Research on Species Responses

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ACC Phthalate Esters Panel

Background

- Panel long interested in differences in species responses – initially focused on peroxisome proliferation, then reproduction.
  - Human hepatocyte responses
  - Adult marmoset/Cynomolgus responses
  - Juvenile marmoset responses
- Biggest challenge has been developmental responses

What have we learned

- Human hepatocytes don't show same responses as rat hepatocytes.
  - Butterworth et al. (1984), Elcombe et al. (1996)
- Adults marmosets or Cynomolgus liver does not respond as rat or mouse liver.
  - Kurata et al. (1998), Hall et al. (1999), Pugh et al. (2000)
- Phenomenology supported by PPAR mode of action.
  - Ward et al. (1998)
- Debate rages on whether there are other MOAs for liver cancer in wild-type rodents.

Reproductive effects - DEHP

- Adult marmoset or Cynomolgus testes not affected like rat testes.
  - Kurata et al. (1998) and Hall et al. (1999) showed lack of testicular response in adult marmoset monkeys treated with up to 2500 mg/kg DEHP for 13 weeks.
  - Pugh et al. (2000) showed lack of effect in adult Cynomolgus monkeys treated with 500 mg/kg DEHP for 2 weeks.

- Juvenile marmoset testes not affected like rat testes.
  - Tomonari et al. (2006) showed lack of testicular effect in weanling marmoset monkeys treated with 2500 mg/kg DEHP for 65 weeks.

Reproductive effects – DEHP & DBP

- Adult human volunteers or children exposed as neonates (ECMO) show no evidence of hormonal or testicular effects.
  - Janjua et al. (2007) showed lack of effect on hormones or testicular function in men exposed to DBP via dermal cream.
  - Rais-Bahrami et al. (2004) showed lack of genital effect in a small population of pubescent children exposed to DEHP as neonates during ECMO.
- Can the phenomenology be supported by a mode of action?

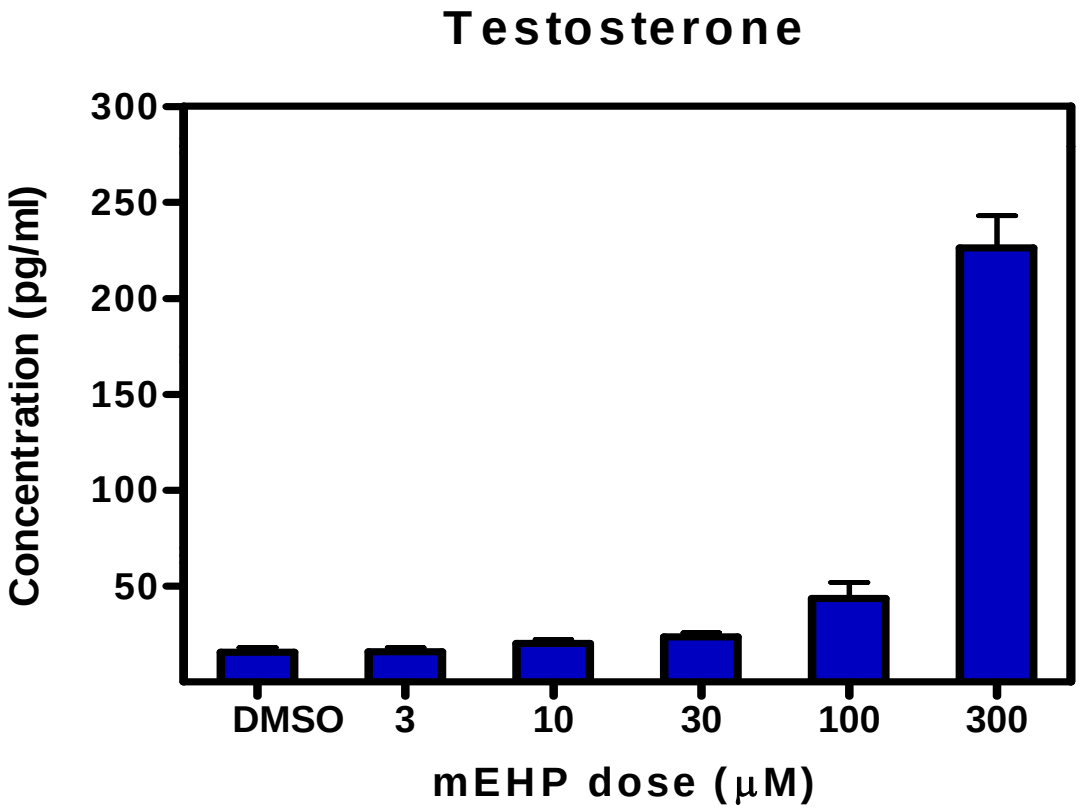
Developmental effects

- Mouse developmental responses different than rat responses:
  - No testicular dysgenesis after DBP (Gaido et al., 2007)
- Marmoset developmental responses different than rat responses
  - No evidence of any developmental effect after DBP (McKinnell et al., 2009). Marmoset develop reported to mimic human (Mitchell et al., 2008).
- What about humans? Swan and others have associated functional effects in humans with high levels of environmental exposure to DBP. How can this reconcile with our understanding of a species differences in response?

Research

- MSU evaluated potential for *in vitro* method to evaluate testosterone-related effects.
  - Looked at mouse Leydig BLTK1 cell model that expresses testosterone for screening purposes.
  - Exposed cells to MEHP or DEHP for up to 48 hours.
  - DEHP does not affect progesterone or testosterone levels in BLTK1 cells.
  - Dose- and time-dependent induction of progesterone and testosterone levels in BLTK1 cells by MEHP.

Effect on Testosterone - MEHP



Research

- Brown Univ. developing trans-species implantation to determine if
  - Host species response or nascent species
    - Thus far, host species (rat versus mouse) does not influence response. Brown Univ. also evaluating human tissue in trans-species. Data too preliminary to comment.
  - Influence of kinetics
    - Not yet determined.
- Will this lead to MOA for developmental effects?

Summary

- Is it appropriate to continue to use the rat as the model species?
  - Mice and marmoset monkeys don't respond the same way. Is the rat unique?
- What evidence would be needed to demonstrate no relevance for humans?