Modeling Inter-individual Variation in Physiological Factors Used in PBPK Models of Humans

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Abstract
Modeling inter-individual variation in internal dose in humans using PBPK models requires data on the variation in the physiological parameters across the population of interest. These data should also capture the correlations between the values in each person. In this project, we developed a tool to provide such data and its correlations. The tool provides a source of data for human physiological parameters where: 1) the parameter values for an individual are correlated with one another, and 2) values of parameters vary according to interindividual variation in the general population, by gender, race, and age. The parameters investigated in this project include: 1) volumes of selected organs and tissues; 2) blood flows for the organs and tissues; and 3) the cardiac output under resting conditions and average daily inhalation rates. These parameters are expressed as records of correlated values for the approximately 30,000 individuals evaluated in the NHANES III survey. Software was developed that allows records to be retrieved randomly from the database with specification of constraints on, age, sex, and ethnicity. The database and accompanying software together provide a convenient tool for parameterization of human PBPK models for the study of interindividual variation. In addition, the data provides a useful information on the variation in physiological parameters in adults and children. This work was funded by the American Chemistry Council.

Approach
This project developed a database of physiological parameters for use in PBPK models and exposure assessments. This database contains a record of “sets” of the records for groups of individuals of specific age, gender, height or weight. The result is a database consisting of approximately 30,000 records. Each record includes:
1. The age, gender, and ethnicity of the individual.
2. Volumes and masses of selected organs and tissue;
3. Blood flows to the organs and tissues; and
4. Surface area, and
5. Average inhalation rate.

Finally, a computer program (Physiological Parameter for PBPK Modeling (P2P)) generates “use” of the records for groups of individuals of specific age ranges, gender, and ethnicity.

Data Gaps in the Models of Physiological Parameters
The project identified a number of gaps in the published literature for model-to-prediction-based models of organ volumes and mass. Future work on modeling inter-individual variation in organ size should seek to address the following issues:
1. Better models of adult organ volumes. If they are not correlated with age, gender, height or weight they are not correlated to LBM. Are there significant correlations between organs?
2. Models for the volume of the breast, GI and the urogenital organs.
5. Additional modeling of body composition in children ages six to twelve years. Existing studies tend to focus on other neonatal or childhood age those and above results in data for this age range.
6. The relationship of CO to organ volumes needs to be better defined. What is the source of the remaining variance that is not predicted by age, height, LBM, and weight?

Future Modeling of Physiological Parameters
The majority of the publications are less than five years old. This reflects the rapid development of the field of modeling organ weights and volumes.

In addition, NHANES IV is currently under way and this survey includes whole body USA assessment that will report THBM, adipose tissue, and LBM for each individual.

Because of the ongoing publications and the NHANES IV data, the estimates of the parameters developed in this project should be revaluated in the near future.

Conclusions
The project successfully developed a tool for modeling anatomic variations among individuals (typically used in PBPK modeling). While data is being collected that will reevaluate the tool, the database and the software provide a useful tool for modeling variation in physiological parameters across different ages, genders and ethnicities.

References

P2P can be downloaded from:
http://www.thelifelinegroup.org