SUMMARY AND RECOMMENDATIONS

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

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CLARITY-BPA: Combined Guideline AND Academic studies to inform risk assessment on BPA safety

**BRAIN**
- **GUIDELINE**
  - Weight
  - Brain stem compression/hemorrhage
- **ACADEMIC**
  - Region-specific gene expression
  - Patterns of ER expression
  - Volume of brain regions

**HEART**
- **GUIDELINE**
  - Weight
  - Cardiomyopathy
  - Cancer
- **ACADEMIC**
  - Weight
  - Left ventricle wall thickness
  - Fibrosis
  - Cardiac lesions

**SPLEEN**
- **GUIDELINE**
  - Weight
  - Incidence of lymphoma
  - Pigmentation
- **ACADEMIC**
  - Cellularity
  - Lymphoid populations
  - Myeloid populations
  - Proliferation
  - Activation of T-cells & NK cells

**UR0GENITAL TRACT**
- **GUIDELINE**
  - Weight
  - Histology
- **ACADEMIC**
  - Urethral Colliculus enlargement
  - Urethra morphometrics
  - Body weight

**BEHAVIOR**
- **GUIDELINE**
  - Seizures
- **ACADEMIC**
  - Sex-specific learning behaviors
  - Anxiety behaviors
  - Memory

**OVARY**
- **GUIDELINE**
  - Weight
  - Cysts
  - Hyperplasia
  - Atrophy
- **ACADEMIC**
  - Number and stage of follicles
  - Follicle health
  - Serum sex hormone levels

**THYROID**
- **GUIDELINE**
  - Weight
  - Histology
- **ACADEMIC**
  - Thyroid hormone levels
  - Thyroid hormone brain endpoints

Adapted from Pat Hunt
REPRODUCIBILITY

- High
- Variation
  - experimental design
  - model
  - time points

CLARITY findings: conclusions remain the same
SENSITIVITY

Affected organs:

- Mammary
- Uterus, Ovary
- Prostate
- Heart
- Brain

- Reproducible endpoints
- *Far more sensitive*

*Ideal for future EDC testing paradigms*
LOW-DOSE and NON-MONOTONIC EFFECTS

• Significant adverse effects at the lowest dose 2.5 µg/kg BW

• Consistent non-monotonic (i.e. non linear) responses

• Integrative mixOmics analysis:
  strong, complex inter-relationships

Strong evidence: low-dose effects are NOT spurious!
STUDY STRENGTHS

✓ Animals treated at FDA under GLP guidelines
✓ Investigators fully blinded
✓ Academic data locked before codes released

All Academic studies meet requirements for inclusion in risk assessment analysis
Prior to CLARITY...

Guideline conclusions: only high doses are toxic

LOAEL = lowest observed adverse effect level; ATI = acceptable tolerable intake, aka RfD = Reference Dose
NOAEL = no observed adverse effect level (calculation); MTD = maximum tolerable dose;

Adapted from Laura Vandenberg
CLARITY-BPA…

New LOAEL is unequivocally $2.5 \, \mu g/kg$

... thus reference dose needs revisiting.

**LOAEL** = lowest observed adverse effect level; **ATI** = acceptable daily intake, aka **RfD** = Reference Dose;
**NOAEL** = no observed adverse effect level (calculation); **MTD** = maximum tolerable dose;

Adapted from Laura Vandenberg
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