Overview of Materials for Chloroprene PBPK Peer Review

- Focus of this peer review and possible next steps
- U.S. EPA Background for Peer Review
- U.S. EPA Charge Questions
- Ramboll PBPK report and supplements (appendices)
- Ramboll model code packages (zip files)
  - Ramboll 2020 Chloroprene In Vitro Code.zip
  - Ramboll 2020 Chloroprene PBPK Code.zip
- Public comments are available at:

https://www.regulations.gov/docket?D=EPA-HQ-ORD-2020-0181

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Focus of Peer Review

- Focus of current peer review: Is the chloroprene PBPK model sufficiently reliable for use in an IRIS Toxicological Review?
  - Prediction of chloroprene tissue concentrations in mice, rats, and humans
  - Prediction of chloroprene oxidative metabolism in lung, liver, and kidney of mice, rats, and humans
- But this peer review is not to address ***how*** the PBPK model will be applied.
- While lung may be the highest risk tissue, review should not focus only on it.
- If the model is found sufficiently reliable, then "how" it is applied would be addressed in a subsequent EPA analysis, which would undergo external review.
- Detailed presentation of charge questions will be covered in Versar presentation.

Items in Package

- **U.S. EPA Background for Peer Review**
  - Provides context for model evaluation
  - Request for Correction / Request for Reconsideration of IRIS Tox Review: https://www.epa.gov/quality/epa-information-quality-guidelines-requests-correction-and-requests-reconsideration#17002
  - If a PBPK model is accepted, EPA usually tries to apply it comprehensively
- **U.S. EPA Charge Questions**
  - Grouped by model component and element of analysis
  - In Vitro Model ➔ PBPK Model ➔ Uncertainty Analysis
  - Includes pointers to specific text and results being addressed

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Items for Review #2

- **Ramboll (2020) report**
  - Primary document gives overview of modeling analysis
  - Technical details in Supplement documents
- **Ramboll model packages (.zip files)**
  - Ramboll 2020 Chloroprene In Vitro Code.zip
  - Ramboll 2020 Chloroprene PBPK Code.zip
- **EPA reviewed, provided comments & suggestions to Ramboll on previous versions**
  - Incorporates two-compartment in vitro model, per EPA's suggestion
  - EPA did not review final version
  - Ramboll authors will be present to answer questions during peer review meeting

Items for Review #3

- **U.S. EPA Uncertainty Analysis (UA)**
  1. Alternate UA of in vitro parameter uncertainty
     - Partly complete due to COVID-19 (access to computer)
     - Evaluation of statistical model & approach requested
     - Results would be reviewed again in next phase
  2. Approach to quantify uncertainty of PBPK model
     - Requires completion of UA #1 as input (and other data)
     - Evaluation of method requested
     - Major flaws, missing elements?
     - Specific details and results would be reviewed again in next phase