Pacific Northwest
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PNNL-31149

# Species Extrapolation of Propyl Acetate Dose Metrics

April 2021

Jordan Smith

U.S. DEPARTMENT OF ENERGY

Prepared for the U.S. Department of Energy
under Contract DE-AC05-76RL01830

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# Abstract

We propose to use a recently developed computational model of propyl acetate pharmacokinetics to better extrapolate dose metrics from animal models to humans. The risk assessment process for chemicals characterizes a dose response of a hazard using animal models. Regulatory agencies commonly extrapolate externally administered doses from the animal model to humans using uncertainty factors (e.g., 10×), sometimes with little consideration of species differences in physiology. These uncertainty factors may or may not be accurate, which creates uncertainty in species extrapolations and derived reference doses. We propose that computational approaches, like physiologically based pharmacokinetic (PBPK) models, offer a more scientifically grounded species extrapolation. PBPK models use physiological and mechanistic differences between animal models and humans to determine and translate internal dose metrics (e.g., chemical concentrations in blood or target organ). PNNL recently published a PBPK model of propyl compounds in rats and humans {Smith, 2020 #25}. We propose to use this published PBPK model to extrapolate internal dose metrics of propyl acetate from rats to humans. We will simulate a study of propyl acetate exposures to rats currently being used in a human risk assessment. We will identify various dose metrics of potential importance and predict human exposure scenarios that would create an equivalent dose metric. This species extrapolation will demonstrate PNNL's published pharmacokinetic capabilities and help to establish PNNL as a leader in pharmacokinetic modeling.

# Summary

Authoritative bodies and regulatory agencies use chemical risk assessments to evaluate potential risks of chemical use on humans and the environment. The risk assessment process typically includes four steps including hazard identification, dose-response evaluation of the identified hazard, exposure assessment of the chemical, and risk characterization bringing the previous three steps together by evaluating the probably of hazard in the context of possible exposures. During the dose-response evaluation, animal models are used to define a no-adverse-effect levels (NOEAL) or some other point of departure used to derive a reference dose or other human reference exposure that is not expected to cause harm. Regulatory agencies commonly extrapolate externally administered doses from the animal model to humans using uncertainty factors (e.g. 10×), sometimes with little consideration of species differences in physiology or metabolism. These uncertainty factors may or may not be accurate, which creates uncertainty in species extrapolations and derived reference doses.

Computational models like physiologically based pharmacokinetic (PBPK) models offer a more scientifically grounded approach for species extrapolation. PBPK models use reference physiological differences (e.g. organ sizes, blood flows, etc.) and mechanistic differences (e.g. species-specific metabolism rates) to translate internal dose metrics (e.g. chemical concentrations in blood or target organ) among species.

PNNL recently published a PBPK model of propyl compounds in rats and humans (Smith et al. 2020). The propyl metabolic series PBPK model simulates the internal dosimetry of propyl acetate, propanol, and propionic acid in humans and rats (Smith et al. 2020). The model was developed and evaluated using measured in vitro metabolism of propyl acetate and propanol in rats and humans, and intravenous and inhalation exposures of propyl acetate, propanol, and propionic acid in rats (Smith et al. 2020). In this report, we will demonstrate the ability of this model to extrapolate internal dose metrics of propyl acetate exposures in rats to humans.

This project will support the BER mission by advancing single cell analysis techniques to support a better understanding of cellular and molecular mechanisms underlying plant resilience and productivity, as well as plant-microbe interactions for bioenergy and environmental sustainability.

# Acknowledgments

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# Materials and Methods

Rats were exposed to propyl acetate in a 90-day subchronic inhalation study using OECD Guideline 413. Male (299.0 g average body weight, high exposure) and female Wistar rats (219.6 g average body weight, high exposure) were exposed to propyl acetate in flow through inhalation exposure chambers at 148.5, 505.2, and 1,528.7 ppm for 90 days using a standard work shift exposure schedule: 5 times per week, 6 hr per day, and 65 total exposures.We used the PBPK model to simulate concentrations of propyl acetate, propanol, and propionic acid in the exposure chamber and blood during these exposures assuming a constant propyl acetate concentration in the exposure chamber. We then simulated concentrations of propyl acetate, propanol, and propionic acid in blood of humans using the same exposure scenarios. Finally, we used the model to predict propyl acetate concentrations in the air that would yield the same propanol concentration in blood area under the curve (AUC) in humans as rats for the 148.5 and 505.2 ppm exposures. With the exception of rat body weights, we used standard reference physiological parameters or other parameters measured or optimized as previously reported (Smith et al. 2020). The PBPK model was coded and implemented in Magnolia version 1.3.9 (https://www.magnoliasci.com).

# Contents

# 1.0 Results

The propyl metabolic series PBPK predicted identical dose metrics in female and male rats (See enclosed “Rat Female Sims.pdf” and “Rat Male Sims.pdf”). Simulated peak concentrations in blood ranged 5.7-58.4 µM for propyl acetate and 13.6-145.1 µM for propanol, respectively, (See enclosed “OECD Dosimetry Sims.xlsx”). AUC values of concentrations in blood ranged from 2211-22759 µM×hr for propyl acetate and 5322-56557 µM×hr for propanol, respectively. Simulations with human females demonstrated 3 and 13% lower concentrations of propyl acetate and propanol in blood, respectively, compared to males (See enclosed “Human Female Sims.pdf” and “Human Male Sims.pdf”) following the same exposures as rats. This observation is consistent with previous simulations with propyl compounds (Smith et al. 2020). As such, the model predicts that females would require propyl acetate inhalation exposures of 207 and 706 ppm to achieve the same propanol concentration in blood AUC as rats inhaling 149 and 505 ppm, respectively. The model predicts human males predicts that human males would require 181 and 617 ppm to achieve the same dose metrics (See enclosed “OECD Dosimetry Sims.xlsx”).

# 2.0 Conclusions

Here we demonstrate the ability of the propyl PBPK model to predict dose metrics of propyl acetate, propanol, and propionic acid from a standard 90-day subchronic inhalation study of propyl acetate in male and female rats. The model was used to predict the same dose metrics in “reference” male and female humans using the same exposure conditions. Finally, we used reverse dosimetry with the model to predict what exposure conditions would lead to the same dose metrics measured in rats. These extrapolations of internal dose metrics based on known species differences in physiology and measured differences in metabolism offer a more scientific species extrapolation than conventional uncertainty approaches, potentially of interest for risk assessment.

# 3.0 References

Smith, J. N., K. J. Tyrrell, J. P. Smith, K. K. Weitz and W. Faber (2020). "Linking internal dosimetries of the propyl metabolic series in rats and humans using physiologically based pharmacokinetic (PBPK) modeling." Regul Toxicol Pharmacol **110**: 104507.

# Appendix A – OECD Dosimetry

| | | g | | ppm | µM×hr | µM×hr | µM×hr | µM | µM | µM |
|---|---|---|---|---|---|---|---|---|---|---|
| species | sex | body.weight | | exposure.conc | propyl.acetate.auc | propanol.auc | propionic.acid.auc | propyl.acetate.cmax | propanol.cmax | propionic.acid.cmax |
| rat | female | 219.6 | 1 | 148.5 | 2210.918 | 5322.011 | 218.0635 | 5.669022 | 13.64689 | 0.5591369 |
| rat | female | 219.6 | 2 | 505.2 | 7521.589 | 18232.12 | 741.7964 | 19.286129 | 46.75802 | 1.9020379 |
| rat | female | 219.6 | 3 | 1528.7 | 22759.805 | 56557.179 | 2243.9647 | 58.358482 | 145.12678 | 5.7537047 |
| rat | male | 299 | 1 | 148.5 | 2210.918 | 5321.988 | 218.0635 | 5.669022 | 13.64689 | 0.5591369 |
| rat | male | 299 | 2 | 505.2 | 7521.589 | 18231.838 | 741.7965 | 19.286129 | 46.75802 | 1.9020379 |
| rat | male | 299 | 3 | 1528.7 | 22759.804 | 56553.787 | 2243.9662 | 58.358482 | 145.12678 | 5.7537047 |
| human | female | 60 | 1 | 148.5 | 2364.259 | 3807.214 | 2586.98 | 5.696097 | 9.459659 | 6.268838 |
| human | female | 60 | 2 | 505.2 | 8043.258 | 13010.745 | 8800.719 | 19.378238 | 32.346764 | 21.324249 |
| human | female | 60 | 3 | 1528.7 | 24338.338 | 40036.599 | 26627.618 | 58.637197 | 99.786028 | 64.496166 |
| human | female | 60 | 4 | 207.44 | 3302.639 | 5322.069 | 3613.743 | 7.956892 | 13.224787 | 8.756797 |
| human | female | 60 | 5 | 705.96 | 11239.545 | 18232.004 | 12297.802 | 27.078901 | 45.345218 | 29.796048 |
| human | male | 73 | 1 | 148.5 | 2431.764 | 4368.669 | 2571.233 | 5.887251 | 10.89967 | 6.239897 |
| human | male | 73 | 2 | 505.2 | 8272.91 | 14919.631 | 8747.126 | 20.028548 | 37.23868 | 21.225988 |
| human | male | 73 | 3 | 1528.7 | 25033.248 | 45803.443 | 26465.209 | 60.60499 | 114.51239 | 64.201509 |
| human | male | 73 | 4 | 180.85 | 2961.512 | 5322.116 | 3131.355 | 7.16976 | 13.27892 | 7.599159 |
| human | male | 73 | 5 | 616.56 | 10096.487 | 18232.146 | 10675.125 | 24.443392 | 45.51288 | 25.90383 |

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