Comments to EPA IRIS on Diisononyl Phthalate (DINP) Review October 29, 2014

From:

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Conflict of Interest Statement

These comments represent my professional opinion on these issues. It was supported by funding from ExxonMobil Biomedical Sciences Inc.

This work was based information in the preliminary meeting materials and select scientific publications cited in my written comments.

Comments for Question 5.
Transparency and Utility of Mechanistic Data

- Mechanistic data are less critical for:
  - Hazard identification
  - Risk assessment of a single compound
- Mechanistic data are essential for cumulative risk assessment
- Cumulative risk assessment must be based upon:
  - Common mechanism of toxicity
  - Common adverse effect
- Currently the literature review excludes reviews or data on other phthalates

Data Review

- Mechanistic studies identified in HERO database
  - Identified all mechanistic studies on DINP
  - Not all studies with relevant data have been included
- Depending upon outcome of interest, not all publications may be relevant
- *In vitro* studies using diesters may not be predictive of monoester (metabolite) toxicity

Context for DINP Review

- Not all phthalates are active
- Reviews and studies on other phthalates must be considered to better understand the nature of the mechanism
- Development of hypotheses for DINP effects
  - Should help assess commonality (or lack thereof) with other phthalates

Example: DINP and "Phthalate Syndrome"

- DINP data show different effects from those phthalates that cause the phthalate syndrome
- At least 3 distinct genetic mechanisms have been shown for the active phthalates; one for each serious adverse effect
- Each adverse effect is associated with a unique mechanistic pathway and DINP does not cause common adverse effects with those mechanisms
- DINP appears to cause effects at high dose levels by a different mechanism that results in reversible and non-adverse effects

Conclusions

- As identification of evidence, the work to date has been solid
- Next steps:
  - Identify endpoints for hazard evaluation
  - Integrate mechanistic data for the selected endpoints