

Internal Dosimetrics Enable Holistic Assessment of Exposures to Environmental and Endogenous Estrogens

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OUTLINE

- Elements of risk assessment – uses of animal and human data for BPA
- PBPK model development – animal and human
- Use of PBPK models to produce HEDF
- Incorporate elements of endogenous estrogen internal exposures and signaling in women (magnitude and variability)
- Human exposures in the context of a hypothesis for “endocrine disruption” by BPA and other dietary estrogens
- State of the uncertainty – BPA 2018

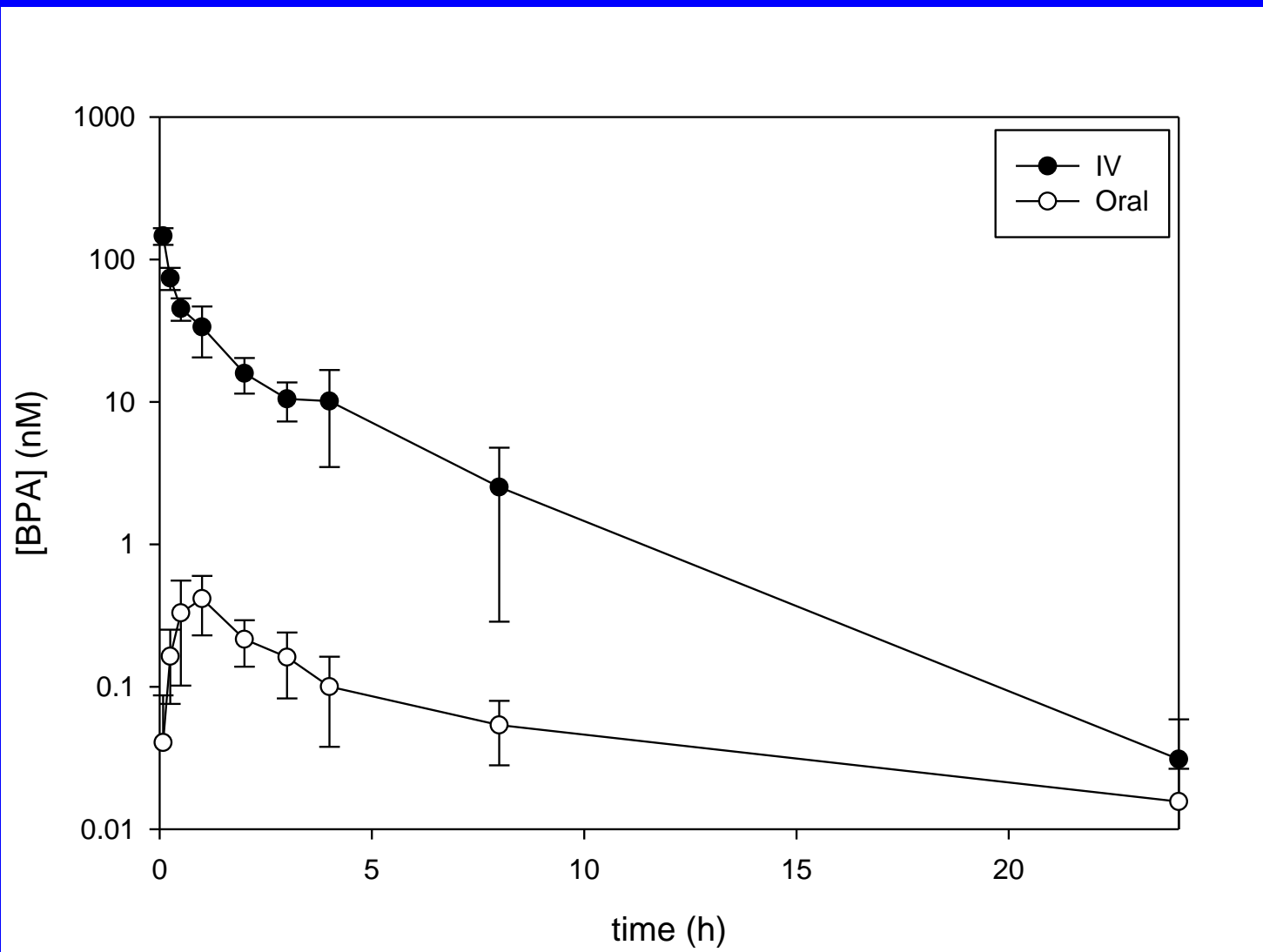
Risk assessment of dietary chemicals

- Hazard identification: toxicokinetics (animal, humans); toxicodynamics (animal toxicity testing, epidemiology)
- Exposure assessment: dietary intake distribution (contaminant levels in different foods, portion size, frequency P50/P90); biomonitoring (total daily intake); age groups
- Risk = hazard x exposure
- HBGV = BMDL or NOAEL x PK/PD factors comprising uncertainties and/or variabilities
- MOE = ratio of exposure to effect dose

NCTR/FDA-NTP BPA study goals 2008

- Expand PK data from mice, rats, monkeys, and humans to create and validate PBPK models that will predict internal exposures to BPA in target tissues of adults, fetuses, and babies from food contact materials and medical devices.
- Conduct large-scale rat studies under strictly controlled conditions with a multiplicity of doses in the low dose region administered throughout all lifestages to create comprehensive toxicological evaluations of BPA.

Oral bioavailability of BPA Is low in adult monkeys (<1%)



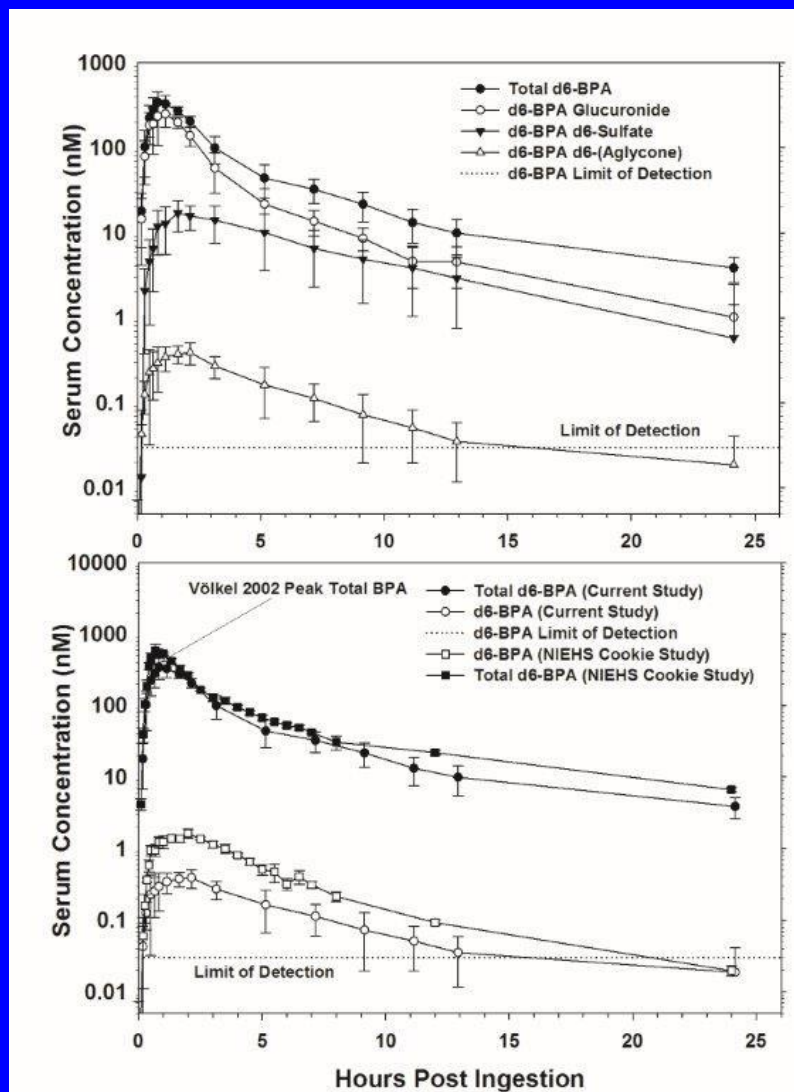
CONCLUSIONS – Adult PK

- PK broadly similar between species for adults: CD-1 mouse, SD rat, rhesus monkey
- BPA oral bioavailability is low in adults of all species – rapid and extensive metabolism in the GI tract and liver; quantitatively excreted
- Systemic Phase II metabolism substantial even after parenteral administration
- Non-persistent, even in adipose tissue

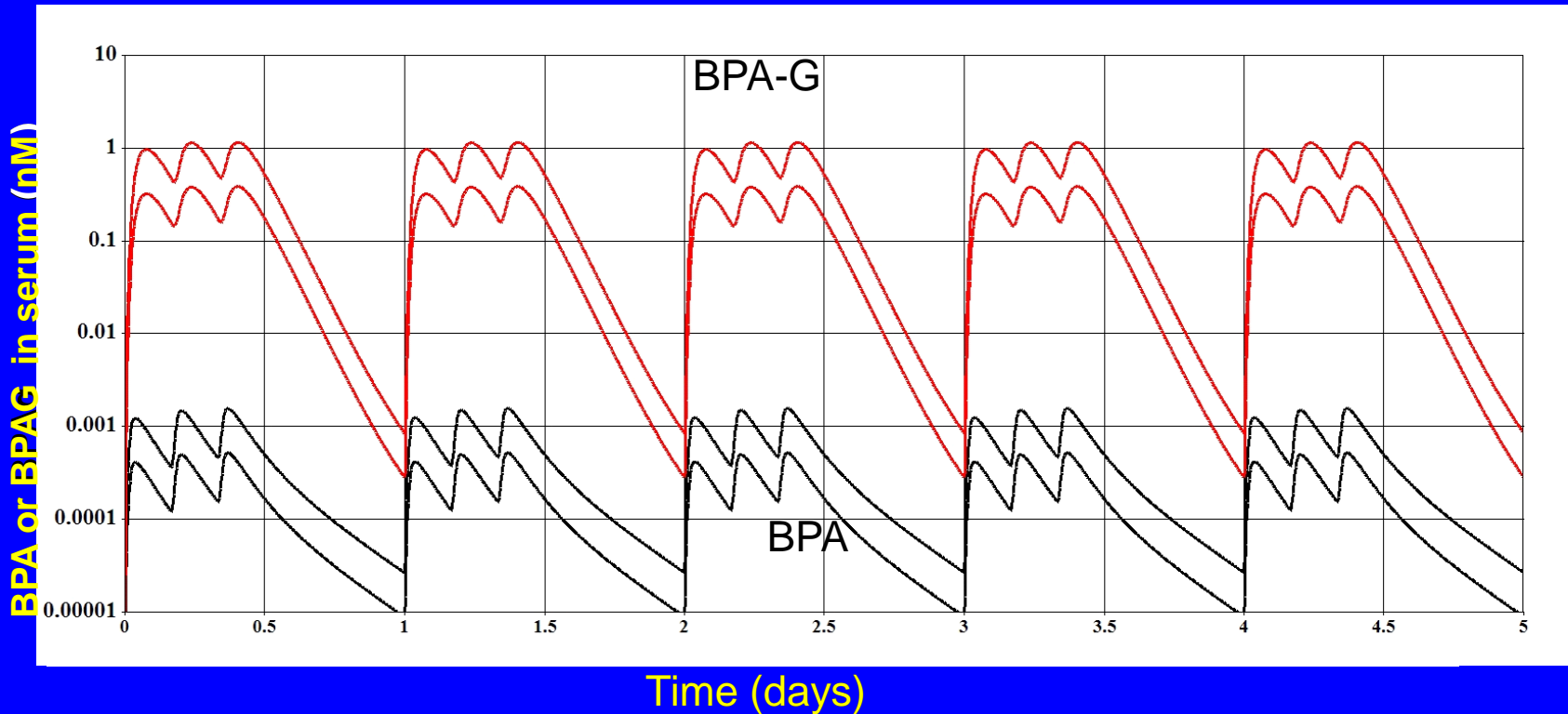
CONCLUSIONS – Perinatal PK

- Phase II metabolism is deficient at birth in rodents and produces ~10-fold higher internal exposures vs. primates
- Neonatal rodents are predicted to be more sensitive than primates based on internal exposure
- Lactational transfer is minimal
- Fetal exposures are \leq maternal levels and fetal Phase II metabolism increases throughout gestation
- Placenta – Phase II activity in tissue; no evidence for significant deconjugation in vivo
- Amniotic fluid levels < maternal serum for both unconjugated and conjugates
- Evidence for absence of fetal accumulation of BPA
- Maternal metabolism determines fetal exposures

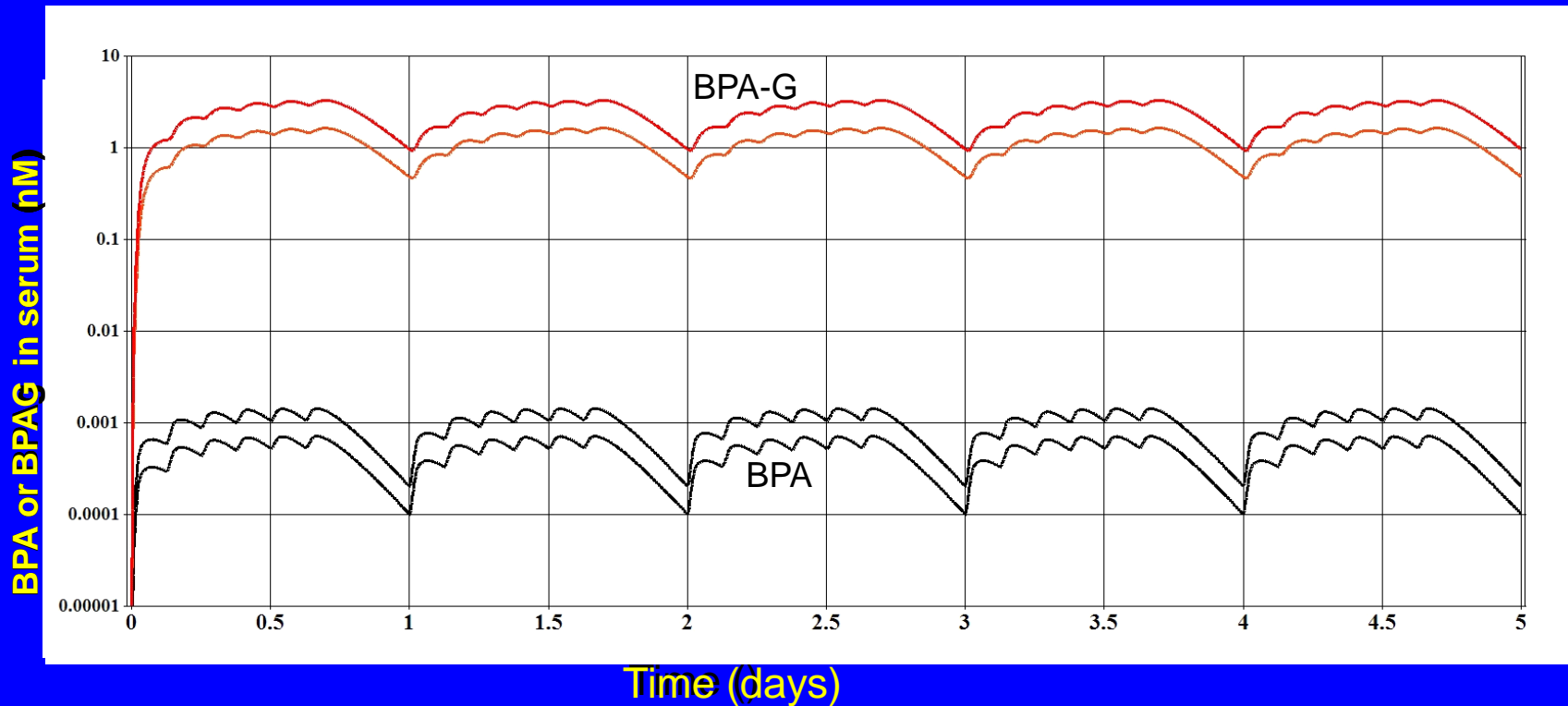
Human serum pharmacokinetics of d6-BPA - consistent across three studies



PBPK simulations of BPA ingestion in adults 3 meals, 0.1 (mean) and 0.3 (90th) $\mu\text{g}/\text{kg}$ bw/d



PBPK simulations of BPA ingestion in infants 6 meals, 0.3 (mean) and 0.6 (90th) $\mu\text{g}/\text{kg}$ bw/d



Inter-individual variability of measured human BPA PK parameters

| Study | AUC/$\mu\text{g}/\text{kg bw}$ | C_{max}/$\mu\text{g}/\text{kg bw}$ |
|---|--|--|
| Teeguarden et al., (2015) (n = 10) | 0.047-0.19 (4.1x) | 0.01-0.023 (2.3x) |
| Thayer et al., (2016) (n = 14) | 0.12-0.34 (2.6x) | 0.036-0.16 (4.4x) |

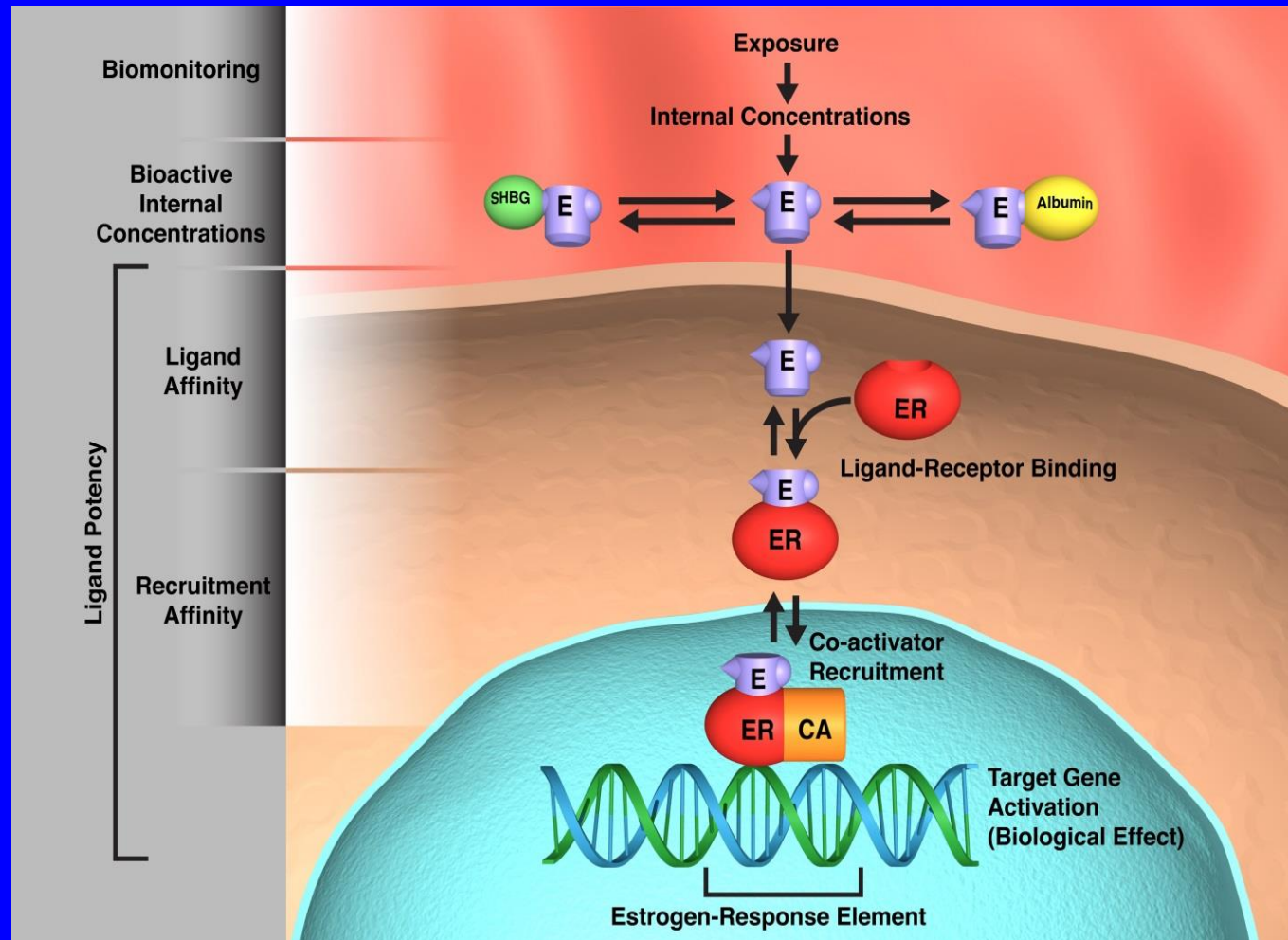
Inter-species comparisons in PBPK model prediction of serum PK parameters for BPA (50 µg/kg bw; Yang et al., 2013; 2015).

| Species-Age | AUC (nM x h/d) | AUC Ratio | Ratio BW^{3/4} Scaling |
|----------------------------|---------------------------|----------------------|---|
| Rat-neonate (8 g) | 31 | | |
| Human-infant (5 kg) | 1.5 | 21 | 5 |
| Rat-adult (300 g) | 3.7 | | |
| Human-adult (70 kg) | 1.8 | 2.0 | 4 |

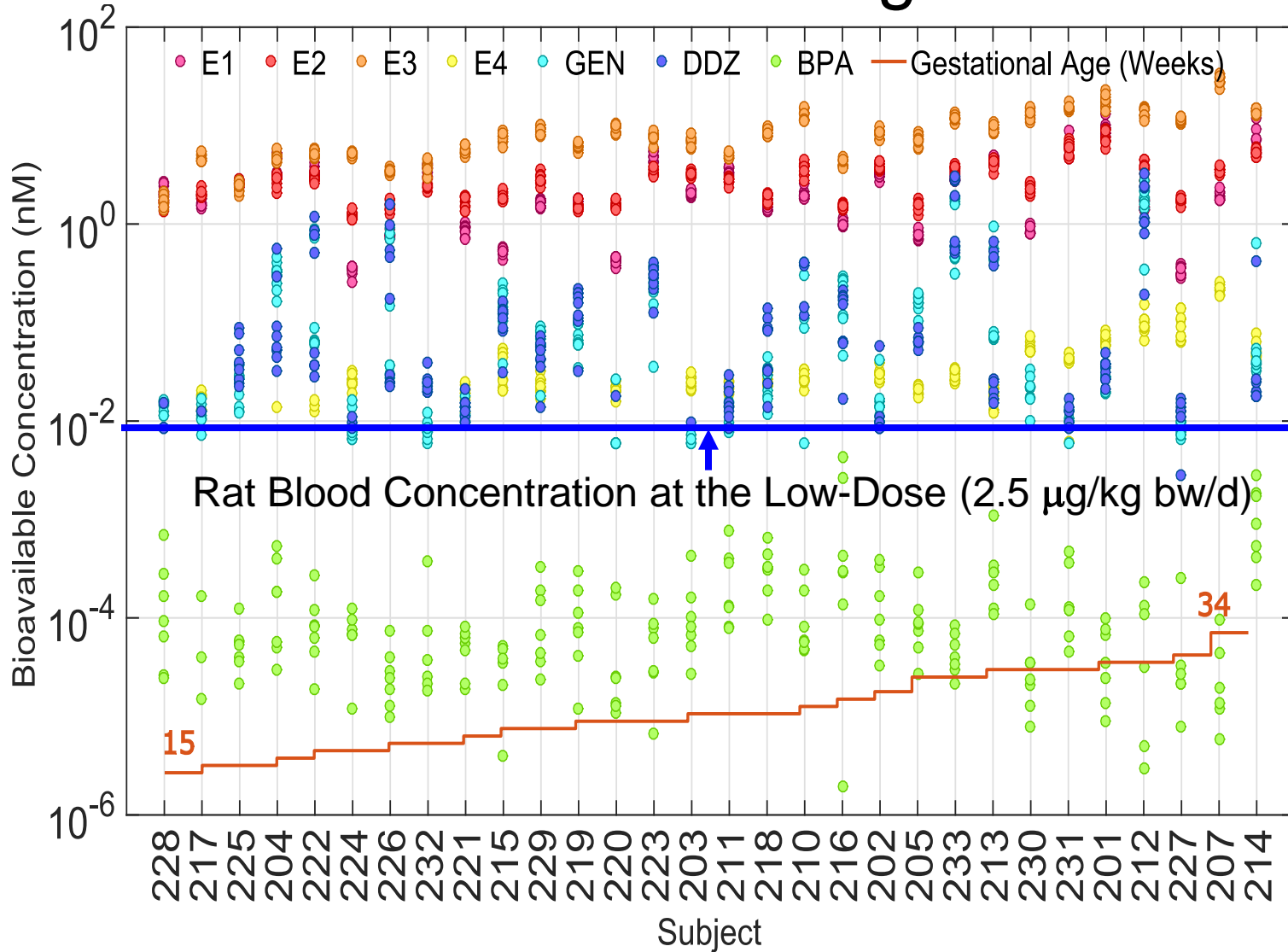
Comparative estrogenicity of dietary and endogenous ER ligands during pregnancy

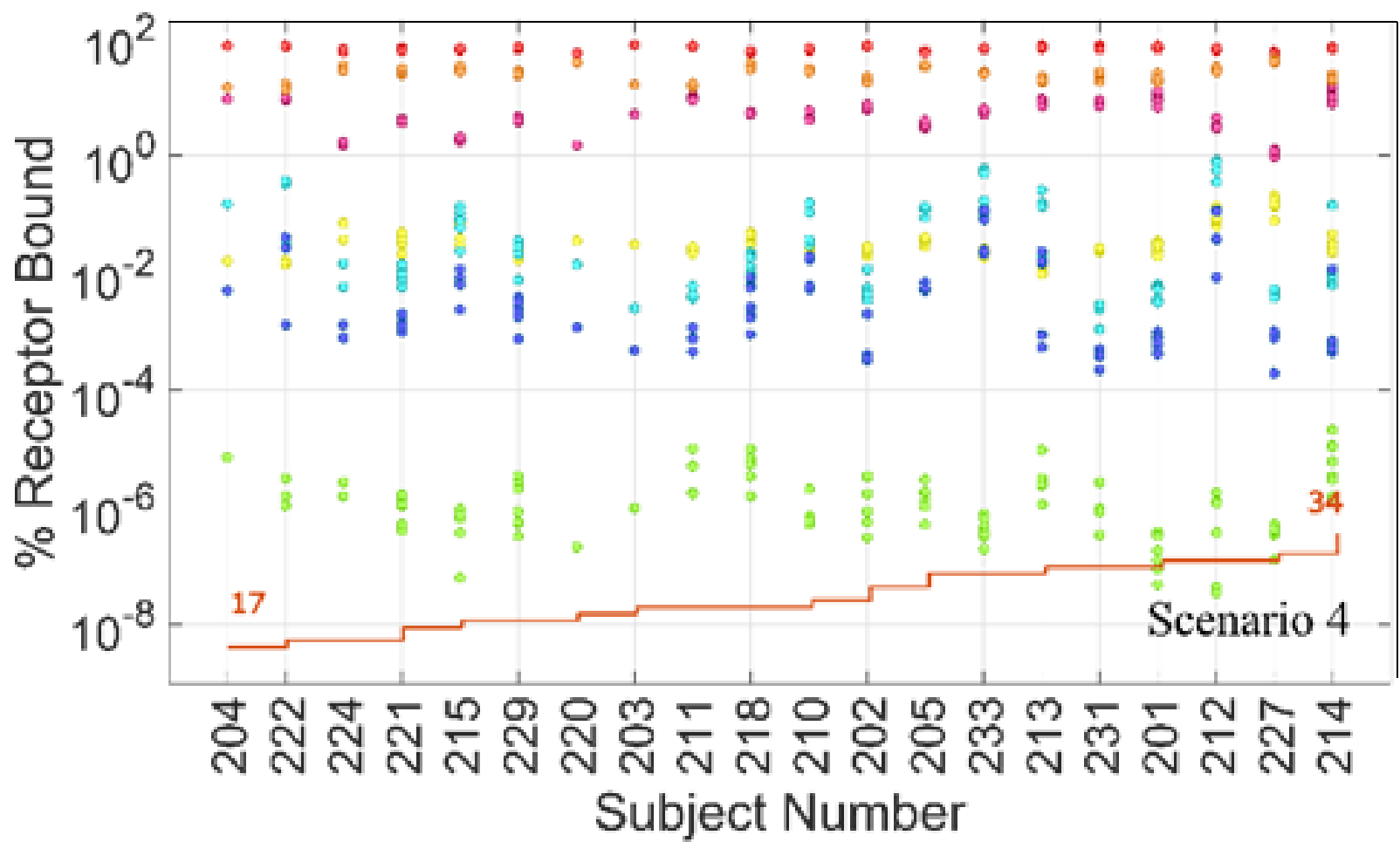
- Cohort of 30 pregnant women – recruited for canned food consumption and receipt handling (n=20); soy food consumption (n=10)
- Different stages of gestation
- BPA
- Soy isoflavones (genistein and daidzein)
- Maternal and fetal steroid hormones (E1-E4)
- Repeatedly measure serum/urine concentrations over 1d
- Daily and inter-individual variability
- Calculate bioavailable fractions in serum
- Calculate ER occupancy
- Estimate total estrogen responses (transcriptional regulation)
- Compare exogenous ligand contribution in terms of daily variability of total endogenous estrogenicity

Calculated estrogen receptor occupancies for dietary and endogenous estrogens in serum from pregnant women



Calculated bioavailable concentrations of serum estrogens





Endogenous estrogens dominate receptor interactions in women

- Receptor occupancy from bioavailable concentrations of E2, E3, E1
- Pregnant women - 94-99% for ER- α
- Normal cycling women 67-89% for ER- α
- Soy isoflavones <10% for ER- β ; <1% for ER- α
- BPA negligible ($\sim 10^{-3}\%$)
- Similar results obtained when total response calculated (ligand-specific co-activator recruitment)
- BPA estrogenic contributions negligible when considered within the context of clinical variability in pregnant and normally cycling women (intra-day and inter-individual)

Risk Assessment –

Combining human exposure and animal toxicity

- Toxicology testing for regulatory risk assessment specifically includes effects on endocrine-regulated processes as well as organ-specific toxicities and carcinogenicity
- Well-defined perinatal and adult exposures (internal dosimetry)
- Holistic consideration of exogenous and endogenous estrogen activities and variability
- U.S. dietary intake (adults/infants) : 0.1/0.3-0.3/0.6 $\mu\text{g}/\text{kg}$ bw/d (mean-P90)
- U.S. total intake (NHANES): 0.03/0.3 $\mu\text{g}/\text{kg}$ bw/d (P50)
- Chemical-specific adjustment factors from rat and human PBPK models are available (21-neonatal; 2-adult)
- No biologically significant effects in rats from BPA at doses of 2.5-2,700 $\mu\text{g}/\text{kg}$ bw/d

CONCLUSIONS

State of the Uncertainty – 2018

- Minimal uncertainty surrounding BPA internal exposures in animals and humans (magnitude and variability)
- Minimal uncertainty surrounding BPA exposure assessment (dietary intake/biomonitoring)
- Minimal internal exposures, even at P95
- Some uncertainty surrounding route (dietary vs. dermal)
- Some uncertainty surrounding mechanism - estrogenic hypotheses have been predominant
- Interpretation of results from animal toxicology testing and epidemiological associations

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