Characterizing the Disposition and Effects of Dimethylformamide in Humans Using in Silico Modeling

Any other logos you need to include? NSF? Or???

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Background

- Target compound: Dimethylformamide
- Pharmacokinetic and Physiologically Based Modeling
- Utilize PKSim software
- Calibrate with company data

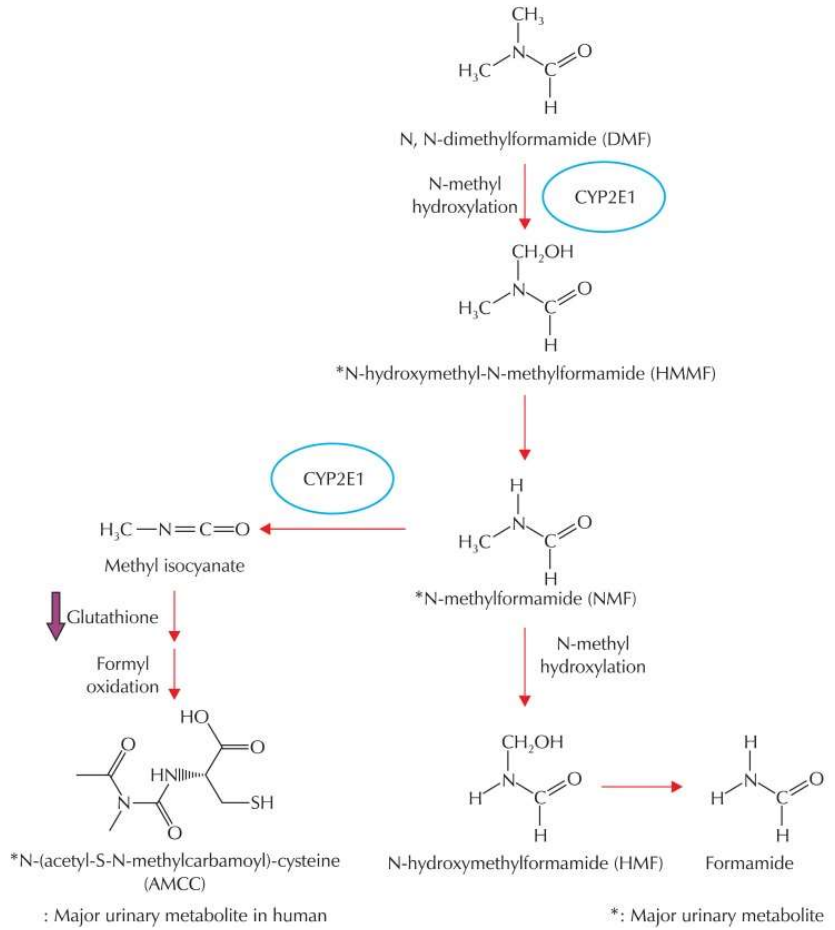

Figure 1. DMF metabolism *in vivo.* https://pubmed.ncbi.nlm.nih.gov/22953193/

Methods/Experimental Setup

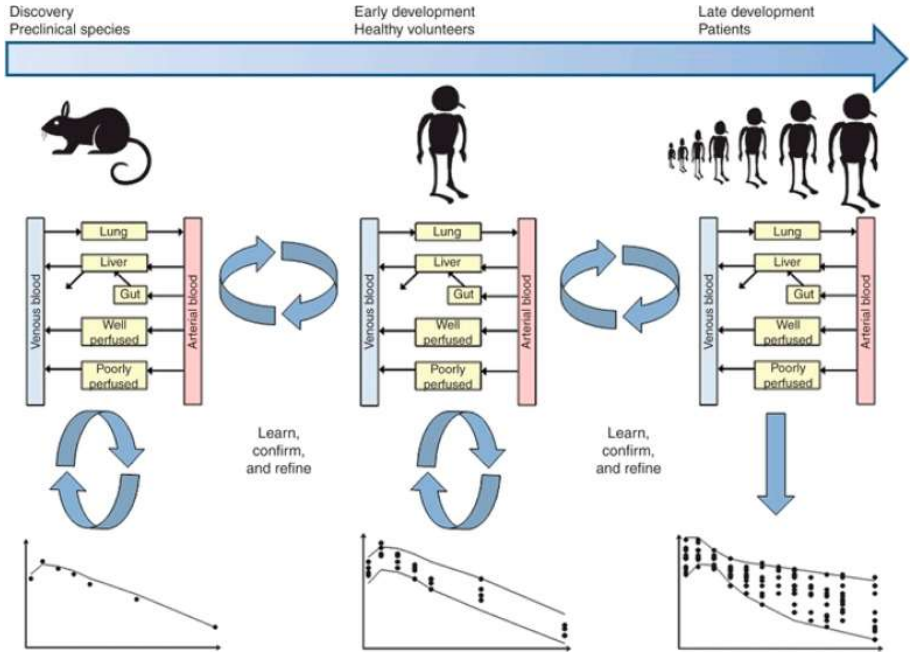

Figure 2. Basic PBPK model strategy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3828005/

Figure 3. Specific metabolite strategy for DMF

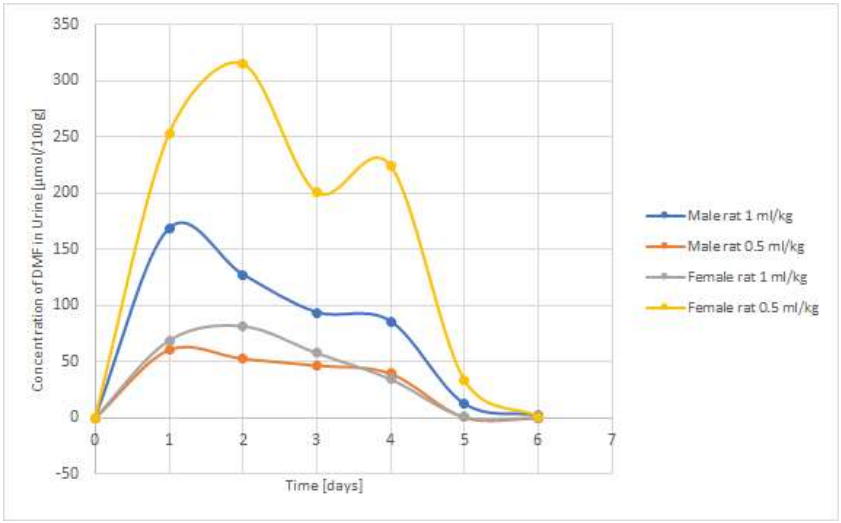

Figure 4. Rat data from Scailteur et al.
https://pubmed.ncbi.nlm.nih.gov/6695383/

Results

Model Inputs

Name	Top Container	Organ	Molecule	Value	Value Origin
Compound type 0			Dimethyl Formamide	Base	Unknown
Is small molecule			Dimethyl Formamide	Yes	
Molecular weight			Dimethyl Formamide	73.09 g/mol	
pKa value 0			Dimethyl Formamide	6.70	Unknown
Plasma protein binding partner			Dimethyl Formamide	Unknown	
Lipophilicity			Dimethyl Formamide	1.46 Log Units	
Fraction unbound (plasma, refer...			Dimethyl Formamide	95.00 %	
Infusion time	Applications	Test 2		60.00 min	
Infusion time	Applications	Test 2		60.00 min	
Infusion time	Applications	Test 2		60.00 min	
Infusion time	Applications	Test 2		60.00 min	
Solubility at reference pH			Dimethyl Formamide	1000000.00 mg/l	
Reference pH			Dimethyl Formamide	7.00	
In vitro CL/recombinant enzyme	Dimethyl Formamide-CYP2E1...			0 µl/min/pmol rec. enzyme	
CLspec/[Enzyme]	Dimethyl Formamide-CYP2E1...			2.52 l/µmol/min	Unknown

Figure 5. Basic inputs necessary to run the model.

Model Outputs

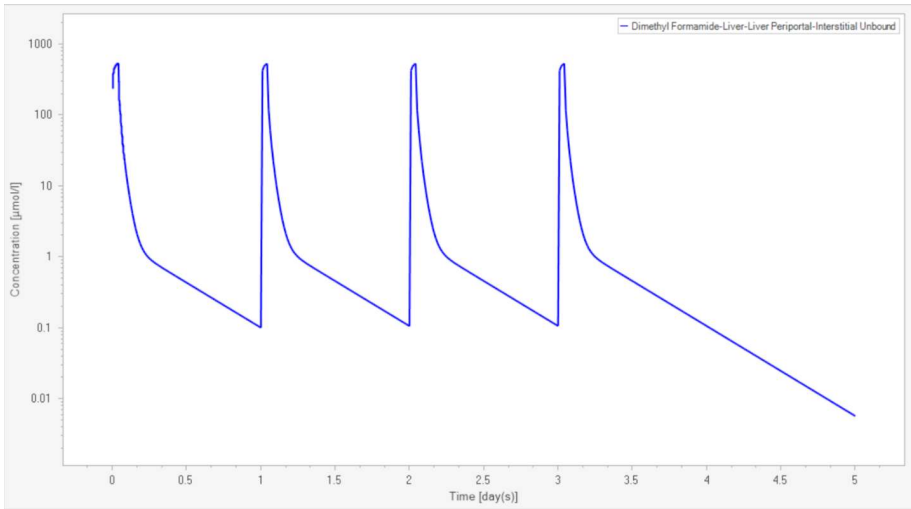

Figure 6. Output of the DMF model.

Discussion/Next Steps

- Further parameterize the PKSim model to increase its accuracy.
- Compare the outputs against the biomonitoring data received from a corporate partner.
- Further calibrate the model with the corporate partner data.
- Utilize the PK Sim model to improve predictions of exposure versus adverse effects.
- Develop a pharmacodynamic model to pair with the pharmacokinetic model.

Conclusions

- The current model is showing the concentration over time of DMF in the urine that would be expected.
- The final outputs are consistent with DMF concentrations over a similar exposure plan (Scailteur et al.) .
- We now plan to target our research to include more all main DMF metabolites rather than just HMMF and then extrapolate this model to humans.
- Our current approach of *in silico* modeling seems to be a promising method for accurate predictions of DMF concentrations.

What benefits did you get from you SURE experience?

- Had the opportunity to work in a collaborative team with people from different majors, levels of experience and backgrounds.
- Learned how to use and became comfortable with a completely new software program with the help of my teammates and mentor.
- Had the opportunity to dive deep into a single project for the length of a semester and begin to understand the goal at hand comprehensively rather than just a small part of it.
- Applied knowledge I learned from different classes to real life problems and helped to bring more meaning to the topics and techniques being taught.

References & Acknowledgements

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[2] Scailteur, V., et al. “Study on in Vivo and in Vitro Metabolism of Dimethylformamide in Male and Female Rats.” Toxicology, vol. 29, no. 3, Jan. 1984, pp. 221–234., doi:10.1016/0300-483x(84)90023-4.

[3] Li, Ming-Jun, and Tao Zeng. “The Deleterious Effects of N,N-Dimethylformamide on Liver: A Mini-Review.” Chemico-Biological Interactions, vol. 298, 25 Jan. 2019, pp. 129–136., doi:10.1016/j.cbi.2018.12.011.

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Thank you to the Suzanne and Walter Scott Foundation, Tointon Family Foundation, The Filsinger Family, Caterpillar Inc., and Contributors to the Dean’s Innovation fund for making the SURE program possible.

Thank you

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