CLARITY-BPA: Data integration, analysis and interpretation of eight academic studies

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Healthy Environment and Endocrine Disruptor Strategies (HEEDS.ORG), Commonweal
CLARITY-BPA: Overview

- A new collaborative model

Goals:
- Integrate strength of guideline study with molecular and disease associated endpoints from independent scientists into one study.
- To improve safety assessment.

Partners:
- NIEHS NTP and Extramural Grants Program
- FDA NCTR and CFSAN
- 14 NIEHS-funded academic grantees
Current Approach to Risk Assessment

Guideline Studies
- Standard Design
- Standard Endpoints
- Government Approved

Independent Scientist Studies
- Diverse Design
- Diverse Endpoints
- Fewer animals/gp

Regulatory agency assessment and recommendation
CLARITY Approach to Risk Assessment

Merge... guideline and independent scientist studies
- CORE STUDY
- INDEPENDENT SCIENTIST STUDY

Regulatory agency assessment and recommendation

Government approved design

More comprehensive assessment of toxic effects
### CLARITY-BPA: Study Details

<table>
<thead>
<tr>
<th>Sprague Dawley rat</th>
<th>Dose Groups (μg/kg bw/day)</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA-Core Study</strong></td>
<td>Vehicle only</td>
<td>Gavage: GD 6-Birth,</td>
</tr>
<tr>
<td>50 animals/dose</td>
<td>BPA</td>
<td>PND 1 to PND 21</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>OR 2 years</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>250</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,500</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25,000</td>
<td></td>
</tr>
<tr>
<td><strong>Independent Scientist</strong></td>
<td>EE₂</td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>~10 animals/dose</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>
CLARITY-BPA: Study Design

FDA-CORE Study

Independent Scientist Studies

INDEPENDENT SCIENTIST STUDIES

Gavage daily

Mating E6  Birth  P21

Continuous - 1 year
Continuous - 2 year
Stop Dose - 1 year
Stop Dose - 2 year

↑ 1 YEAR  ↑ 2 YEARS

↓ 1
↓ 15
↓ 21
↓ 90
↓ 180
↓ 1 YEAR
<table>
<thead>
<tr>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA-Core Study</strong></td>
</tr>
<tr>
<td>Clinical chemistry</td>
</tr>
<tr>
<td>Sperm parameters</td>
</tr>
<tr>
<td>Histopathology of all tissues</td>
</tr>
<tr>
<td>Estrus cyclicity</td>
</tr>
<tr>
<td>Body weight</td>
</tr>
<tr>
<td>Organ weights of selected tissues</td>
</tr>
</tbody>
</table>

| Independent Scientist Studies |
| Prostate |
| Fred vom Saal |
| Gail Prins |
| Testis function |
| Kim Boekelheide |
| Penile dysfunction |
| Nestor Gonzalez-Cadavid |
| Cardiovascular |
| Scott Belcher |
| Immune function |
| Norbert Kaminski |
| Breast cancer |
| Ana Soto |
| Uterine cancer |
| Shuk Mei Ho |
| Ovarian function |
| Jodi Flaws |
| Obesity |
| Nira Ben Jonathon |
| Diabetes/liver |
| Andrew Greenberg |
| Thyroid function |
| Tom Zoeller |
| Brain development |
| Cheryl Rosenfeld |
| Heather Patisaul |
Publication Status

• Core guideline study
• 10/14 independent/academic studies
• No integrated publication of all the independent studies
• No integrated publication of all CLARITY-BPA data, core and independent scientist
Today: Unique Manuscript

• This is a final report of 8 independent/academic studies that presents their data and puts it in perspective to previously published data

AND

• Integrates all the findings and interprets them as a whole.
Independent Scientist Studies Published, NOT INCLUDED

**Testis function**
*Kim Boekelheide*

**Immune function**
*Norbert Kaminski*

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Independent Scientist Studies NOT PUBLISHED

- **Diabetes/liver**
  *Andrew Greenberg*

- **Obesity**
  *Nira Ben Jonathon*

- **Penile dysfunction**
  *Nestor Gonzalez-Cadavid*

- **Uterine cancer**
  *Shuk Mei Ho*
Independent Studies Included

Prostate Cancer/Stem cell Progenitor numbers
Gail Prins

Male Urogenital abnormalities
Fred vom Saal, William Ricke

Cardiovascular Function
Scott Belcher

Mammary Gland Development/Cancer/ Nature of Dose Response
Ana Soto

Ovarian function
Jodi Flaws

Thyroid Function
Tom Zoeller

Learning and Behavior/transcriptomics
Cheryl Rosenfeld, Shuk Mei Ho

Behavioral Changes/Brain transcriptomics
Heather Patisaul

Data Integration Across Organs/Dose and Time
Cheryl Rosenfeld, Juide Mao
Manuscript Organization

• For Each Organ System
  • Previous Publications
  • Hypothesis
  • Methodology
  • Data Summary
  • Discussion
    • Major Findings
    • Compare to Previous Publications
    • Study Differences

• Data Integration across organs, dose, time
• Discussion of data integration
• Final integrated Discussion
Presentations...

• Gail Prins, U Illinois Chicago
  Prostate Cancer/Stem Cell Progenitor number

• Ana Soto, Tufts University
  Mammary Gland Development/Cancer/Nature of the dose response

• Cheryl Rosenfeld, University of Missouri
  Integrated Data Across Organs/Doses/Times

• Gail Prins, U Illinois Chicago
  Summary and Key Messages