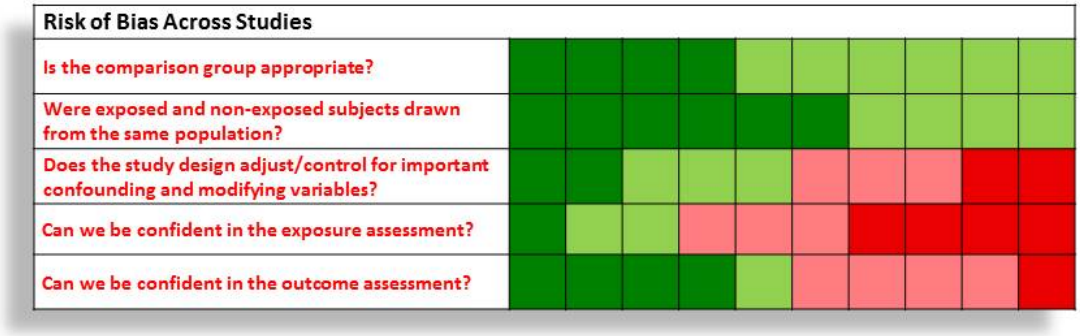
# Risk of Bias for Individual Studies

| Risk of Bias | Confidence | Symbol |
|---|---|---|
| definitely yes | high | |
| probably yes | low/moderate | |
| probably no | low/moderate | |
| definitely no | high | |
| N/A | N/A | |

| Bias | Criterion | Birnbaum 2012 | Bucher 1969 | Faustman 2009 | Eastman 2010 |
|---|---|---|---|---|---|
| **Selection** | Was treatment adequately randomized? | | | | |
| | Was treatment allocation adequately concealed? | | | | |
| | **Is the comparison group appropriate?** | | | | |
| | Was the subject recruitment strategy uniform across study groups? | | | | |
| | **Were exposed and non-exposed subjects drawn from the same population?** | | | | |
| | **Does the study design adjust/control for important confounding and modifying variables?** | | | | |
| **Performance** | Did researchers adjust/control for other exposures or interventions that may bias results? | | | | |
| **Attrition** | In RCT, cohort studies, does follow-up length differ between groups? In case-control studies, is the time period between exposure/intervention and outcome the same for cases and controls? | | | | |
| | Was the attrition rate uniformly low? | | | | |
| | Is the analysis conducted on an intention-to-treat basis? | | | | |
| | Was follow-up long enough to assess the outcome of interest? | | | | |
| **Detection** | Can we be confident that the outcome of interest did not precede exposure? | | | | |
| | Were the outcome assessors blinded to the exposure or intervention status of participants? | | | | |
| | Is inclusion/exclusion criteria measured reliably, implemented consistently? | | | | |
| | **Can we be confident in the exposure assessment?** | | | | |
| | **Can we be confident in the outcome assessment?** | | | | |
| | Are confounding variables assessed using reliable and consistent measures? | | | | |
| **Reporting** | Are outcomes pre-specified by the researchers? Are all pre-specified outcomes reported? | | | | |

# Risk of Bias Across Studies

| Risk of Bias | Confidence | Symbol |
|---|---|---|
| definitely yes | high | |
| probably yes | low/moderate | |
| probably no | low/moderate | |
| definitely no | high | |
| N/A | N/A | |



## Next Steps in Methods for Evaluating "Risk of Bias"

- Risk of bias guidance is most developed for human studies of medical intervention, i.e., RCT studies
  - Assess applicability for environmental health studies
  - Modify RCT elements for animal studies?
  - Use as a basis for potentially excluding studies or conducting stratified analyses
  - Assess consistency of response across reviewers
  - Compare to other risk of bias tools

## Synthesizing Results
## The Next Step…

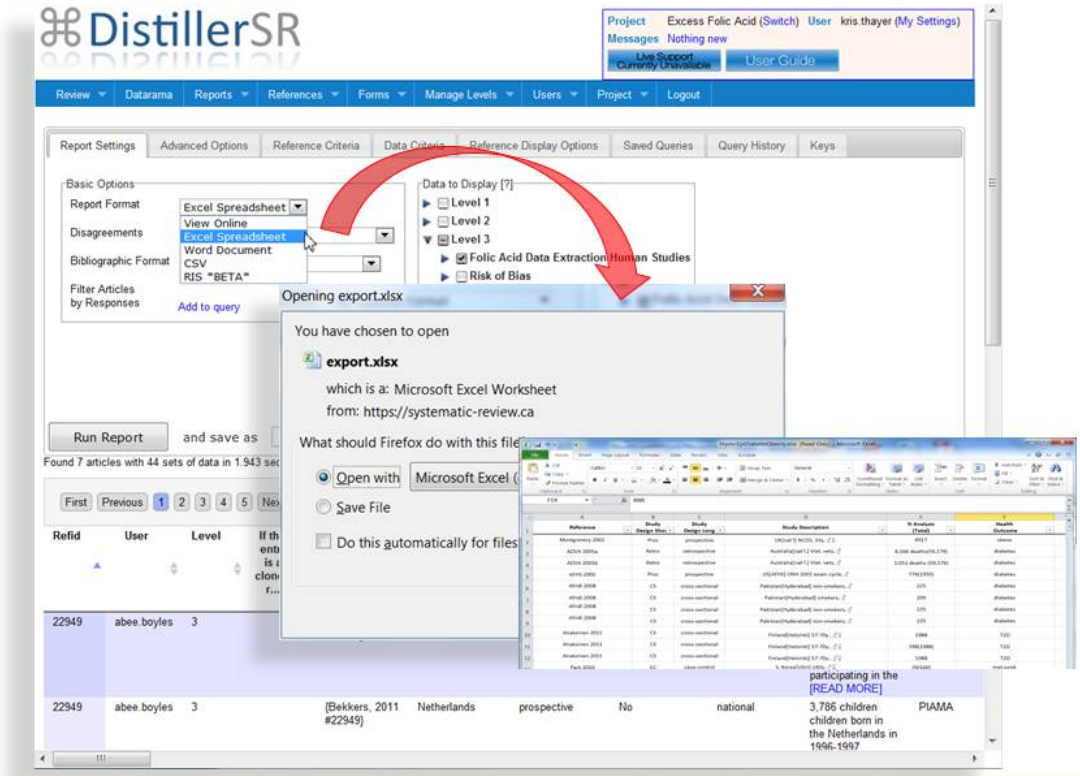
## Evaluate Body of Evidence Across Studies

- Evaluate evidence across studies for each major outcome
- Consider risk of bias, precision, directness, consistency, dose-response associations, impact of confounding, magnitude of association, and publication bias
  - Existing guidance developed for clinical practice guidelines for healthcare interventions
  - Conclusions reflect confidence in evidence & need for additional research
- Currently examining approaches for NTP products
  - Incorporate philosophy from existing guidance to extent possible
  - Link to evidence of toxicity conclusions?
  - Integrate across human, animal, and mechanistic data?
  - Link to level of concern conclusions?

## 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
- Data Dissemination & New Tools of Data Display
- Next Steps

# Data Extraction Files Can Be Publicly Available



## Applications of Data Extraction Files

- Import data into statistical packages
- Create customized appendix tables
- Visual data mining and creating graphics in MetaData Viewer

# Meta Data Viewer Graphing Software

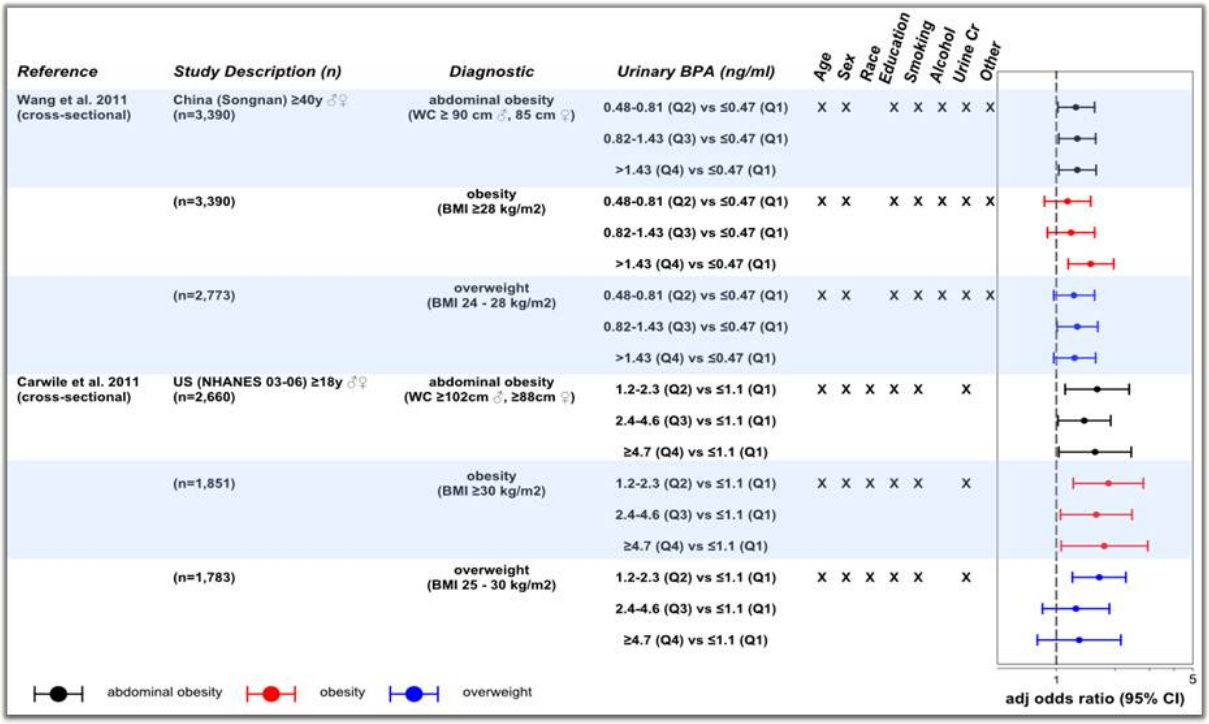
- Publically accessible for free
  - http://ntp.niehs.nih.gov/go/tools_metadataviewer
- Excel file input
- Display up to 10 data points and 15 text columns
- Portrait and landscape orientation
- Log and ordinal scale axes
- Many sort, grouping, filtering, and formatting options

Boyles AL, Harris SF, Rooney AA, Thayer KA. 2011. Forest Plot Viewer: a fast, flexible graphing tool. *Epidemiology 22(5): 746-747.*

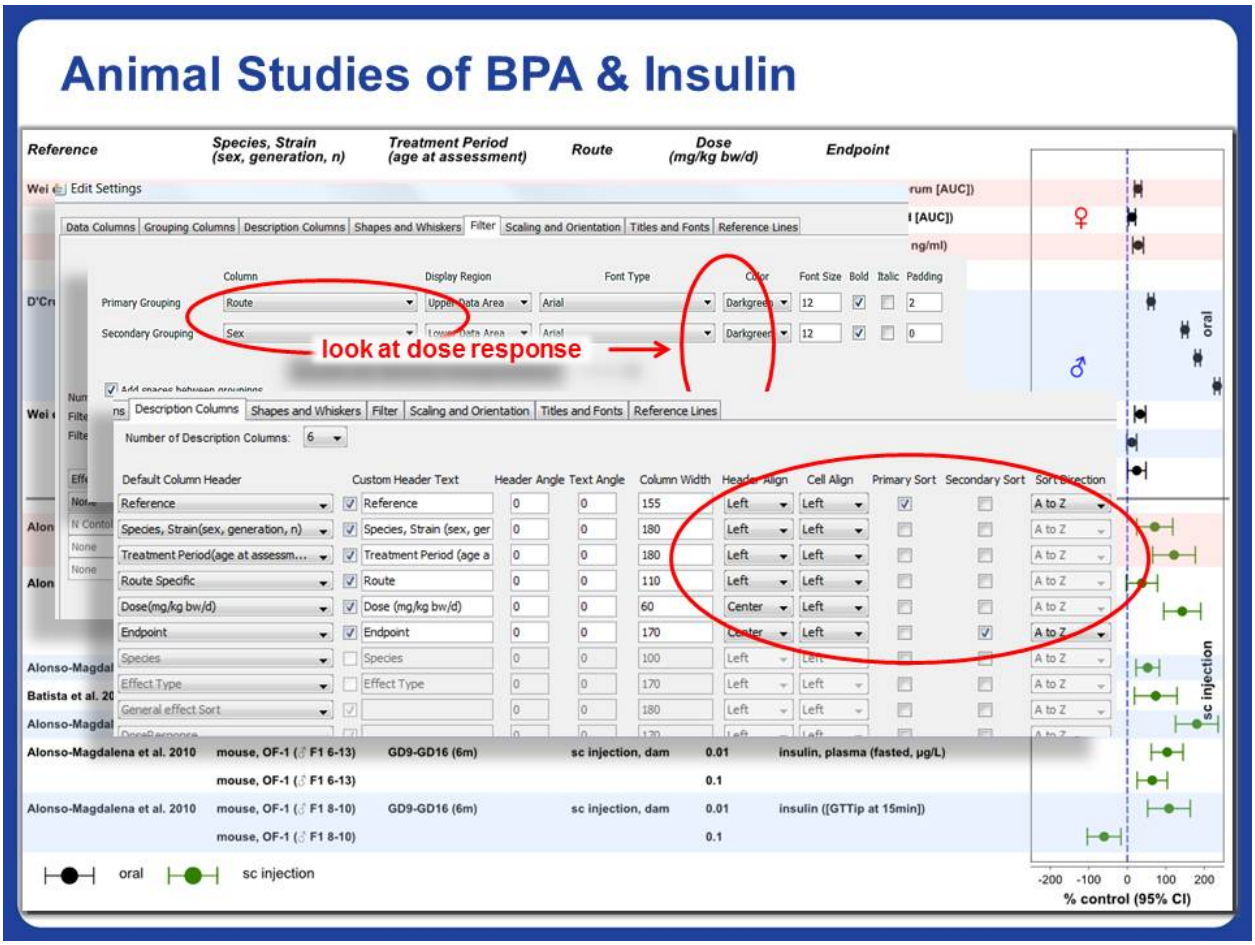
# Meta Data Viewer Example Formats
## Effect Size Display for Human & Animal Studies

# BPA & Obesity-Related Outcomes

| Reference | Study Description (n) | Diagnostic | Urinary BPA (ng/ml) | Age | Sex | Race | Education | Smoking | Alcohol | Urine Cr | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wang et al. 2011 (cross-sectional) | China (Songnan) ≥40y ♂♀ (n=3,390) | abdominal obesity (WC ≥ 90 cm ♂, 85 cm ♀) | 0.48-0.81 (Q2) vs ≤0.47 (Q1) | X | X | | X | X | X | X | X |
| | | | 0.82-1.43 (Q3) vs ≤0.47 (Q1) | | | | | | | | |
| | | | >1.43 (Q4) vs ≤0.47 (Q1) | | | | | | | | |
| | (n=3,390) | obesity (BMI ≥28 kg/m2) | 0.48-0.81 (Q2) vs ≤0.47 (Q1) | X | X | | X | X | X | X | X |
| | | | 0.82-1.43 (Q3) vs ≤0.47 (Q1) | | | | | | | | |
| | | | >1.43 (Q4) vs ≤0.47 (Q1) | | | | | | | | |
| | (n=2,773) | overweight (BMI 24 - 28 kg/m2) | 0.48-0.81 (Q2) vs ≤0.47 (Q1) | X | X | | X | X | X | X | X |
| | | | 0.82-1.43 (Q3) vs ≤0.47 (Q1) | | | | | | | | |
| | | | >1.43 (Q4) vs ≤0.47 (Q1) | | | | | | | | |
| Carwile et al. 2011 (cross-sectional) | US (NHANES 03-06) ≥18y ♂♀ (n=2,660) | abdominal obesity (WC ≥102cm ♂, ≥88cm ♀) | 1.2-2.3 (Q2) vs ≤1.1 (Q1) | X | X | X | X | X | | X | |
| | | | 2.4-4.6 (Q3) vs ≤1.1 (Q1) | | | | | | | | |
| | | | ≥4.7 (Q4) vs ≤1.1 (Q1) | | | | | | | | |
| | (n=1,851) | obesity (BMI ≥30 kg/m2) | 1.2-2.3 (Q2) vs ≤1.1 (Q1) | X | X | X | X | X | | X | |
| | | | 2.4-4.6 (Q3) vs ≤1.1 (Q1) | | | | | | | | |
| | | | ≥4.7 (Q4) vs ≤1.1 (Q1) | | | | | | | | |
| | (n=1,783) | overweight (BMI 25 - 30 kg/m2) | 1.2-2.3 (Q2) vs ≤1.1 (Q1) | X | X | X | X | X | | X | |
| | | | 2.4-4.6 (Q3) vs ≤1.1 (Q1) | | | | | | | | |
| | | | ≥4.7 (Q4) vs ≤1.1 (Q1) | | | | | | | | |



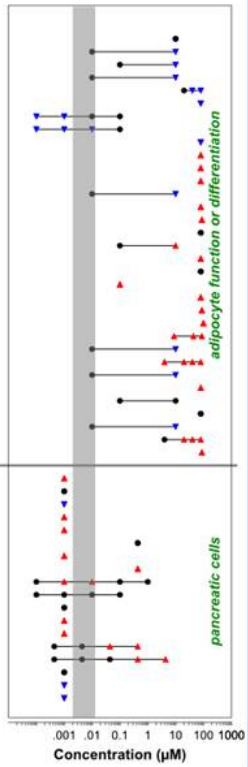
# Animal Studies of BPA & Insulin



# Meta Data Viewer Example Formats
# Dose or Concentration Levels for Animal & *In Vitro* Studies

# *In Vitro* Effects of BPA on Adipocytes & Pancreatic Cells: Each Concentration Tested

| Reference | Cell Type | Concentrations, μM* | Endpoint |
|---|---|---|---|
| Biemann 2011 | C3H/10T1/2 MSC | 10 | adipocyte number |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | adipocyte number |
| Lee 2008 | 3T3-L1 fibroblast | 0.1, 10* | adiponectin mRNA |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | adiponectin mRNA |
| Kidani 2010 | 3T3-L1 fibroblast | 20, 40*, 80* | adiponectin production |
| Kidani 2010 | 3T3-L1 fibroblast | 80* | adiponectin protein |
| Hugo 2008 | adipose (human breast ♀) | 0.0001*, 0.001*, 0.01, 0.1 | adiponectin release |
| Hugo 2008 | adipose (human abdominal ♀) | 0.0001*, 0.001*, 0.01*, 0.1 | adiponectin release |
| Kidani 2010 | 3T3-L1 fibroblast | 80* | Akt & pAkt protein |
| Masuno 2005 | 3T3-L1 fibroblast | 80* | Akt & pAkt protein |
| Masuno 2005 | 3T3-L1 fibroblast | 80* | aP2 mRNA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80* | C/EBPβ mRNA |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | FABP4 mRNA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80* | FAS mRNA |
| Masuno 2002 | 3T3-L1 fibroblast | [87.6*] | GPDH activity |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80 | leptin concentration |
| Lee 2008 | 3T3-L1 fibroblast | 0.1, 10* | leptin mRNA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80* | leptin mRNA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80 | lipid accumulation |
| Sargis 2010 | 3T3-L1 fibroblast | 0.1* | lipid accumulation |
| Masuno 2005 | 3T3-L1 fibroblast | 80* | lipid accumulation |
| Masuno 2002 | 3T3-L1 fibroblast | [87.6*] | lipid accumulation |
| Wang 2010 | 3T3-L1 fibroblast | 100* | lipid accumulation |
| Masuno 2002 | 3T3-L1 fibroblast | [8.76*, 43.8*, 87.6*] | LPL activity |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | LPL mRNA |
| Masuno 2005 | 3T3-L1 fibroblast | 80* | LPL mRNA |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | PPARγ2 mRNA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80* | Pref-1 mRNA |
| Lee 2008 | 3T3-L1 fibroblast | 0.1, 10 | resistin mRNA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80 | triglyceride content |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | triglyceride content |
| Masuno 2005 | 3T3-L1 fibroblast | 4, 20*, 40*, 80* | triglyceride content |
| Masuno 2002 | 3T3-L1 fibroblast | [87.6*] | triglyceride content |
| Quesada 2002 | islets, β-cells (Swiss OF1 mouse) | 0.001* | [Ca2+]i concentration |
| Soriano 2012 | islets, β-cells (ERβ -/-, C57 mouse) | 0.001 | [Ca2+]i oscillation frequency |
| Alonso-Magdalena 2005 | islets, α-cells (Swiss OF1 mouse) | 0.001* | [Ca2+]i oscillation frequency |
| Nadal 2000 | islets, β-cells (Swiss OF1 mouse) | 0.001* | [Ca2+]i oscillation frequency |
| Soriano 2012 | islets, β-cells (ERβ WT, C57 mouse) | 0.001* | [Ca2+]i oscillation frequency |
| Makaji 2011 | TC-6 β cells | [0.438] | CHOP/GADD153 protein |
| Quesada 2002 | islets, β-cells (Swiss OF1 mouse) | 0.001* | CREB phosphorylation |
| Makaji 2011 | TC-6 β cells | [0.438*] | HSP70, GRP78, GRP94 proteins |
| Alonso-Magdalena 2008 | islets (Swiss OF1 mouse) | 0.0001, 0.001*, 0.01*, 0.1, 1 | insulin content |
| Soriano 2012 | islets (C57 mouse) | 0.0001, 0.001, 0.01, 0.1 | insulin release |
| Soriano 2012 | islets (ERβ -/-, C57 mouse) | 0.001 | insulin secretion |
| Soriano 2012 | islets (ERβ WT, C57 mouse) | 0.001* | insulin secretion |
| Soriano 2012 | islets (human) | 0.001* | insulin secretion |
| Adachi 2005 | islets (Wistar rat) | [0.000438, 0.00438, 0.0438*, 0.438*] | insulin secretion |
| Makaji 2011 | TC-6 β cells | [0.000438, 0.00438, 0.0438, 0.438*, 4.38*] | insulin secretion |
| Soriano 2012 | islets (ERβ -/-, C57 mouse) | 0.001 | KATP channel activity |
| Soriano 2012 | islets (ERβ WT, C57 mouse) | 0.001* | KATP channel activity |
| Soriano 2012 | islets, β-cells (human) | 0.001* | KATP channel activity |




● no statistical significant effects observed

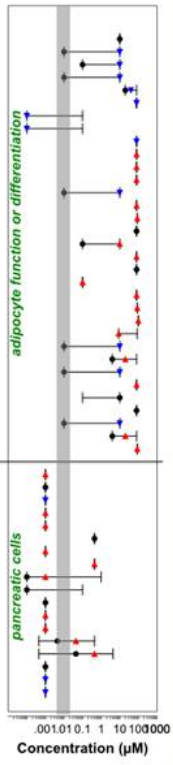
▲ statistically significant increase

▼ statistically significant decrease

estimated range of unconjugated BPA in human blood samples (Vandenberg et al. 2010)

# *In Vitro* Effects of BPA on Adipocytes & Pancreatic Cells: Exposure Response Array

| Reference | Cell Type | Concentrations, μM* | Endpoint | Dose Response |
|---|---|---|---|---|
| Biemann 2011 | C3H/10T1/2 MSC | 10 | adipocyte number | NA |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | adipocyte number | monotonic |
| Lee 2008 | 3T3-L1 fibroblast | 0.1, 10* | adiponectin mRNA | monotonic |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | adiponectin mRNA | monotonic |
| Kidani 2010 | 3T3-L1 fibroblast | 20, 40*, 80* | adiponectin production | monotonic |
| Kidani 2010 | 3T3-L1 fibroblast | 80* | adiponectin protein | NA |
| Hugo 2008 | adipose (human breast ♀) | 0.0001*, 0.001*, 0.01, 0.1 | adiponectin release | non-monotonic |
| Hugo 2008 | adipose (human abdominal ♀) | 0.0001*, 0.001*, 0.01*, 0.1 | adiponectin release | non-monotonic |
| Kidani 2010 | 3T3-L1 fibroblast | 80* | Akt & pAkt protein | NA |
| Masuno 2005 | 3T3-L1 fibroblast | 80* | Akt & pAkt protein | NA |
| Masuno 2005 | 3T3-L1 fibroblast | 80* | aP2 mRNA | NA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80* | C/EBPβ mRNA | NA |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | FABP4 mRNA | monotonic |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80* | FAS mRNA | NA |
| Masuno 2002 | 3T3-L1 fibroblast | [87.6*] | GPDH activity | NA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80 | leptin concentration | NA |
| Lee 2008 | 3T3-L1 fibroblast | 0.1, 10* | leptin mRNA | monotonic |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80* | leptin mRNA | NA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80 | lipid accumulation | NA |
| Sargis 2010 | 3T3-L1 fibroblast | 0.1* | lipid accumulation | NA |
| Masuno 2005 | 3T3-L1 fibroblast | 80* | lipid accumulation | NA |
| Masuno 2002 | 3T3-L1 fibroblast | [87.6*] | lipid accumulation | NA |
| Wang 2010 | 3T3-L1 fibroblast | 100* | lipid accumulation | NA |
| Masuno 2002 | 3T3-L1 fibroblast | [8.76*, 43.8*, 87.6*] | LPL activity | monotonic |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | LPL mRNA | monotonic |
| Masuno 2005 | 3T3-L1 fibroblast | 80* | LPL mRNA | NA |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | PPARγ2 mRNA | monotonic |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80* | Pref-1 mRNA | NA |
| Lee 2008 | 3T3-L1 fibroblast | 0.1, 10 | resistin mRNA | NA |
| Phrakonkham 2008 | 3T3-L1 fibroblast | 80 | triglyceride content | NA |
| Biemann 2011 | C3H/10T1/2 MSC | 0.010, 10* | triglyceride content | monotonic |
| Masuno 2005 | 3T3-L1 fibroblast | 4, 20*, 40*, 80* | triglyceride content | monotonic |
| Masuno 2002 | 3T3-L1 fibroblast | [87.6*] | triglyceride content | NA |
| Quesada 2002 | islets, β-cells (Swiss OF1 mouse) | 0.001* | [Ca2+]i concentration | NA |
| Soriano 2012 | islets, β-cells (ERβ -/-, C57 mouse) | 0.001 | [Ca2+]i oscillation frequency | NA |
| Alonso-Magdalena 2005 | islets, α-cells (Swiss OF1 mouse) | 0.001* | [Ca2+]i oscillation frequency | NA |
| Nadal 2000 | islets, β-cells (Swiss OF1 mouse) | 0.001* | [Ca2+]i oscillation frequency | NA |
| Soriano 2012 | islets, β-cells (ERβ WT, C57 mouse) | 0.001* | [Ca2+]i oscillation frequency | NA |
| Makaji 2011 | TC-6 β cells | [0.438] | CHOP/GADD153 protein | NA |
| Quesada 2002 | islets, β-cells (Swiss OF1 mouse) | 0.001* | CREB phosphorylation | NA |
| Makaji 2011 | TC-6 β cells | [0.438*] | HSP70, GRP78, GRP94 proteins | NA |
| Alonso-Magdalena 2008 | islets (Swiss OF1 mouse) | 0.0001, 0.001*, 0.01*, 0.1, 1 | insulin content | non-monotonic |
| Soriano 2012 | islets (C57 mouse) | 0.0001, 0.001, 0.01, 0.1 | insulin release | montonic |
| Soriano 2012 | islets (ERβ -/-, C57 mouse) | 0.001 | insulin secretion | NA |
| Soriano 2012 | islets (ERβ WT, C57 mouse) | 0.001* | insulin secretion | NA |
| Soriano 2012 | islets (human) | 0.001* | insulin secretion | NA |
| Adachi 2005 | islets (Wistar rat) | [0.000438, 0.00438, 0.0438*, 0.438*] | insulin secretion | monotonic |
| Makaji 2011 | TC-6 β cells | [0.000438, 0.00438, 0.0438, 0.438*, 4.38*] | insulin secretion | monotonic |
| Soriano 2012 | islets (ERβ -/-, C57 mouse) | 0.001 | KATP channel activity | NA |
| Soriano 2012 | islets (ERβ WT, C57 mouse) | 0.001* | KATP channel activity | NA |
| Soriano 2012 | islets, β-cells (human) | 0.001* | KATP channel activity | NA |

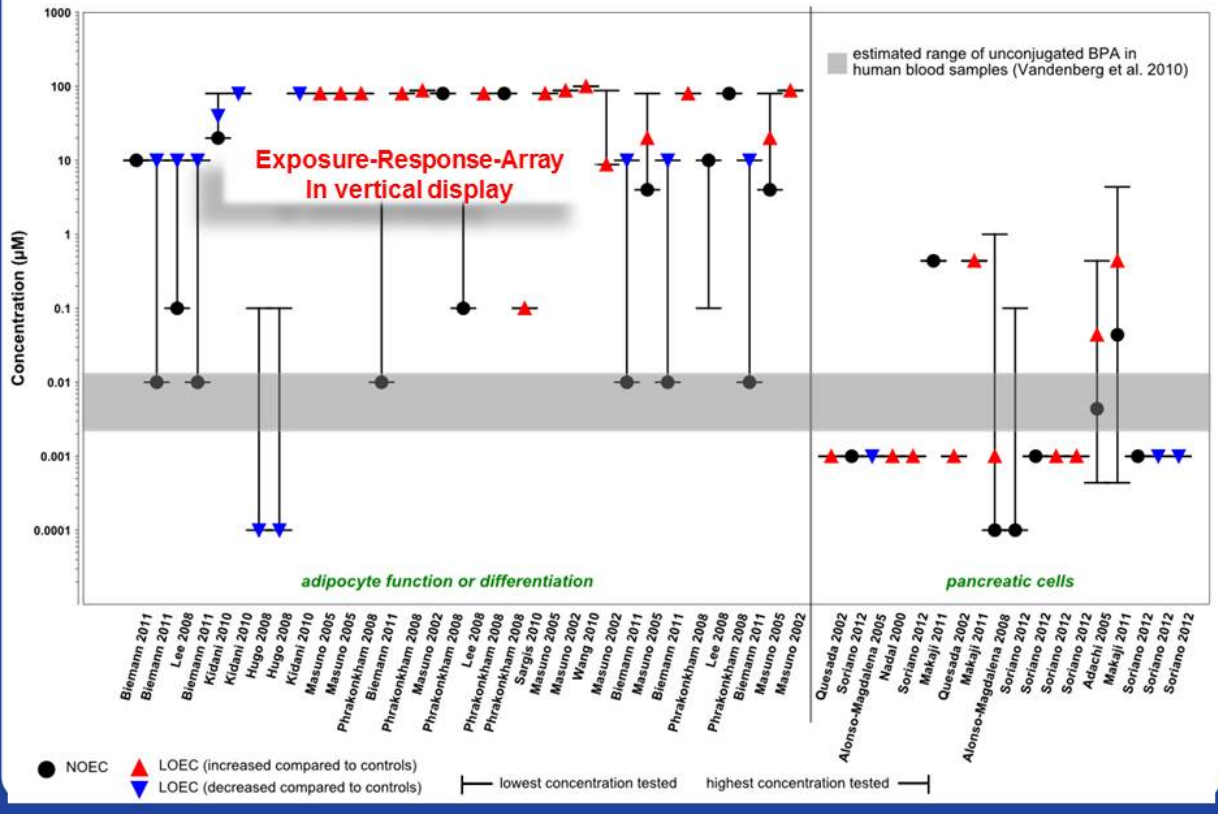



● NOEC ▲ LOEC (increased compared to controls) ▼ LOEC (decreased compared to controls)

— lowest concentration tested — highest concentration tested —

estimated range of unconjugated BPA in human blood samples (Vandenberg et al. 2010)

# Horizontal or Vertical Display



## Examples of Filtering, Sorting, & Grouping Variables

- Study features
  - Study design, country, cohort, number of exposed cases, health outcomes, diagnostic, exposure (relative and numerical), etc.
  - Species, strain, route of administration, control for litter effects, diet, dose level, etc.
  - Cell type, cellular signaling endpoints, concentration level, LOEC/NOEC, $AC_{50}$
- Magnitude of effect (human and animal data)
- Statistical power
- Risk of bias domains
- Lifestage at exposure and health outcome assessment
- Many others…..

## 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

## Systematic Review and Integrating Evidence

- Develop framework for reaching evidence assessment conclusions to address environmental health questions
  - Obtain review on the suitability and transparency of a draft approach for developing evidence assessment conclusion from a NTP Board of Scientific Counselors working group (Late Summer 2012)
  - Present approach to NTP Board of Scientific Counselors (Dec 11-12, 2012 or Spring 2013)

## Information Management

- Beta test data extraction forms
  - For use by contractors
  - Continue interagency collaboration
- Beta test utility of data extraction files for data mining
- Develop process for QA/QC of data extraction files and storage in Chemical Effects in Biological Systems (CEBS) database

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- **SRA International**
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  - Sean Chiou
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  - **Gordon Guyatt,** Professor, Clinical Epidemiology & Biostatistics, McMaster University
  - **Malcolm Macleod,** CAMARADES Centre, University of Edinburgh
  - **Karen Robinson,** Co-Director, Evidence-Based Practice Center, The Johns Hopkins Bloomberg School of Public Health
  - **Holger Schunenmann**, Co-chair, GRADE working group, McMaster University
  - **Tracey Woodruff,** Director, Program on Reproductive Health and the Environment, UCSF