

PNNL-31149

Species Extrapolation of Propyl Acetate Dose Metrics

April 2021

Jordan Smith

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor Battelle Memorial Institute, nor any of their employees, makes **any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights.** Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof, or Battelle Memorial Institute. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

PACIFIC NORTHWEST NATIONAL LABORATORY
operated by
BATTELLE
for the
UNITED STATES DEPARTMENT OF ENERGY
under Contract DE-AC05-76RL01830

Printed in the United States of America

Available to DOE and DOE contractors from
the Office of Scientific and Technical Information,
P.O. Box 62, Oak Ridge, TN 37831-0062

www.osti.gov
ph: (865) 576-8401
fox: (865) 576-5728
email: reports@osti.gov

Available to the public from the National Technical Information Service
5301 Shawnee Rd., Alexandria, VA 22312
ph: (800) 553-NTIS (6847)
or (703) 605-6000
email: info@ntis.gov
Online ordering: <http://www.ntis.gov>

Species Extrapolation of Propyl Acetate Dose Metrics

April 2021

Jordan Smith

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

Pacific Northwest National Laboratory
Richland, Washington 99354

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 $\times$), 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 probability of hazard in the context of possible exposures. During the dose-response evaluation, animal models are used to define a no-adverse-effect levels (NOEL) 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

This research was supported by the **Biological and Earth System Science Mission Umbrella Project**, under the Laboratory Directed Research and Development (LDRD) Program at Pacific Northwest National Laboratory (PNNL). PNNL is a multi-program national laboratory operated for the U.S. Department of Energy (DOE) by Battelle Memorial Institute under Contract No. DE-AC05-76RL01830.

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

Abstract..... ii

Summary iii

Acknowledgments..... iv

Materials and Methods..... v

1.0 Results 1

2.0 Conclusions..... 2

3.0 References..... 3

Appendix A – OECD Dosimetry A.1

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 $\mu\text{M}\times\text{hr}$ for propyl acetate and 5322-56557 $\mu\text{M}\times\text{hr}$ 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	$\mu\text{M}\times\text{hr}$	$\mu\text{M}\times\text{hr}$	$\mu\text{M}\times\text{hr}$	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

Pacific Northwest National Laboratory

902 Battelle Boulevard
P.O. Box 999
Richland, WA 99354

1-888-375-PNNL (7665)

www.pnnl.gov