



NTP
National Toxicology Program

Systematic Review & New Tools of Information Management

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Sciences

NTP Board of Scientific Counselors Meeting
June 21 – 22, 2012

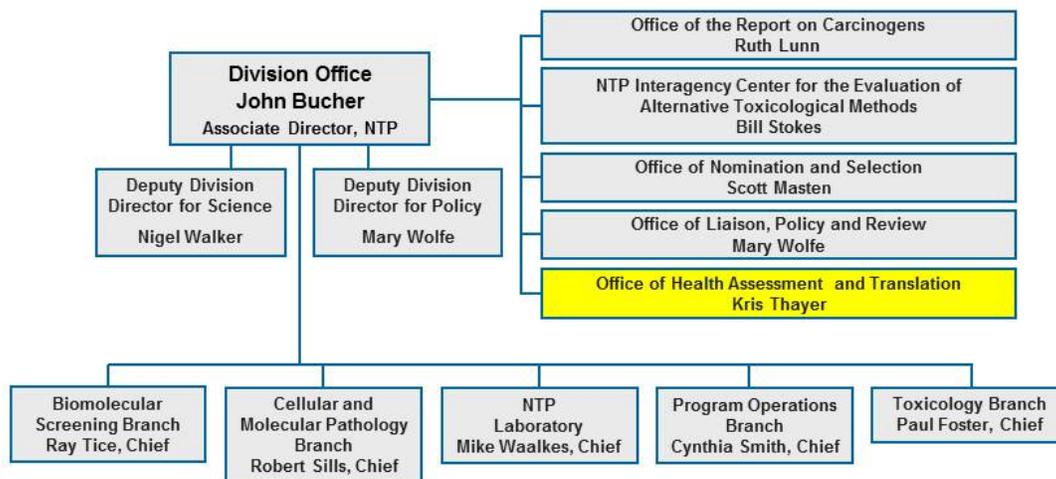


Outline

- Overview of OHAT
- Systematic Review
 - Key elements
 - Implications for process of developing OHAT evaluation topics
- Methodology and Infrastructure Tools
- Assessing Study Quality & Synthesizing Results
- Information Management
 - Data Dissemination & New Tools of Data Display
- Next Steps



NIEHS Division of the National Toxicology Program

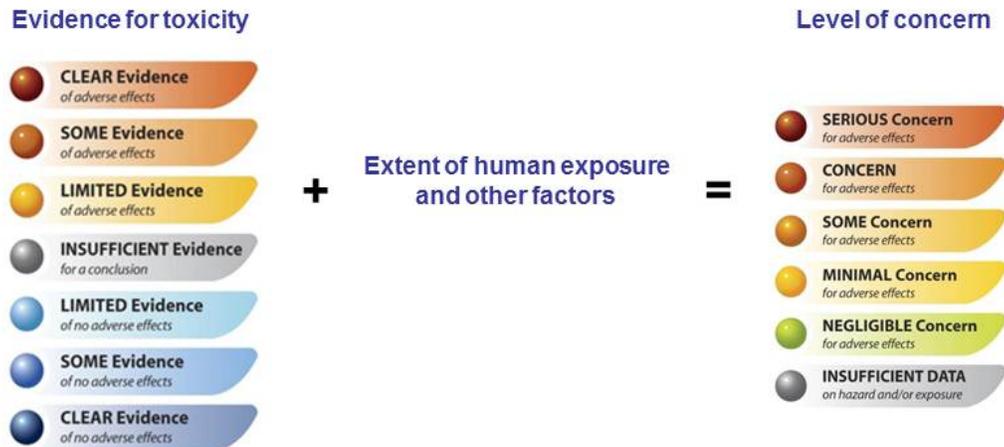


Office of Health Assessment and Translation

- Incorporates and expands scope of former Center for the Evaluation of Risks to Human Reproduction (CERHR) from 1998-2010
- Conduct literature-based evaluations
 - NTP opinions (public peer-review)
 - State-of-science evaluation
 - Organize research projects to address data needs
- Flexible process
 - Evaluation process tailored to meet needs of each project
 - External scientific input, i.e., NTP Board of Scientific Counselors, technical advisors, listening sessions, etc.
 - Include opportunities for public comment & interagency review

NTP Level of Concern Conclusions

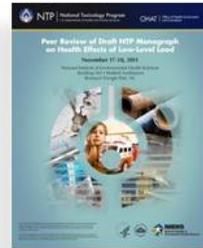
- Level of concern
 - Integrate evidence for toxicity + extent of human exposure



- acrylamide, BPA, bromopropanes, fluoxetine, ethylene & propylene glycol, hydroxyurea, methanol, phthalates, amphetamines & methylphenidate, soy infant formula, styrene

Other Peer-Reviewed Conclusions & Products

- NTP Monograph on Health Effects of Low-level Lead (June 2012)
- Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy (October 1-2, 2012)
- Role of Environmental Chemicals in Diabetes and Obesity: A National Toxicology Program Workshop Review (EHP 2012 Jun;120(6):779-89)



Systematic Review

- A scientific investigation that focuses on a specific question, and uses explicit, pre-specified methods to identify, select, summarize, and assess the findings of similar but separate studies.
 - Used to develop evidence-based conclusions, clinical or public health recommendations, and clarify need for additional research
 - May or may not result in a quantitative meta-analysis
 - Traditionally used for assessment of healthcare interventions



Systematic Review & New Tools

- Why?
 - Enhance transparency
 - More consistent data collection
 - More efficient information management
 - Develop publically accessible data extraction repository
 - Reduce duplication of efforts across agencies & research community
- How?
 - Engage technical experts in systematic review
 - Interagency communication
 - Webinars
 - Interagency Information Management Workgroup
 - Co-chairs: George Woodall (EPA) and Andrew Rooney (NTP)
 - EPA, NTP, NIOSH, ATSDR

What Does A Systematic Review Not Do?

- Does not eliminate the need for expert judgment
 - Goal is be transparent in communicating scientific judgments
- Does not guarantee reproducibility of conclusions
 - Increased transparency does not necessarily eliminate differences in scientific judgment
- Does not provide guidance on how to reach evidence of toxicity conclusions
- Does not provide guidance how to integrate evidence across human, animal, & mechanistic studies

Importance of Systematic Review Protocol

- Pre-defined approach for conducting the systematic review
 - Background, rationale, question(s) being addressed
 - Literature search strategy
 - Inclusion/exclusion criteria for selecting studies
 - Approach for data collection and reporting study results
 - Evaluation of study quality (“risk of bias”)
 - Approach for synthesizing results
- Conducting a systematic review is an iterative process

Topic Focus & Refinement

- Systematic review methodology oriented towards specific question
 - PICO
 - Patient population, Intervention, Comparison, Outcomes
- Environmental health questions are often broad
- Strategies to refine scope for broad topics
 - Use previous evaluations to help focus and refine scope
 - Exploratory screening stage to identify “added value” question
 - Engage technical experts and the public early in protocol development

Phased Approach for Topic Selection

- Release FR announcing topic under consideration
 - Public comment, request for information, identify experts
 - Create list-serve for interested parties
- Develop draft protocol with assistance of federal partners and technical experts
- Present draft protocol to NTP BSC
 - Opportunity for public comment
- Begin systematic review
 - Website to disseminate progress and document protocol modifications

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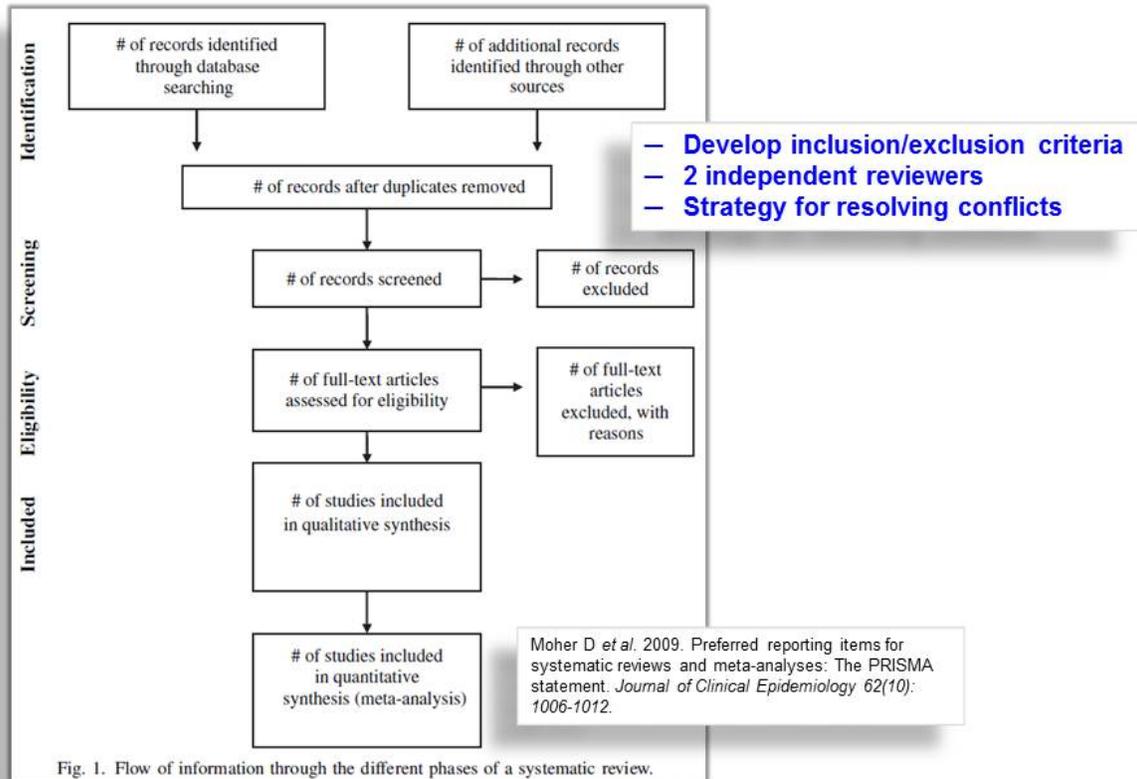


Literature Search

<p>Outdoor Air</p> <p>"air pollution"[mh:noexp] OR "air pollution"[tiab] OR "air pollutants"[pa] OR "air pollutant"[tiab] OR "air pollutants"[tiab] OR</p> <p>"particulate matter"[mh] OR "particulate matter"[tiab] OR PM2.5[tiab] OR "PM(2.5)"[tiab] OR PM10[tiab] OR "PM(10)"[tiab] OR smog[tiab] OR ash[tiab] OR soot[tiab] OR particulate*[tiab] OR ((air[tiab] OR coarse[tiab] OR ultrafine[tiab] OR fine[tiab]) AND particle*[tiab]) OR</p> <p>"vehicle en OR car[tiab] fume"[tiab]</p> <p>((air[tiab] C "sulfur diox "hydrogen oxides"[tiab]</p> <p>"volatile or gasoline"[tiab] "coal ash"[tiab]</p> <p>"hydrocarb aromatic[n benzo(a)py benzopyre</p> <p>"confined a husbandry broiler"[tiab] (methane[waste[tiab] dust"[tiab])</p>	<p>Transgenerational</p> <p>No MeSH</p> <p>(Successive OR later OR subsequent OR several OR consecutive OR future OR across OR multiple) AND (generation* OR progeny OR offspring)</p> <p>"fourth generation" "third generation" F3 OR F4 Grandchild* Grandfather* Grandmother* granddaughter* Grandparent* Grandson* Intergeneration* Multigeneration* Transgeneration* trans-generation*</p>	<p>Epigenetic</p> <p>"Epigenesis, genetic"[mh] (incl. chromosomal position effects, x chromosom inactivation, gene silencing, genomic imprinting)</p> <p>- RNA interference "histone code"[mh] "Histone Deacetylases"[mh] "Histone Demethylases"[mh] "Histones" [mh] Methyltransferases[mh] "Protein Processing, Post Translational"[mh] MicroRNAs[mh] "RNA, Small Interfering"[mh]</p>	<p>Environmental Exposure</p> <p>"Toxic Actions"[mh] - Incl. environmental pollutants, noxae, pesticides "Environmental pollutants"[mh]</p> <p>Toxicity[sh] Chemically induced[sh]</p> <p>Chemical* OR toxic* OR toxin* OR Pollution OR pollutant* Environment* AND (factor* OR influence* OR exposure* OR determinant*) Endocrine disrupt* Hazard* AND (material* OR</p>
<p>Indoor Air</p> <p>"air pollutio environme</p> <p>(smoke[tiab]</p>			

- use of librarian trained in systematic review
- biased to not miss studies
- search multiple databases (PubMed, TOXNET, EMBASE, Scopus, ...etc.)
- protocol should present search strategy for at least one database such that it could be reproduced

Document Flow of Information



Distiller Systematic Review Software

- Industry standard software to manage systematic review
 - Facilitate screening process
 - Develop customizable data extraction forms
 - Software is proprietary, but customized reports can be exported into public disseminations (e.g., Excel, Word)

Systematic Review Software

web-based

Project Excess Folic Acid (Switch) User kris.thayer (My Settings)
Messages Nothing new
Live Support User Guide

tracks which studies were included/excluded and why

	Unreviewed	Some Reviews	Included	Excluded	Conflict	Fully Reviewed
Level 1 - Title/Abstract Screening	12255	434	2692	7365	228	10285
Level 2 - PDF Screen	1178	165	1205	144	0	1349
Level 3 - Folic Acid Data Extraction Human Studies	96					7
Level 3 - Risk of Bias	12					
Level 3 - Meta Analysis	26	0	0	0	0	3
	Unreviewed	Some Reviews	Included	Excluded	Conflict	Fully Reviewed

project management and workflow

upload references from Endnote or other reference managers
— PDFs of articles can also be uploaded

Screening Level Form

Y. Kim and B. K. Lee. 2011. Association between urinary arsenic and diabetes mellitus in the Korean general population according to KNHANES 2008. Sci Total Environ 409(19): 4054-62.

INTRODUCTION: We present data from the Korean National Health and Nutrition Examination Survey (KNHANES) 2008 on the associations between urinary arsenic and diabetes mellitus in a representative sample of the adult Korean population.

METHODS: This study was based on data obtained in KNHANES 2008, which was conducted for three years (2007-2009) using a rolling sampling design involving a complex, stratified, multistage, probability-cluster survey of a representative sample of the noninstitutionalized civilian population of South Korea.

RESULTS: Geometric means of total urinary arsenic concentration in females and total participants with diabetes mellitus were significantly higher than in participants without diabetes mellitus after adjustment for covariates, including age, seafood consumption, body mass index (BMI), hypertension, area of residence, regional area, education level, and smoking and drinking status. Multiple regression analysis after similar adjustment showed that total urinary arsenic concentration was associated with diabetes status in the females and total participants. In addition, after similar adjustment, the odds ratios (ORs) for diabetes mellitus in female participants and all participants were 1.502 (95% CI, 1.038-2.171) and 1.312 (95% CI, 1.040-1.655), respectively, for doubling of the level of urinary total arsenic concentration.

CONCLUSION: This study showed an association between total urinary arsenic concentration and the prevalence of diabetes mellitus in a representative sample of the adult population, especially women, with environmental arsenic exposure after adjustment for seafood intake and relevant diabetes risk factors.

and go to or [Skip to Next](#)

Do the title or abstract suggest the article contains original data related to a topic of interest?

- yes
- yes (non-English)
- yes, but is a review, commentary, or letter with no original data
- no, not relevant
- not directly relevant, but could be supportive material
- unsure

Add text here to described screening level criteria for relevance:

Inclusion criteria

- bullet format
- bullet format

Exclusion criteria

- bullet format
- bullet format

Comments

and go to or [Skip to Next](#)

[View Audit Log](#)

Exclusion Report

DistillerSR

Review | Datarama | Reports | References | Forms

Select a Level: All Levels

Level	Exclusions [7]	Form	Question
Level 1	35	Abst Score	Do the title or abstract contain...

Download Exclusion Document with format: No Custom Format

exclusion-3.doc [Read-Only] - Microsoft Word

File Home Insert Page Layout References Mailings Review View Add-Ins EndNote X4 Acrobat

Clipboard Font Paragraph Styles

Review, commentary, or letter with no original data

T. T. Schug, A. Janesick, B. Blumberg and J. J. Heindel. 2011. Endocrine disrupting chemicals and disease susceptibility. *J Steroid Biochem Mol Biol* 127(3-5): 204-15.

J. Legler, T. Hamers, M. van Eck van der Sluijs-van de Bor, G. Schoeters, L. van der Ven, M. Eggesbo, J. Koppe, M. Feinberg and T. Tmovec. 2011. The OBELIX project: early life exposure to endocrine disruptors and obesity. *Am J Clin Nutr* 94(6 Suppl): 1933S-1938S.

J. L. Tang-Preonard, H. R. Andersen, T. K. Jensen and B. L. Heitmann. 2011. Endocrine-disrupting chemicals and obesity development in humans: a review. *Obes Rev* 12(8): 622-36.

J. L. Schnoor. 2011. Obesogens, the exposome, and ES&T. *Environ Sci Technol* 45(7): 2517.

A. Janesick and B. Blumberg. 2011. Minireview: PPARgamma as the target of obesogens. *J Steroid Biochem Mol Biol* 127(1-2): 4-8.

F. Grun. 2010. Obesogens. *Curr Opin Endocrinol Diabetes Obes* 17(5): 453-9.

R. R. Newbold. 2010. Impact of environmental endocrine disrupting chemicals on the development of obesity. *Hormones (Athens)* 9(3): 206-17.

J. R. Barrett. 2010. To each his own: DEHP yields species-specific metabolic phenotypes. *Environ Health Perspect* 118(2): A81.

D. Sharp. 2009. Environmental toxins, a potential risk factor for diabetes among Canadian Aboriginals. *Int J Circumpolar Health* 68(4): 316-26.

C. Casals-Casas, J. N. Feige and B. Desvergne. 2008. Interference of pollutants with PPARs: endocrine disruption meets metabolism. *Int J Obes (Lond)* 32 Suppl 6(6issue#): S53-61.

No relevant data

M. P. Alexander, S. H. Nasr, D. C. Watson, G. P. Mendez and H. G. Renke. 2011. Renal crescentic alpha heavy chain deposition disease: a report of 3 cases and review of the literature. *Am J Kidney Dis* 58(4): 621-5.

E. A. Wilkes, A. L. Selby, A. T. Cole, J. G. Freeman, M. J. Rennie and Z. H. Khan. 2011. Poor tolerability of thalidomide in end-stage oesophageal cancer. *Eur J Cancer Care (Engl)* 20(5): 593-600.

A. Makhlof, Y. Tonaka and H. Takeuchi. 2011. Design and evaluation of novel pH-sensitive chitosan nanoparticles for oral insulin delivery. *Eur J Pharm Sci* 42(5): 445-51.

S. Oh, S. J. Kim, J. H. Moon, H. Y. Lee, M. L. Ro, J. Park, Y. S. Jo, Y. K. Kim, C. H. Lee, K. P. Kwang, M. Shong and S. B. Park

Words: 988 | 74%

Data Extraction Files

- Customized forms
- Library of template forms that can be tailored to specific project
- Data extraction is transparent and consistent
- Files can be disseminated for data mining

Reference	Study Description (n)	Statistic aOR (95% CI)	Exposure	Endpoint	Dose Response
Giang et al. 2009	Europe (8 countries) CBSAR, 9-12y, ≥ 0.820	1.28 (1.05, 1.55)	yes/no	adipocyte number	NA
Tsuchida et al. 2002	Germany (Bavaria) 5-9y (1995), ≥ 0.801	1.82 (1.29, 2.60)	yes/no	adipocyte number	NA
Tsuchida et al. 2003	Germany (Bavaria) 5-9y (2001/2002), ≥ 0.876	2.22 (1.33, 3.85)	yes/no	adipocyte number	NA
Tsuchida et al. 2007	Germany (Bavaria) 5-9y (2001/2002), ≥ 0.472	1.76 (1.26, 2.45)	yes/no	adipocyte number	NA
Van Kraaij 2002	Germany (Bavaria) 5-9y, ≥ 0.482	2.08 (1.37, 3.23)	yes/no	adipocyte number	NA
Van Kraaij 2003	Germany (Bavaria) 5-9y, ≥ 0.839	1.81 (1.2, 2.7)	yes/no	adipocyte number	NA
Ito et al. 2011	Japan (Kumagaya) 9-10y, ≥ 0.569	1.68 (0.87, 3.07) [only prevOR]	yes/no	adipocyte number	NA
Alm et al. 2011	UK (Murraydale) 5-7y, ≥ 0.599	1.61 (1.16, 2.24)	yes/no	adipocyte number	NA
Alm et al. 2011	Germany (Bavaria) 9y, ≥ 0.804	1.81 (0.99, 3.28)	yes/no	adipocyte number	NA

Reference & Study Design	Study population	Outcome & Diagnostic	Chemical	Risk Estimate (95% CI)	Exposure Comparison	Adjustment factors
(Chang et al. 2010) cross-sectional	Turkey (SR) near PCF factory, ≥ 2 N Analysis (Total 3): 1,234(1,476) Inclusion status: included	HOMA-B-0/05 ≥ 71 th percentile	PCB-DK-DF	1.3 (0.91-1.91) aOR	≥ 2 vs < 2 vs < 1 WHOIS-TEQDF g lipid (year)	age, sex, BMI, smoking, weight control, physical activity, and family history of diabetes
(Chang et al. 2010) cross-sectional	Turkey (SR) near PCF factory, ≥ 2 N Analysis (Total 3): 1,234(1,476) Inclusion status: included	HOMA-B-0/05 ≥ 71 th percentile	PCB-DK-DF	1.7 (0.91-3.12) aOR	≥ 2 vs < 2 vs < 1 WHOIS-TEQDF g lipid (year)	age, sex, BMI, smoking, weight control, physical activity, and family history of diabetes
(Chang et al. 2011) cross-sectional	Turkey (SR) near PCF factory, ≥ 2 N Analysis (Total 3): 1,234(1,476) Inclusion status: excluded	HOMA-B-0/05 ≥ 71 th percentile	PCB-DK-DF	1.41 (0.91-2.12) aOR	≥ 2 vs < 2 vs < 1 WHOIS-TEQDF g lipid (year)	age, gender, smoking, physical activity, waist circumference, systolic blood pressure, diastolic blood pressure, and a family history of diabetes
(Chang et al. 2011) cross-sectional	Turkey (SR) near PCF factory, ≥ 2 N Analysis (Total 3): 1,234(1,476) Inclusion status: excluded	HOMA-B-0/05 ≥ 71 th percentile	PCB-DK-DF	4.89 (0.91-26.12) aOR	≥ 2 vs < 2 vs < 1 WHOIS-TEQDF g lipid (year)	age, gender, smoking, physical activity, waist circumference, systolic blood pressure, diastolic blood pressure, and a family history of diabetes

Reference	Study Design	Study Design Long	Study Description	N Analysis (Total)	Health Outcome
Montgomery 2002	Pros	prospective	US (NHANES III), 39y, ≥ 2	4917	obese
AOVA 2005a	Retro	retrospective	Australia (nat'l) Viet. vets, ≥ 2	6,166 deaths (59,179)	diabetes
AOVA 2005b	Retro	retrospective	Australia (nat'l) Viet. vets, ≥ 2	1,052 deaths (59,179)	diabetes
AHIS 2005	Pros	prospective	USA (NHIS) OHW 2002 exam cycle, ≥ 2	776(1950)	diabetes
AHIS 2008	CS	cross-sectional	Pakistan (Hyderabad) non-smokers, ≥ 2	225	diabetes
AHIS 2008	CS	cross-sectional	Pakistan (Hyderabad) smokers, ≥ 2	209	diabetes
AHIS 2008	CS	cross-sectional	Pakistan (Hyderabad) non-smokers, ≥ 2	225	diabetes
AHIS 2008	CS	cross-sectional	Pakistan (Hyderabad) smokers, ≥ 2	225	diabetes
Atrakinen 2011	CS	cross-sectional	Finland (Finnish) 57-70y, ≥ 2	1988	T2D
Atrakinen 2011	CS	cross-sectional	Finland (Finnish) 57-70y, ≥ 2	1988(1988)	T2D
Atrakinen 2011	CS	cross-sectional	Finland (Finnish) 57-70y, ≥ 2	1988	T2D
Park 2010	CC	case-control	S. Korea (Ileul) 540y, ≥ 2	20(100)	met. synd.



Data Extraction Forms – General Features

Refid: 144, Maternal arsenic exposure and impaired glucose tolerance during pregnancy
A. S. Ettinger, A. R. Zota, C. J. Amarasiwardena, M. R. Hopkins, J. Schwartz, H. Hu and R. O. Wright

Attachments
[Ettinger2009_144.pdf](#)

and go to or

- Upload file for a reference**
- multiple files okay
 - bulk upload option

Study Design [Instructions]

cross-sectional

Select an Answer
cohort prospective
cohort retrospective
cross-sectional
case-control
case-control, nested
case report
case series
RCT
other

When possible use multiple choice or "check all that apply" to control vocabulary

III. STUDY POPULATION

Study Design [Instructions]	cross-sectional	Country [Instructions] [Example]	US	Inclusion Criteria [Instructions] [Example]	give live birth at specific hospital, intent to live in study area for 2 yrs, not enrolled with another child, English proficiency for consent form
Study Description (Long) [Instructions] [Example]	532 pregnant women living proximate to the Tar Creek Superfund	Region (country codes)(state codes) [Instructions] [Example]	Tar Creek, OK	Exclusion Criteria [Instructions] [Example]	missing blood As or glucose data
Calendar Years of Enrollment [Instructions] [Example]	2002-2008	Study acronym or unique feature [Instructions] [Example]	near superfund site		
		N [Instructions]	532		
		Sex [Instructions]	pregnant ♀		

Data Extraction Forms – Logic Based Questions

Methods

Animal Model

Sex Animal Source Species Strain

Treatment

Chemical Class Chemical Chemical Purity

Diet

Vehicle

Route of Exposure (general)

Treatment Period

Age at Exposure

Lifestage at Exposure

Study Design

Age at Assessment

Lifestage at Assessment

- Select an Answer
- rat
- mouse
- dog
- fish
- goat
- guinea pig
- hamster
- pig
- rabbit
- other

Species Strain

Chemical

Route of Exposure

Lifestage at Assessment

- Select an Answer
- Select an Answer
- not reported
- albino
- CD
- F344
- Long Evans
- Sprague-Dawley
- Wistar
- other

Data Extraction Forms – Effect Size Conversions (Animal Form)

- Continuous data

	N (as presented)	N (for effect size)	Mean	SD	SEM
Control Group	6-8	7	13.9	0.980	
Treatment Group	6-8	7	15.7	1.225	

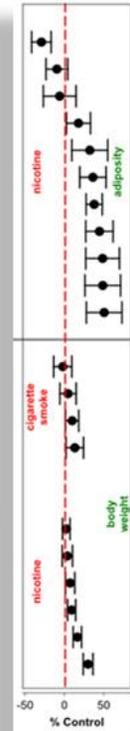
	Effect Size (calculated value)	Lower 95% CI (calculated value)	Upper 95% CI (calculated value)
Normalized Effect Size (% Control)	12.95	5.16	20.74
Standardized Mean Difference	1.62	0.41	2.83

- Categorical data

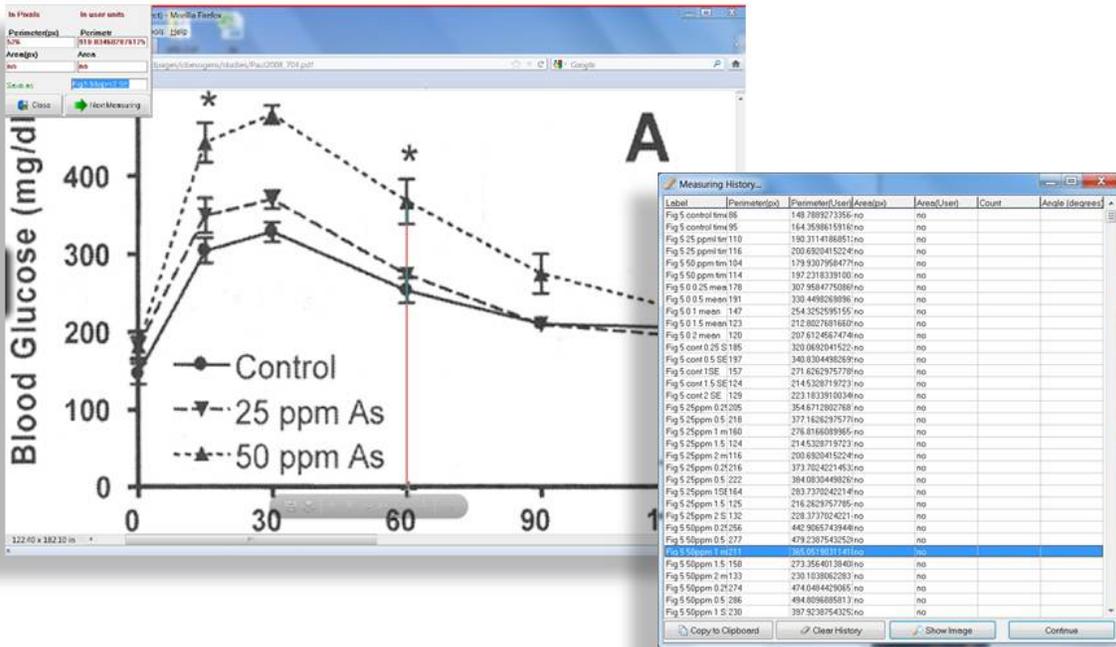
	Number with outcome	Number without outcome
Control Group	5	45
Treatment Group	15	35

	Effect Size (calculated value)	Lower 95% CI (calculated value)	Upper 95% CI (calculated value)
Odds Ratio	3.86	1.28	11.64

automatically calculated



Digital Rulers



Link To Other Toxicology Tools

Administered Doses [Instructions]
 Administered Doses (as presented) 0, 25, 50 Administered Dose Unit (as presented) ppm Does administered dose need to be converted to mg/kg? (use ICF Dosimetry Tool) yes, via ICF tool
 Doses in mg/kg bw [Instructions] Basis of Conversion [Instructions]

Did study asse

The screenshot shows the ICF Dosimetry Tool spreadsheet with the following sections:

- Study Information:**
 - Author: Smith
 - Year: 1980
 - Exposure Type: Oral, Drinking Water
 - Animal: Rat
 - Endpoint: Cancer
 - Dose: ppm or mg/kg food
 - Animal Strain: Sprague-Dawley
 - Gender Animal: Male
 - Gender Human Endpoint: General
 - Type of Study: Chronic
- Common Inputs:**
 - Use Default? (checkbox)
 - Parameter: Total days dosed OR Days dosed per week, Value: 5, Units: days
 - Parameter: Total days of study OR Days per week, Value: 7, Units: days
 - Body Weight (kg) (Default)
 - Body Weight Animal: 0.318 kg
 - Default BW Animal: 0.318 kg
 - Body Weight Human: 70 kg
- Dose Specific Data:**

Doses to Convert	Body Weight per Dose (kg)	Ave Food Consumption per Dose (g/day)	Ave Water Consumption per Dose (L/day)	Show Equations (Mark only one with "x")
0	0.318	0.027176622		
10	0.318	0.027176622		
25	0.318	0.027176622		
50	0.318	0.027176622		
100	0.318	0.027176622		
500	0.318	0.027176622		
1000	0.318	0.027176622		

“Prospective in Spirit” Power Assessment

	N (for effect size)	Mean	SD	SEM
Control Group	<input type="text" value="6"/>	<input type="text" value="13.9"/>	<input type="text" value="0.98"/>	<input type="text"/>

POWER

Sample size for each group to detect a 10% change in the mean value of the control group with 80% power and alpha of 0.05

```
--- Sample Size for ANOVA ---  
  
Alpha: 0.050  
Number of treatment groups: 3  
Minimum detectable difference: 1.39  
Standard deviation of residual: 0.98  
Power: 0.800  
  
Sample size (for each group): 11
```

Does the study appear adequately powered to detect a 10% difference between groups?

Data Collection – Other Features

- Study design and experimental details
- Exposure information: relative category and quantitative
- Effect size conversions for human studies

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Assess the Quality of Individual Studies

- Use predefined criteria to assess internal validity (“risk of bias”)
 - Are you confident in the study findings?
- Studies are assessed with a “domain-based” approach
 - Single summary scores of studies strongly discouraged
 - Requires weighting, a source of subjectivity
 - Endpoint specific
 - Reporting quality checklist ≠ risk of bias tool
 - Risk of bias assessed for individual studies and across studies
 - No consensus on how to assess for observational human studies or animal studies

Bias	Criterion	**major elements					
		RCT	Cohort	Case Control	Case Series	Cross-sectional	Animal
Selection	Was treatment adequately randomized?	X					X
	Was treatment allocation adequately concealed?	X					X
	Is the comparison group appropriate? **		X	X		X	
	Was the subject recruitment strategy uniform across study groups?	X	X				
	Were exposed and non-exposed subjects drawn from the same population? **		X	X	X		
	Does the study design adjust/control for important confounding and other variables? **		X	X	X	X	X
Performance	Did researchers adjust/control for other exposures or events that could affect results?		X	X	X	X	X
Attrition	In RCT, cohort studies, does follow-up of subjects, is the time period for cases and controls similar?		X	X			X
	Was the loss to follow-up similar for both groups?	X	X	X			X
	Is the loss to follow-up related to the exposure or outcome?	X	X				
	Was the loss to follow-up related to the exposure or outcome?	X	X				X
Detection	Can we be confident that the outcome of interest did not precede exposure?	X	X		X		X
	Were the outcome assessors blinded to the exposure or intervention status of participants?	X	X	X	X	X	X
	Is inclusion/exclusion criteria measured reliably, implemented consistently?	X	X	X	X	X	X
	Can we be confident in the exposure assessment? **	X	X	X	X	X	X
	Can we be confident in the outcome assessment? **	X	X	X	X	X	X
	Are confounding variables assessed using reliable and consistent measures?	X	X	X	X	X	X
Reporting	Are outcomes pre-specified by the researchers? Are all pre-specified outcomes reported?	X	X	X	X	X	X

DRAFT
 (based on AHRQ 2011 guidance and feedback from technical advisors – still being refined)