# Focused QA Discussion of Chloroprene Model Updates

Options and Path Forward

Meeting of EPA and Denka Performance Elastomers representatives

USEPA

Research Triangle Park, NC

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# In Vitro Mass Transfer Experiments

- EPA believes that the recent experiments are a good measure of mass transfer in the system at 60 rpm shaker speed, but that the presence of 1 mg/ml microsomal protein would not significantly increase mass transfer from air into the incubation medium (water + microsomes)
- Given that Himmelstein used 500 rpm, a reasonable assumption is to adjust KG by 500/60, hence from 0.024 L/h to 0.2 L/h
- Preliminary results with that value (Vmax = 0.25 umol/h/mg protein, Km = 0.7 uM for male mouse liver) appear to be acceptable
- Note: this was accomplished using the 10-zone version of the model, but at 500 rpm, the original model version may be more realistic

# Why didn’t EPA previously consider increased mixing (~ 10x) as an explanation?

- We assumed one would not want to “beat it to a froth”

Int J Pharm. 2012 Feb 28;423(2):264-80. doi: 10.1016/j.ijpharm.2011.11.044. Epub 2011 Dec 8.

**Computational fluid dynamics (CFD) insights into agitation stress methods in biopharmaceutical development.**

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**Abstract**

Agitation of small amounts of liquid is performed routinely in biopharmaceutical process, formulation, and packaging development. **Protein degradation commonly results from agitation**, but the specific stress responsible or degradation mechanism is usually not well understood. Characterization of the agitation stress methods is critical to identifying protein degradation mechanisms or specific sensitivities. In this study, computational fluid dynamics (CFD) was used to model agitation of 1 mL of fluid by four types of common laboratory agitation instruments, including a rotator, orbital shaker, magnetic stirrer and vortex mixer. Fluid stresses in the bulk liquid and near interfaces were identified, quantified and compared. The vortex mixer provides the most intense stresses overall, while the stir bar system presented locally intense shear proximal to the hydrophobic stir bar surface. The rotator provides gentler fluid stresses, but the air-water interfacial area and surface stresses are relatively high given its low rotational frequency. The orbital shaker provides intermediate-level stresses but with the advantage of a large stable platform for consistent vial-to-vial homogeneity. Selection of experimental agitation methods with targeted types and intensities of stresses can facilitate better understanding of protein degradation mechanisms and predictability for "real world" applications.

# Next steps for completing EPA model review

- Re-fitting of Vmax and Km across all species, sexes, and tissues? [DPE]
  - Possible option:
    - Test change in KG on fits for specific data sets (i.e., with Vmax and Km at current values)
    - If impact is < 1% (5%?, 10%?), leave be.
    - Refit those with larger changes.
  - While these changes will likely not significantly impact the in vivo predictions vs. mouse PK data, those plots should be revised to be sure.
- Complete model QA [EPA]
  - Had mostly completed last fall, but...
  - For example, sampling of headspace may be insignificant vs. liver metabolism, but significant vs. lung metabolism in humans; need correct schedule & volume for each experiment
- Revise report summarizing model (remove risk calculations) [DPE]
  - DPE may wish to wait until QA is complete to finalize

# External peer review[EPA]

- Setting up the contract, selecting reviewers, etc., takes some time
- QA can occur during those initial steps
- But QA should be completed before sending to reviewers
- Develop peer review charge questions
- An expert in mass transfer should be included on review of model
  - Analysis of relationship between KG and estimated Km should be included in material presented to the panel to show impact of this choice
  - Summary information on Km for other halogenated compounds could also be included, but for each chemical:
    - 4 papers on methylene chloride (using the same PK data) is not an “n” of 4!

# Chemical entities & Km values (partial list)

| Chemical | References | Km (µM) |
|---|---|---|
| Trichloroethylene | Andersen et al. (1987b) | 1.9 |
| 1,1-Dichloroethylene | Andersen et al. (1987b) | 1.0 |
| Methylene chloride (dichloromethane, $CH_2Cl_2$) | Andersen et al. (1991)<br>Andersen et al. (1994)<br>Gargas et al. (1986)<br>*Marino et al. (2006)* | 6.8 (CV = 0.42) |
| $CH_2BrCl$ | Gargas et al. (1986) | 3.1 |
| $CH_2Br_2$ | Gargas et al. (1986) | 2.3 |
| Vinyl chloride | Clewell et al. (2001) | 1.6 |
| ... | | |

# Summary

- Re-fit Vmax and Km across species, sexes, and tissues, as impacted by change in KG [DPE]
- Complete model QA [EPA]
- Prepare a report summarizing the model [DPE]
- Develop peer review charge questions [EPA]
  - Share charge questions with DPE [EPA]
- Execute peer review [EPA]
- Receive peer review report [EPA]
  - Evaluate report and relevance to the RfR [EPA]
  - Address peer review comments, if appropriate [DPE]
- If appropriate, apply model to update risk calculations via IRIS Update process [EPA]
  - Per response to Request for Correction
- If appropriate, send IRIS Update through review process – IRIS Steps 2-7 [EPA]