other tools for literature review and automated data extraction

Questions?