

SUMMARY AND RECOMMENDATIONS

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

JJ Heindel, S Belcher, JA Flaws, GS Prins, SM Ho, M Jiude,
HB Patisaul, W Ricke, CS Rosenfeld, AM Soto, FS vom Saal, RT Zoeller

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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

UROGENITAL TRACT

GUIDELINE

Weight
Histology

ACADEMIC

Urethral Colliculus enlargement
Urethra morphometrics
Body weight

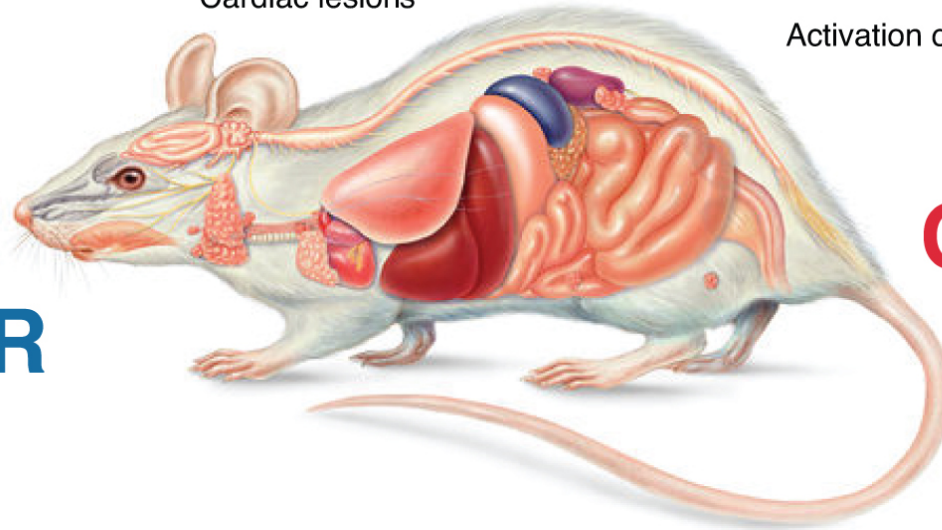
BEHAVIOR

GUIDELINE

Seizures

ACADEMIC

Sex-specific learning behaviors
Anxiety behaviors
Memory



Adapted from Pat Hunt

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

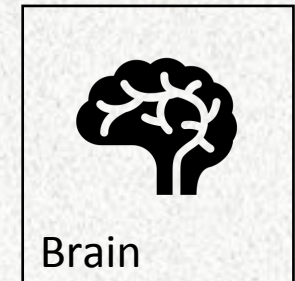
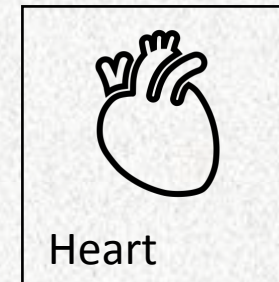
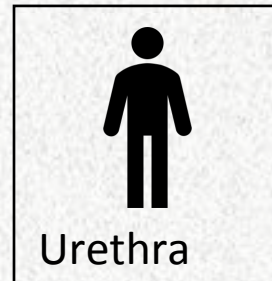
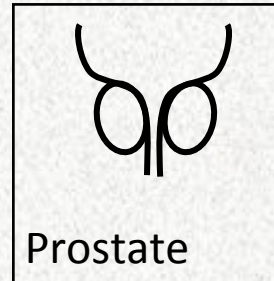
REPRODUCIBILITY

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

CLARITY findings: conclusions remain the same

SENSITIVITY

Affected organs:



- 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

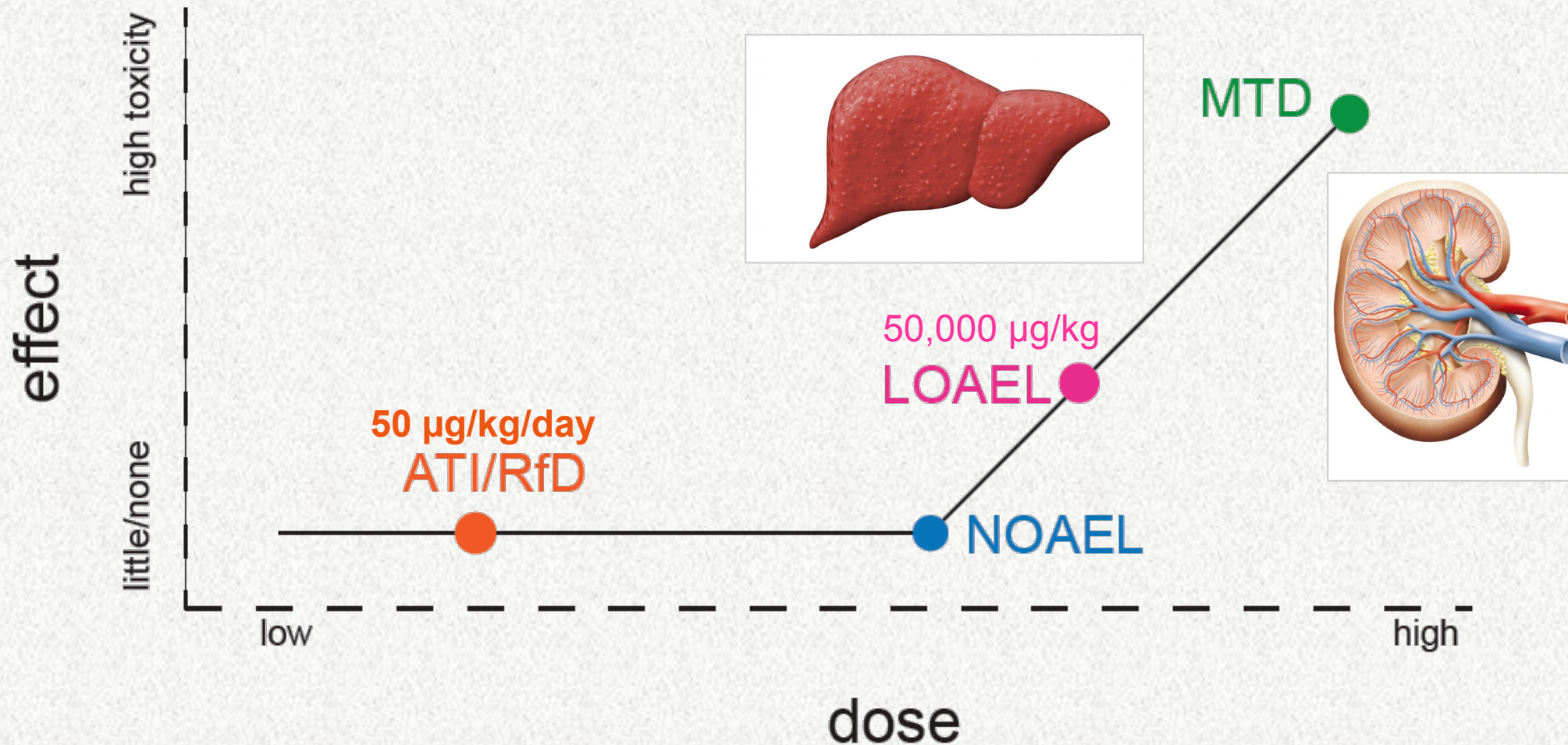
- ✓ Animals treated at FDA under GLP guidelines
- ✓ Investigators fully blinded
- ✓ Academic data locked before codes released



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**

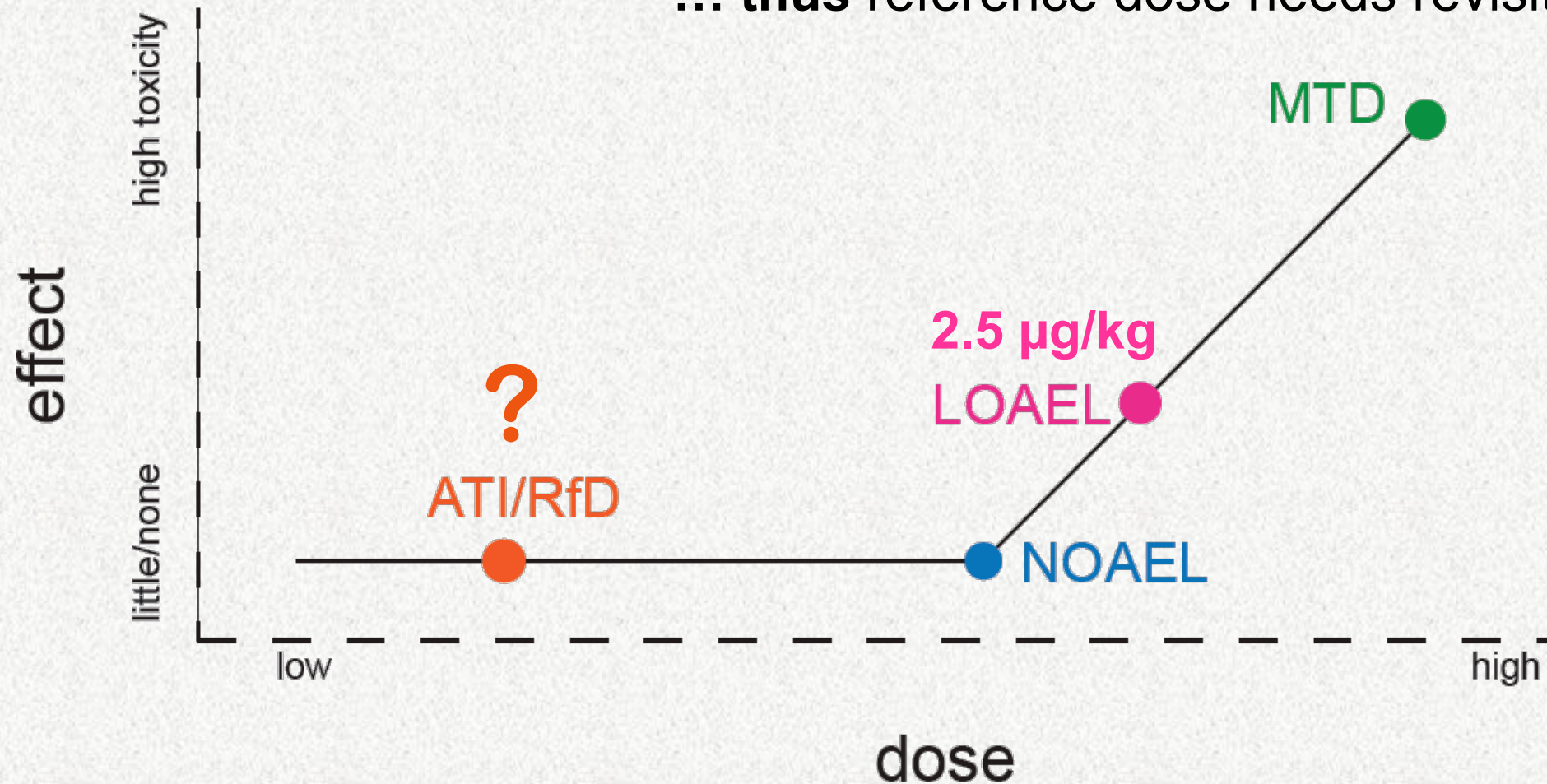
NOAEL = no observed adverse effect level (calculation); **MTD** = maximum tolerable dose;

Adapted from Laura Vandenberg

CLARITY-BPA...

New LOAEL is unequivocally **2.5 µg/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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