Advanced Physiologically Based Pharmacokinetic Modeling Dose Estimating Exposure Model: DEEM

Jerry Blancato[1], Fred Power[2], Edward Kantor[1], Edwin Furtaw[1], Marc Rigas[1]

[1]U.S. EPA, National Exposure Research Laboratory, HEASD, Human Exposure Research Branch, Las Vegas, NV

[2]Anteon Corporation, Las Vegas, NV

1. Abstract

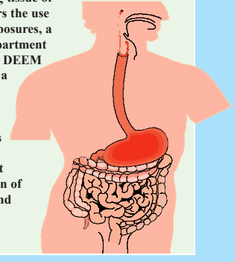
DEEM is an advanced physiologically based pharmacokinetic (PBPK) computer model which mathematically describes and predicts toxicologically relevant doses within the body (e.g. concentration of exposure chemical within tissues, concentration of the chemical's metabolites within body, etc.). The basic goal of DEEM is to provide toxicologists, exposure assessors, and risk assessors with an easy to use standard framework for calculating and predicting dose within the body. The mechanics of this model and how it works is described in this poster.

2. DEEM "The Process"

DEEM has several possible exposure routes for chemical introduction into humans or animals: inhalation, ingestion, dermal, and injection. For ingestion, DEEM models absorption via the digestive tract into the portal blood which flows directly to the liver. For other routes chemical is absorbed into the systemic circulation from the capillaries and circulates around the body. Metabolism can be modeled in any organ in which it occurs. The amount of free and bound chemical within the body is continuously changing due to the interplay of metabolism, binding, and elimination.

3. DEEM "Construction"

A compartment in DEEM is an organ or partitioned section in which an activity occurs that requires a mathematical solution by the integration of one or more differential equations. DEEM has 31 such compartments which can be divided into five groups; 1) the main body which includes the following ten compartments; 2) the lung sub-model with six compartments; 3) the gastrointestinal sub-model tract with eleven compartments; 4) the dermis; and 5) the intraperitoneal and intramuscular injections. In DEEM metabolism is expressed in blocks and can occur in 14 of the 31 compartments. Metabolism can occur in the spleen, liver, carcass, kidney, fat, slowly perfused tissue, rapidly profused tissue, brain, stomach wall, duodenum wall, small intestine wall, colon wall, lung tissue of the breathing lung, and the static lung. DEEM offers the use of two lung sub-models for simulating inhalation exposures, a static lung in which the lung is modeled as one compartment and a breathing lung which has five compartments. DEEM offers the choice of two gastrointestinal sub-models, a basic gastrointestinal model that has stomach and intestine and a full GI sub-model consisting of four organs: the stomach, duodenum, lower small intestines, and the colon. DEEM allows for simultaneous exposure to occur for more than one chemical. Chemical exposures can be modeled in either a short version or long version of DEEM; that is one version of the model can have entries for up to six chemicals and three metabolites, and the other version up to 10 chemicals and six metabolites.



4. DEEM "Mechanics"

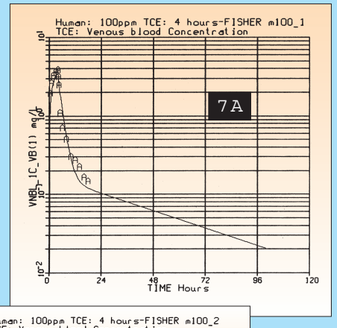
In six of the nine exposure routes, all chemicals are modeled to be distributed in the blood and in all organs for a finite period of time. For the digestive and portal blood injection exposures, chemicals first go to the liver where they can be metabolized or bound before distribution throughout the body. Metabolism can occur in 14 organs. DEEM has default values for the physiological parameters for humans, mouse, and rat. DEEM offers the user the option of turning off individual compartment or sub-systems. Compartments are turned off when no data are available, the compartment has no contribution to the chemical exposure, or the user wants to do an experimental run to realize the impact the compartment has on the simulation. The DEEM model allows for the testing of the impact of nine possible time scenarios for each of the nine chemical exposure routes (two ingestion routes, two inhalation routes, four injection routes, and one dermal absorption route). DEEM can produce a time history of the description of the sequence of exposures to a chemical that an individual receives.

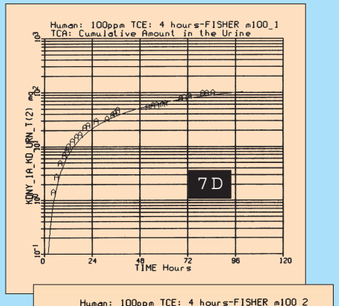
5. DEEM "The Inputs"

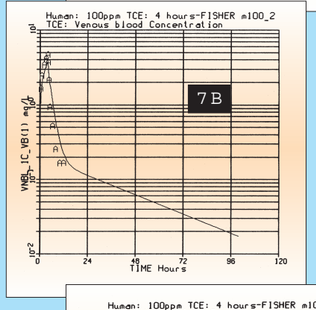
Chemical input parameters for DEEM are the names of up to ten chemicals, the names of up to six metabolites, and their molecular weights. DEEM offers the user a choice of nine exposure routes: two ingestion, two inhalation, four injection, and one dermal route. DEEM has 32 compartments that can be turned on or off depending upon the modeling preferences of the user. Metabolism can occur in 14 of these compartments. Organ (compartment) size, body weight, and blood flow to these organs must be specified. The DEEM model has at present four sub-models, the two gastrointestinal sub-models and two lung sub-models. Depending upon the chemicals being modeled, the user can choose which sub-model will be most appropriate for the chemical physiology they want to model. The chemico/physiological processes that can be inputted are 1) types and rate of reactions [linear or saturable], 2) chemical inhibitions [competitive, pure non-competitive, uncompetitive and mixed], 3) binding coefficients, 4) permeation coefficients, 5) diffusion coefficients, 6) partition coefficients, 7) flow rates and 8) elimination rates. Up to nine exposure scenarios can be entered in DEEM. Beginning, ending, and duration times must be selected for these scenarios and if a time history is required, time history parameters must be entered as well.

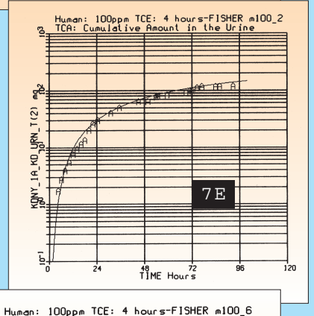
6. "Examples of DEEM Outputs"

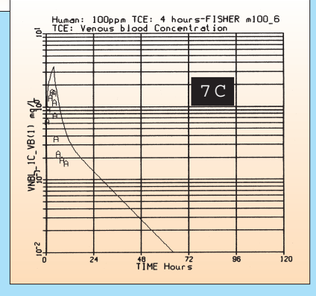
There are 15 default output types in DEEM, specifically concentrations of parent compounds and metabolites in all organs. Approximately 700 outputs are possible from DEEM but these must be specified as output requirements by the user. Examples of some of the outputs of DEEM are as follows: Chemical concentration in a specific organ can frequently be an indicator of adverse health effects. Rate of concentration of change may be indicative of the rate of formation of a harmful metabolite. Area under the curve of concentration versus time is indicative of the total mass of a chemical in an organ over a set period of time. It is the most common method for determining exposure and is used as an accumulative measure of long term exposure. It is directly related to dose and is used to calculate other important values. Mass Balance is a quality control check to account for all the mass of chemical within the system. In some cases peak concentrations may be more indicative of adverse health effects than the area under the curve. This is particularly true in cases where a threshold amount must be reached for organ or cell damage to occur. Rate of metabolic formation determines how fast a metabolite is formed. It may be a good indicator of initial chemical concentration or the physiology of the subject, and is an indicator of adverse, or the avoidance of adverse, health effects. Clearance is a parameter characterizing the rate at which a chemical is removed from blood. Clearance may also be viewed as a proportionality constant between blood concentration and rate of chemical elimination from the body. The amount of chemical or metabolite bound to molecules normally present within a body organ. Elimination is the amount of chemical physically removed from the body.

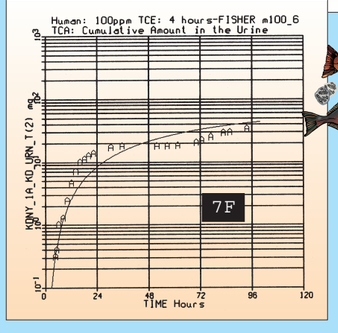












7. TCE and TCA Concentration in Venous Blood of Test Subjects

The figures 7A through 7F show the concentration of Trichloroethylene in the blood of test subject one, two and three after a four-hour inhalation exposure to TCE at approximately 100 ppm in closed chamber air; Test subject "one" was a 71 kg male with 17% body fat. The "As" on the graphs are the actual test data courtesy of Dr. Jeffrey Fisher of Armstrong Laboratory, Wright-Patterson AFB, Ohio. The solid line shows the concentration of TCE as predicted by DEEM after inputs were evaluated and then adjusted to obtain the best predictor for this exposure. As can be seen from the graph, the DEEM prediction of TCE concentrations in blood was virtually identical to the experimental data. Test subject two was a 82 kg male with 14% body fat. Except for percent body fat, three unvarying Km values, and the adjustment factor for TCA in urine, the same 39 parameters, scaled to body weight, were used for test subject "two" as in test subject one. As can clearly be seen in this figure, the DEEM prediction of TCE blood concentration and the actual test data are nearly the same. Test subject three was a 52 kg male with 6% body fat. As stated previously, except for percent body fat, the three unvarying Km values, and the adjustment factor for TCA in urine, the same 39 parameters, scaled to body weight, were used for test subject "three". In comparing body weight and percent fat of the 7 other test subjects to test subject "one", test subject "three" was the most different in body weight and percent fat. This being the case it is remarkable that the correlation of DEEM's simulation of TCE concentration in blood with subject "three's" experimental data was off only by a factor of 2.5. Subject "three" is representative of the worst-case correlation between the model and the experimental data. Four of the seven subjects' simulation outputs were nearly identical to the experimental data and three were close. Similar results were obtained for TCA in urine.

Figure Captions

7A. TCE Concentration in Venous Blood of Test Subject One.
7B. TCE Concentration in Venous Blood of Test Subject Two.
7C. TCE Concentration in Venous Blood of Test Subject Three.
7D. TCA Concentration in Urine of Test Subject One.
7E. TCA Concentration in Urine of Test Subject Two, and.
7F. TCA Concentration in Urine of Test Subject Three.

8. "Future Developments"

- Front End for Users
- Multi-compartment Dermal Subsystem
- Uncertainty, Variance, and Sensitivity Analysis
- Testing the Model for Inhibition and Binding Simulations
- Computational Enhancements
- Continuation of Model Collapse and Expansion Strategy
- Mathematical Formulations for Dose in Sub-cellular Fractions