United States Environmental Protection Agency

Exposure Related Dose Estimating Model (ERDEM)

A Physiologically-Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model for Assessing Human Exposure and Risk

RESEARCH AND DEVELOPMENT

EPA/600/R-06/061
June 2006
www.epa.gov

Exposure Related Dose Estimating Model (ERDEM)

A Physiologically-Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model for Assessing Human Exposure and Risk

Jerry N. Blancato
Fred W. Power
Robert N. Brown
Curtis C. Dary

U.S. Environmental Protection Agency
Office of Research and Development
Human Exposure and Atmospheric Sciences Division
Exposure and Dose Research Branch
Post Office Box 93478
Las Vegas, NV 89193-3478

237EDRB05.RPT ❖ 7/31/06

Table of Contents

Section 1

Introduction

The U.S. EPA, as part of its mission to protect human health, develops tools (methods, measures and models) to improve the risk assessments that are used by the Agency to predict adverse effects from exposure to environmental agents. As with any predictive approach, there is often considerable uncertainty associated with these assessments. To reduce this uncertainty and to increase confidence in our policy decisions, the Agency must use the best and most-up-to-date science. Current approaches include the use of state-of-the-science predictive models to describe the physical, chemical, and biological processes that may be impacted by an exposure to a chemical of concern. Scientists often need to predict the dose of chemicals within the body that results from an environmental exposure. This requires the knowledge of many biological processes and chemical factors both inside and outside of the body. Predictive mathematical models, which can accurately describe the biology and chemistry within the human body, are used to estimate and predict the dose. With improved dose models, risk assessors can better predict possible health impacts and insure that the Agency's risk management decisions are founded on high quality science.

Over recent years, physiologically based pharmacokinetic (PBPK) models have been used to better describe internal doses resulting from exposures to chemicals in the environment. PBPK models are mathematical descriptions of how chemicals are absorbed into, transported through, eliminated from, and stored in the body. More recently, physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) models are being used to mathematically describe not only the disposition of a chemical in the body, but also how some normal biologic processes are altered as a result of the chemical in the body. PBPK/PD models should provide the ability to evaluate, estimate, and predict measures of toxicologically relevant doses.

The Exposure Related Dose Estimating Model (ERDEM) is a PBPK/PD modeling system that was developed by EPA's National Exposure Research Laboratory (NERL). The ERDEM framework provides the flexibility either to use existing models and to build new PBPK and PBPK/PD models to address specific science questions. Over the past several years, ERDEM has been enhanced to improve ease of operation and to provide additional modeling capabilities. With these enhancements, ERDEM has been applied to a variety of chemicals as part of the regulatory risk assessment process. Applications for malathion and N- methyl carbamate were presented to and peer-reviewed by the FIFRA Scientific Advisory Panel.

This report provides information on the use of ERDEM and related software. ERDEM can be found on the web at: www.epa.gov/heasd/erdem/erdem.htm. For the user, ERDEM requires no special software other than the basic Windows environment commonly used on PCs. The ERDEM system includes three components

- the *ERDEM Front End*,
- the *ERDEM Model(s)* built in Advanced Continuous Simulations Language (ACSL),
- the *ACLS Viewer*.

The *ERDEM Front End* is a Windows-based application that allows the user to enter exposure, pharmacokinetic, and pharmacodynamic parameters and data and to store them in a database for later use and export to a command file for input to the ERDEM Model. The ERDEM modeling engine contains differential equations that use the physiological, biological, and pharmacodynamic modeling data that are entered via the ERDEM Front End. The various features (compartments, metabolism, exposure, and enzyme inhibition) of the modeling engine are accessed by flags that are set by the user. The ACSL viewer is part of the ACSLTOX modeling engine environment that allows the user to start and view model run results.

This introduction is dedicated to explaining and exploring the *ERDEM* system. Section 2 takes the user through the installation process. Section 3 introduces the computer screens of the *ERDEM Front End*, where toxicologists and risk assessors may enter exposure, pharmacokinetic (PK) and pharmacodynamic (PD) parameters and data.. Section 4 presents the export of the entered data into a command file for input to the ERDEM model engine(s). Section 5 discusses the use of the ACSL Viewer used to run the model. This is followed by a mathematical description of the exposure pathways (Section 6), the absorption and of the exposure chemicals through the lung, gastro-intestinal (GI) tract, and the skin (Section 7), the disposition and metabolism throughout the various compartments (Section 8), and the pharmacodynamics of enzyme kinetics provided in Section 9.

ERDEM consists of the following compartments: Arterial Blood, Brain, Carcass, Closed Chamber, Derma, Fat, Intestine, Kidney, Liver, Rapidly Perfused Tissue, Slowly Perfused Tissue, Spleen, Static Lung, Stomach, and Venous Blood. The mathematical equations for these compartments are presented in Section 7. Each of the compartments (Brain, Carcass, Fat, Kidney, Liver, Lung Tissue, Rapidly and Slowly Perfused Tissues, Spleen, and the Static Lung) have two forms of elimination, an equilibrium binding process, and multiple metabolites. System diagrams for the Static Lung (Figure 1) and Breathing Lung (Figure 2) are presented. The model diagram of the Breathing Lung shows the movement of chemical across the three boundaries. The Breathing Lung utilizes the compartments: Alveoli, Lower Dead Space, Lung Tissue, Pulmonary Capillaries, and Upper Dead Space. Lastly, there are two diagrams showing the Gastro-Intestinal (GI) Model (Figure 3) and further details (Figure 4) of the GI. *ERDEM* allows for multiple circulating compounds with multiple metabolites entering and leaving each compartment. The Gastro-Intestinal

model consists of the Wall and Lumen for the Stomach, Duodenum, Lower Small Intestine, and Colon with Lymph Pool and Portal Blood compartments included. Bile flow is treated as an output from the Liver to the Duodenum Lumen. All chemicals including their metabolites are treated as circulating. Nonspecific ligand binding, e.g., plasma protein binding, is represented in Arterial Blood, Pulmonary Capillaries, Portal Blood, and Venous Blood.

REFERENCES

Okino, M.S., Power, F.W., Tornero-Velez, R., Blancato, J.N., and Dary, C.C., ***Assessment of Carbaryl Exposure Following Turf Application Using a Physiologically based Pharmacokinetic/Pharmacodynamic Model.*** FIFRA Science Advisory Panel Open Meeting, Arlington, VA, February 15-18, Docket Number: OPP-2004-0405, Washington DC., 2005.

Report, "***Use of Exposure-Related Dose Estimating Model (ERDEM) for Assessment of Aggregate Exposure of Infants and Children to N-Methyl Carbamate Insecticides***": Appendix to "ESTIMATION OF CUMULATIVE RISK FROM N-METHYL CARBAMATE PESTICIDES: Preliminary Assessment", to FIFRA Scientific Advisory Panel (SAP) Open Meeting, August 23-26, 2005, Docket Number: OPP-2004-0172, Washington DC.

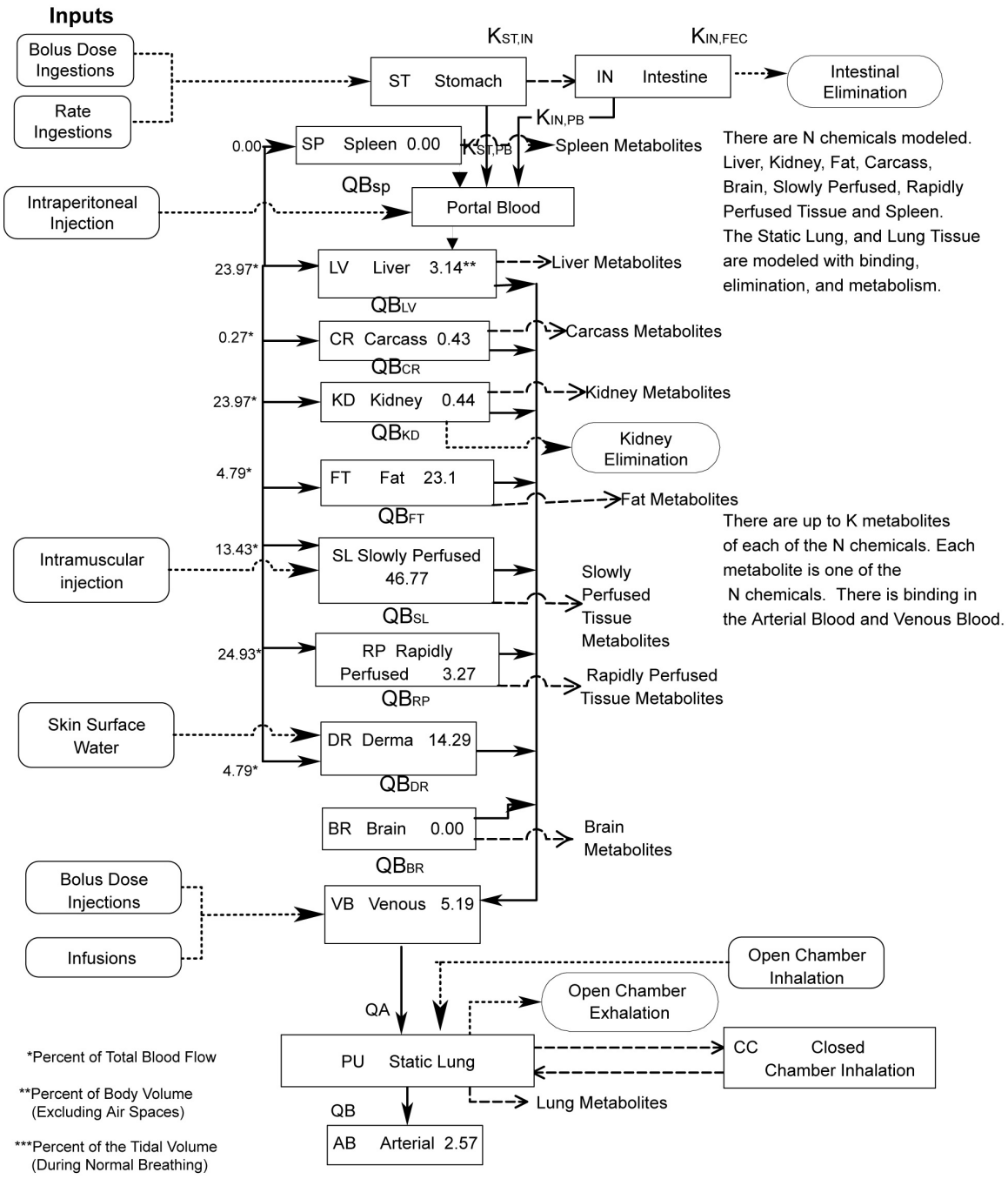


Figure 1. ERDEM System Flow with Static Lung and Stomach Intestine.

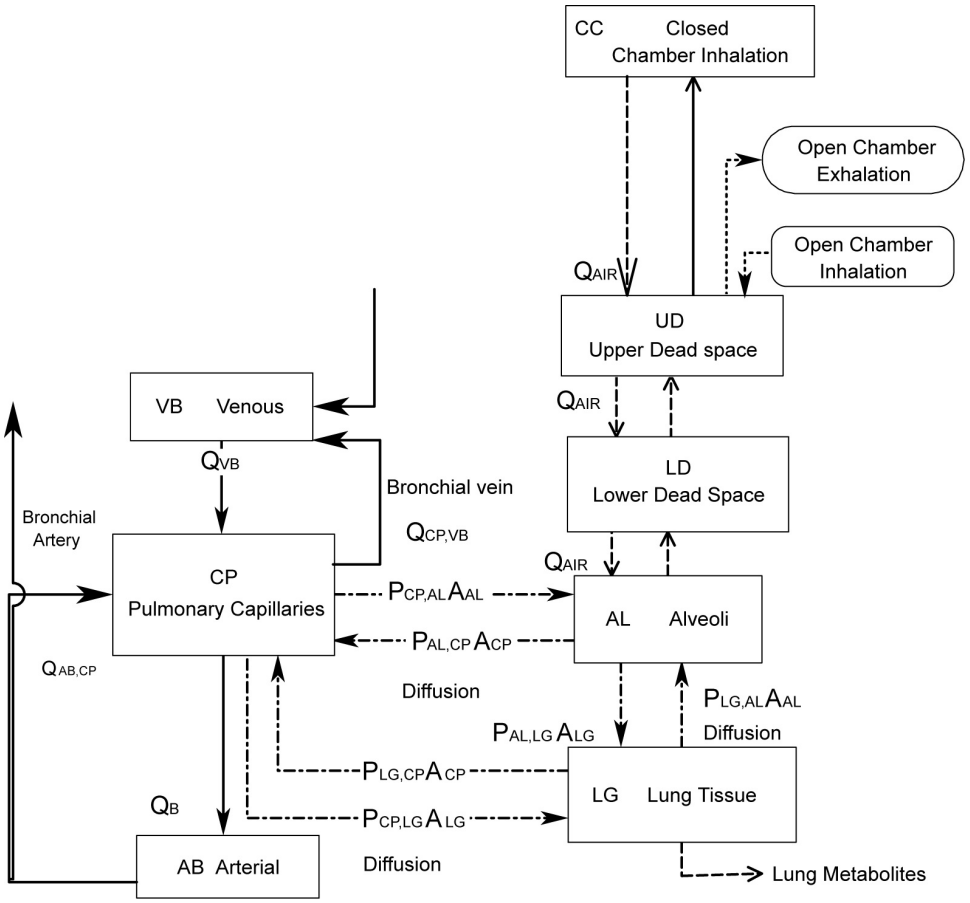


Figure 2. Breathing Lung Compartment Flow.

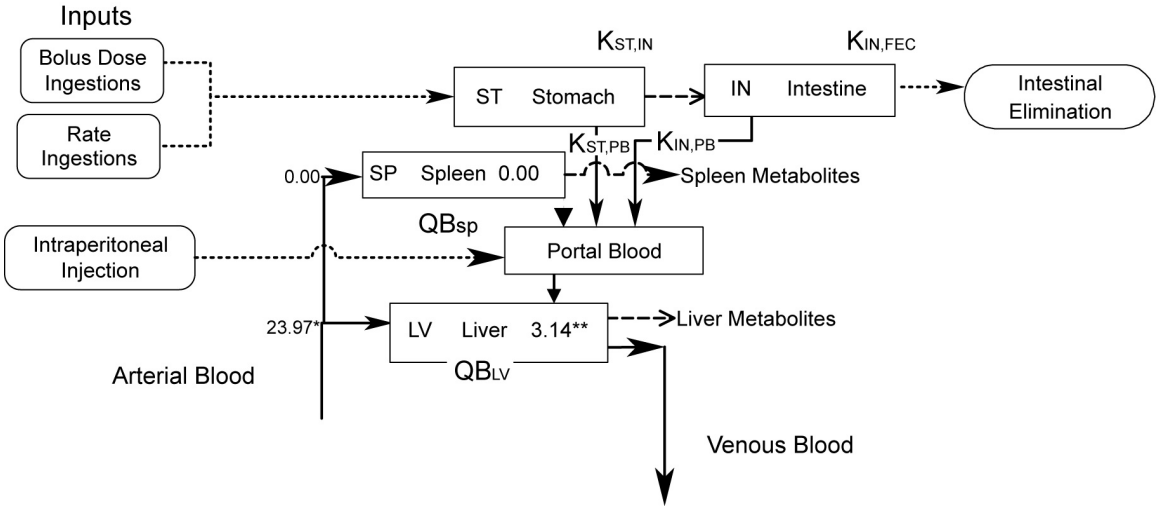


Figure 3. Stomach/Intestine Gastro-Intestinal Model.

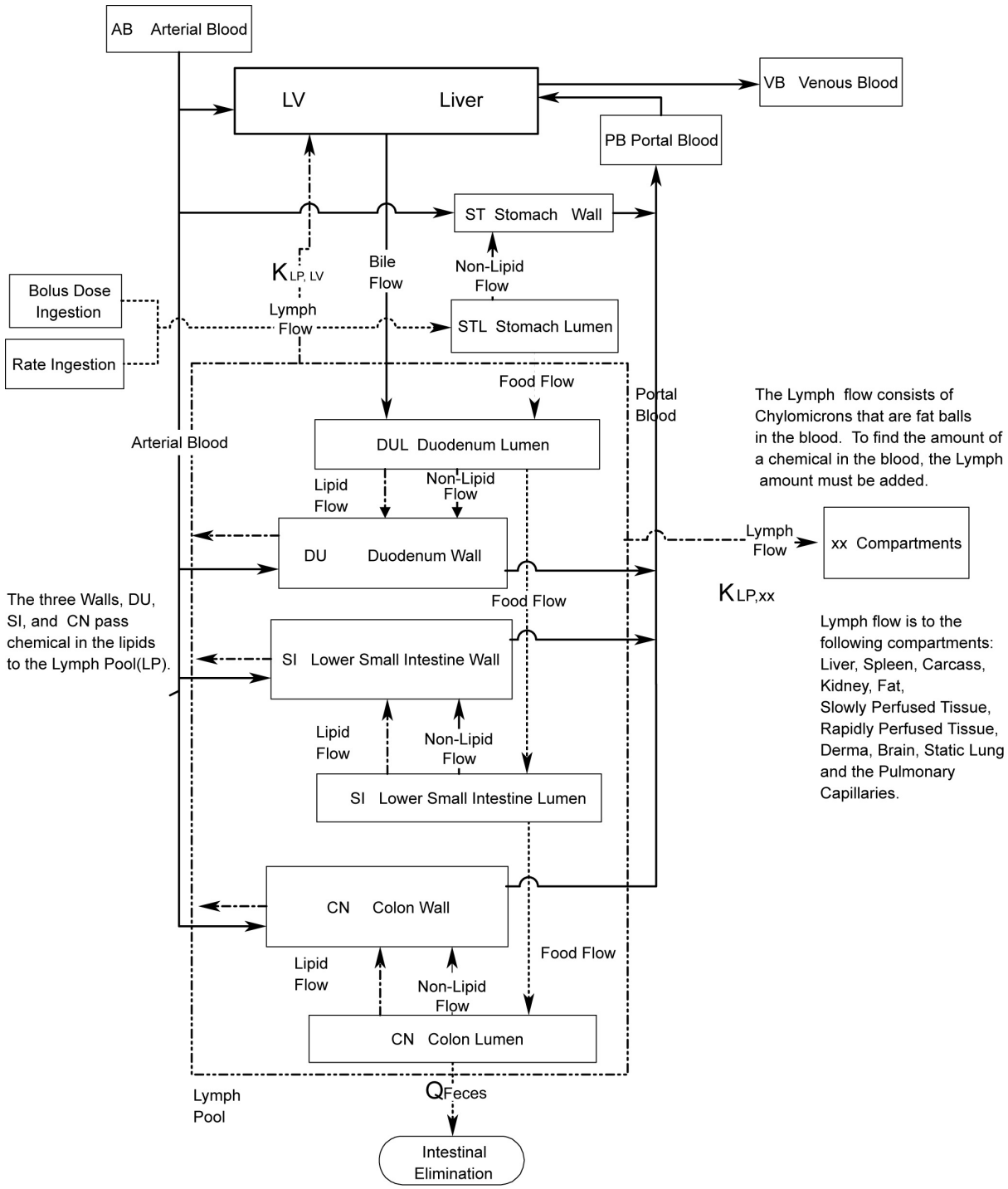


Figure 4. Detailed Gastro-Intestinal Tract Model.

Section 2

ERDEM Front End User Guide
Beta Version 4.1.1

2.1 Installation

1. Insert the *ERDEM Beta, Version 4.1.1* CD-ROM into your CD-ROM drive.

If Auto Run is active on your system, the "ERDEM Installer" window will automatically appear.

2a. Follow the "ERDEM Installer" instructions that are displayed.

- OR -

2b. If AutoRun is <u>not</u> active on your system, do the following:

b1. Select "Run" from the *Windows* Start menu.

b2. Type the drive letter for your CD-ROM and the following path: D:\ERDEM_INSTALLER.HLP (In this instance, "D:" is the CD-ROM drive path; it may be different on your computer.)

Note: You can also use *Windows Explorer* to navigate to your CD-ROM drive and double-click on the "ERDEM-INSTALLER.HLP" file.

b3. Press the "Enter" key.

The "ERDEM Installer" window will appear.

b4. Follow the "ERDEM Installer" instructions that are displayed.

Important:
If you have a previous version of ERDEM installed, the system will inform you that the previous version must first be uninstalled. This installation then will guide you through the uninstall of your previous version, back up the user's database, if it exists,

and return you to the ERDEM Install program. As directed, click the “ERDEM Install” icon again to complete the installation.

It is recommended that you do a standard installation, accepting all default settings. That is, click “Yes,” “OK,” “Next,” or “Finished,” as appropriate on the various windows. The Install program will install ERDEM and all related components.

For your convenience, this user guide is also available from *ERDEM Online Help*.

Section 3

Using the ERDEM Front End

3.1 Introduction

As a comprehensive modeling system, ERDEM contains a PBPK model engine component that can create scenario-based simulations and target dose estimates for exposure of a species to multiple chemicals, metabolites, compartments, enzymes, and exposures. The input management component uses a Windows-based graphical user interface and relational database that enables the user to enter, edit, report, and export data sets of user-assigned physiological information. ERDEM takes away the tedious and error-prone activities associated with entering, maintaining, and exporting physiological inputs and assessing outputs for PBPK models.

The ERDEM Graphical User Interface (GUI), also known as the ERDEM Front End, provides an efficient method for entering pharmacokinetic modeling and exposure parameters and storing them in a database for later use and export to the ERDEM Model. This section introduces you to the ERDEM Front End interface. Details on data entry and window dependencies are provided in the ERDEM Online Help and the Tutorial, using icons that can be found on your desktop after installation.

3.1.1 Recommended Screen Settings

It is recommended that your screen resolution be set to 1024 x 768 pixels and that your screen colors be set to Windows Standard or Windows Classic. This will ensure that you can see complete windows and that marks in selection boxes are visible.

3.1.2 Model Data Sets

The ERDEM Front End uses the concept of the Model Data Set (MDS) to organize, store, and retrieve entered data. All data entered via the ERDEM Front End must belong to a model data set. An MDS consists of a full set of simulation data records. That is, it contains all the data that was entered via the ERDEM windows and that eventually will be exported to the ERDEM Model for estimating exposure-related dose. The MDS you have open at a given time is called **the current MDS**.

3.1.3 Data Entry Pipeline

Data is entered in a specified sequence, or pipeline, that validates for data integrity as data entry proceeds. The steps of this sequence are accessed as individual windows that allow for adding, saving, editing, or deleting data. The menu selections can be thought of as joints, or segments, in the pipeline. The sequence proceeds from left to right across the "Main" menu, and from top to bottom on each submenu.

The ERDEM Front End has built-in safeguards that prevent you from missing steps in the pipeline. For example:

- Required data entry fields have blue field names. If you attempt to save a window before completing all the required fields, you will be prompted to fill in the required fields and you will be directed to the appropriate fields.

- If you attempt to enter data at some stage of the pipeline before opening an MDS, you will be given an opportunity at that stage to open an MDS. The MDS you open then becomes the current MDS.

- If you attempt to enter data at a later stage of the pipeline (i.e., a later menu) before completing required data entry at an earlier stage (i.e., on an earlier menu), you will be prompted to fill in the missing data and you will be directed to the appropriate menu/window.

ERDEM Front End features include window shortcuts to help you be more productive. Everything in the system has been designed to relieve your burden in terms of accessing and organizing data, maintaining data integrity, and editing data.

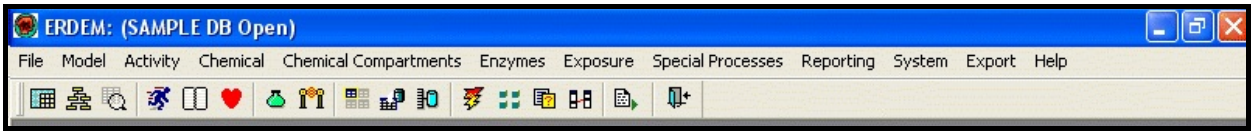
These and other ERDEM Front End features will be discussed in the following sections.

3.2 Accessing the Data: Overview of the *ERDEM* Menu System

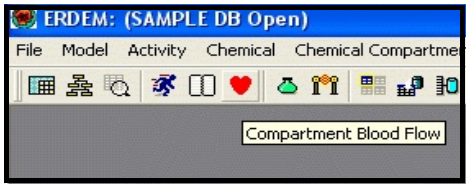
3.2.1 Main Menu

1. Double-click the *ERDEM* software icon, located on your desktop.

The "ERDEM" software will open; the "Main" menu will appear as shown below.



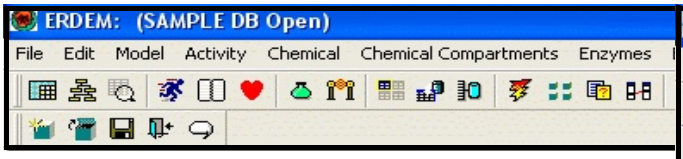
The menu items are icons that provide shortcuts to frequently used functions. Screen tips describing each icon's function appear when you place the mouse pointer over the icon. For example, the heart icon is a shortcut to the "Compartment Blood Flow" entry window, as shown at right.

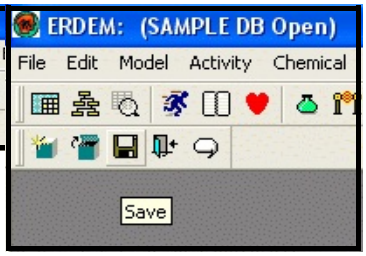


3.2.2 Additional Menu Features

When a data entry window is open, another row of icons providing additional functions appear below the "Main" menu, as shown below.

Again, screen tips describing each icon's function appear when you place the mouse pointer over the icon. For example, as shown at right, the diskette icon is a shortcut to the "Save" function.





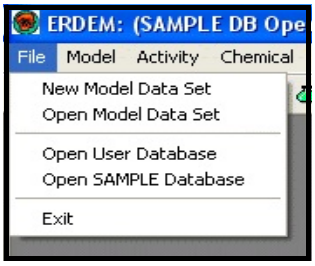
Note: This manual provides an overview of the *ERDEM* Front End menu and window system. Details on menu items, data entry, and window dependencies are provided in the *ERDEM Online Help* and the *Tutorial*.

3.3 Organizing the Data: The Model Data Set Concept

The first step in the data entry pipeline is to define a Model Data Set (MDS). Complete the following steps to create a new MDS:

From the "Main" Menu

1. Select "File".

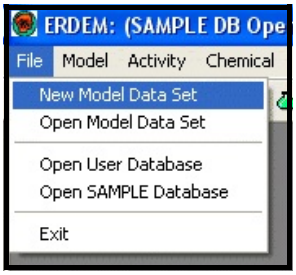


The File menu will appear, as shown at right.

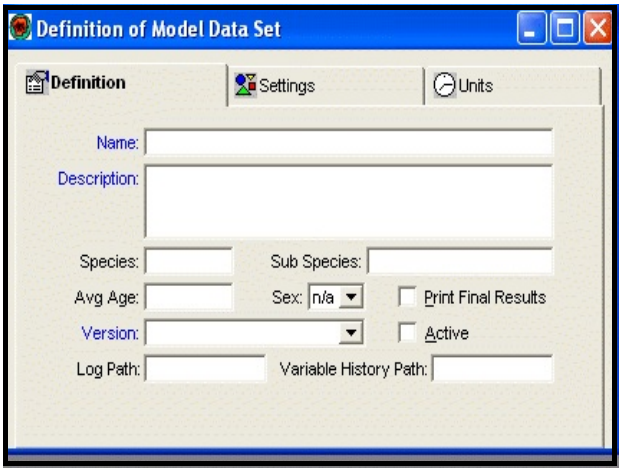
The File menu options allow you to (1) create a New Model Data Set, (2) open an existing Model Data Set, (3) open a User Database, (4) open a SAMPLE Database that is provided by default as part of the ERDEM Install program or (5) Exit the ERDEM Front End.

3.3.1 Define a New Model Data Set

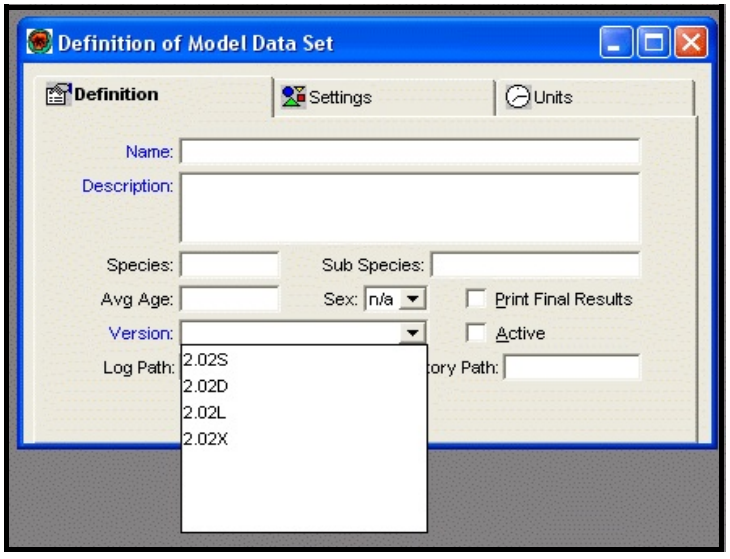
2. Select "New Model Data Set," as shown at right.



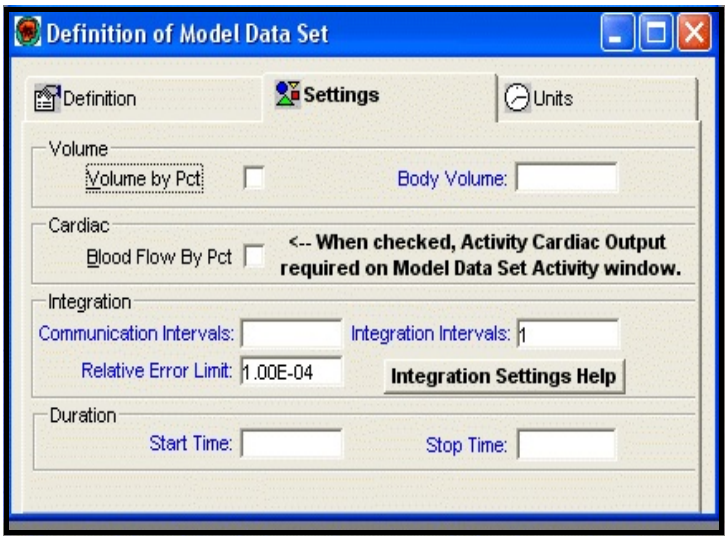
The "Definition of Model Data Set" window will appear, with the "Definition" tab active, as shown below. This window enables you to enter the initial simulation data. (This is the first window in the data entry pipeline. The initial data entered on this window provides the starting data record framework for subsequent windows that are used to build the MDS.)



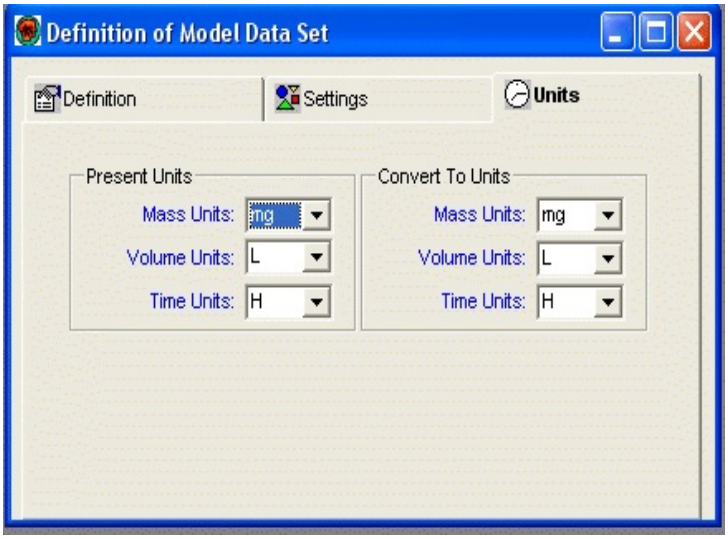
Remember that on all windows in this program, fields with blue field names require information entered in them. Data may be entered in the other fields as appropriate for your Model Data Set. For fields with down arrows, you can enter data by selecting from a drop down, or pick list, as shown below.



3. Click on the "Settings" tab. This selection provides for entry of other parameters.



4. Select the "Units" tab. This selection provides for the setting of measurement units, as shown below.

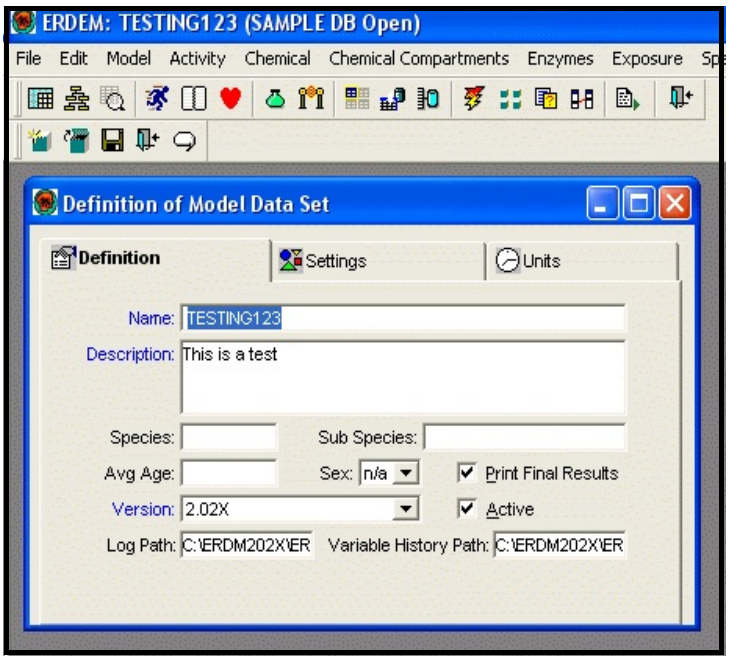


3.3.2 Save the Entered Data

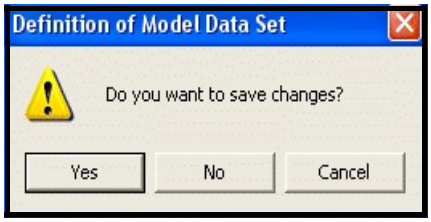
5. Click on the "Save" icon (the diskette icon) below the "Main" menu, *or* select "File," "Save" from the "Main" menu, *or* use key strokes "Ctrl+S."

When you save data, if any of the required fields do not contain data, you will be prompted to enter data in those fields. For example, if you did not enter a Model Data Set name, you would see a message like the one shown at right.

When you have saved your MDS definition, its name appears at the top of the screen. For example, if you named your MDS "TESTING123", the name "TESTING123" would appear at the top of the screen. In the example at right, note that the "Print Final Results" and "Active" fields are checked.



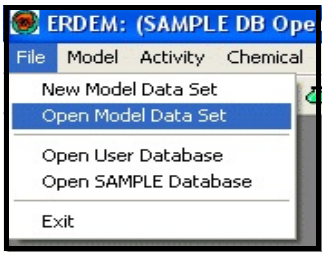
6. **Perform one of the following three functions to close the "Definition of Model Data Set" window: (1) click the red and white "x" in the top right corner of the window, *or* (2) Select "File," "Close" from the "Main" menu, *or* (3) if you prefer to use keystrokes, you can close the window by pressing "Ctrl+F4".**



7. **If you have not saved the MDS definition, a box will pop-up (as shown at right) giving you three options to choose from: (1) *Yes*: To save changes, (2) *No*: To not save changes, or (3) *Cancel*: Return to the "Definition of Model Data Set" window.**

3.3.3 Open an Existing Model Data Set

If the desired MDS already exists in the system, you do not need to re-create it; you need only to open it.

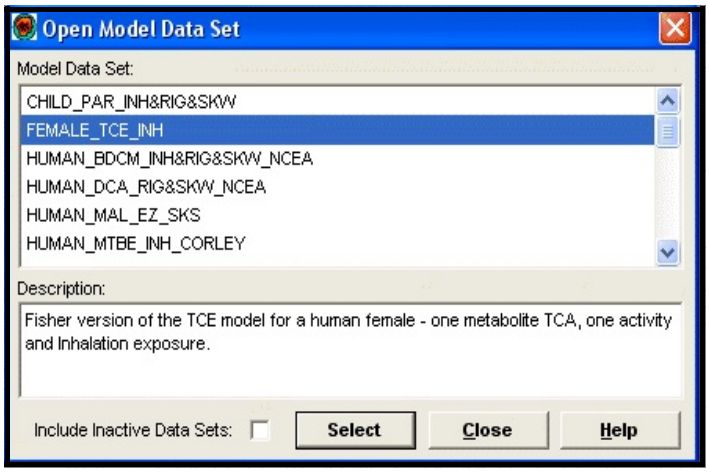


From the "File" Menu

1. **Select "Open Model Data Set", as shown at right.**

The "Open Model Data Set" window will appear, as shown below. Existing MDSs are listed in the upper part of the window. A description of the highlighted MDS appears in the lower part of the window.

2. **Choose an MDS and click on the "Select" button.**



The selected MDS becomes the current MDS, and its data will appear in subsequent windows, as shown at right.

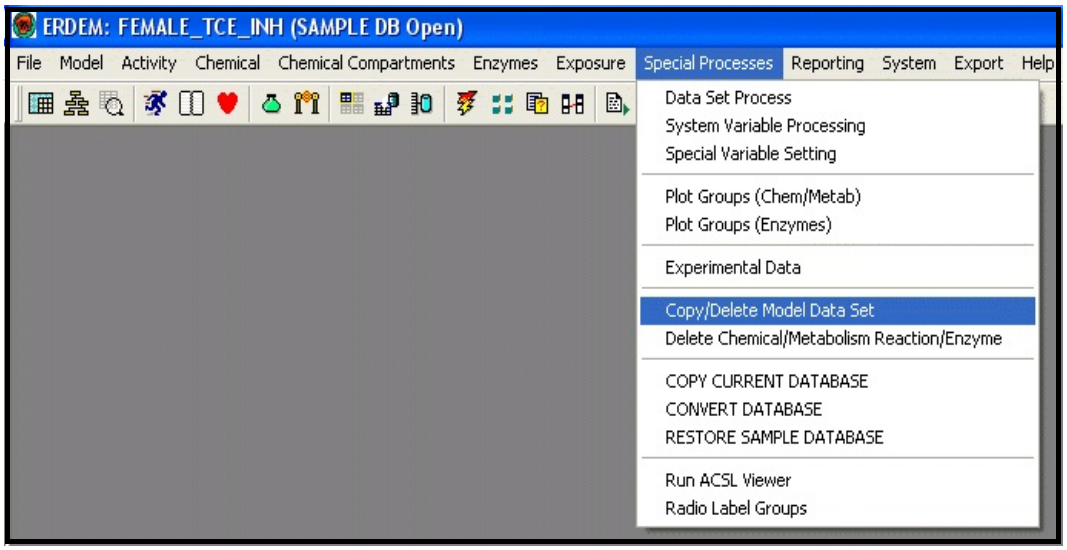
Note that the name of the current MDS appears at the top of the screen. This MDS name will remain at the top of the screen until you open a different MDS. It will be there as you open and work in the various ERDEM windows, so that you will always know which MDS you are working in.

3.3.4 Copy/Delete Model Data Set

3.3.4.1 To Copy the Current MDS:

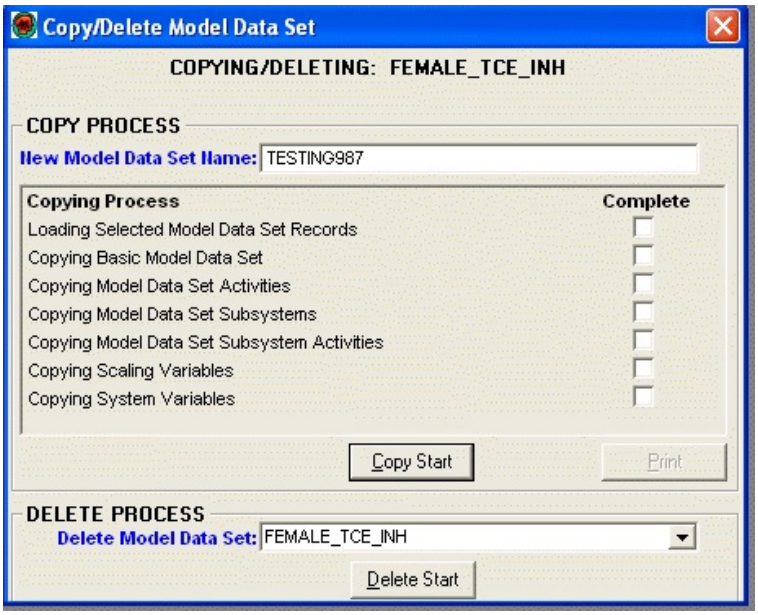
From the "Special Processes" Menu

1. Select "Copy/Delete Model Data Set," as shown below.

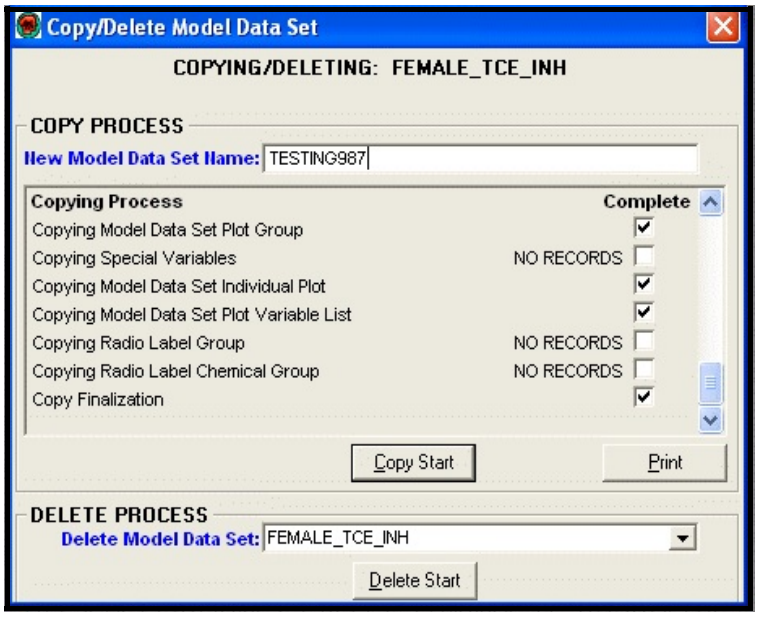


The "Copy/Delete Model Data Set" window appears, as shown below.

Note that the name of the current MDS appears in the upper part of the window.

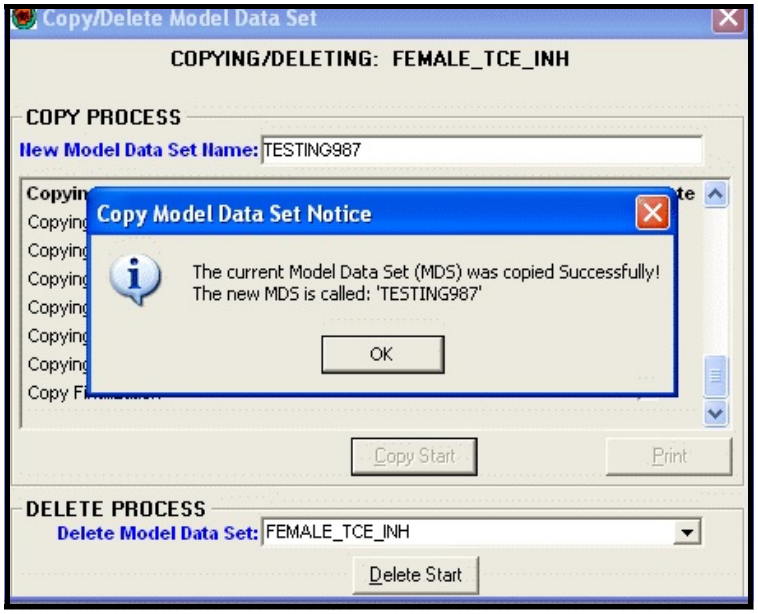


2. **In the "New Model Data Set Name" field, enter a new MDS name.** In the example below, the new MDS name is "TESTING987".



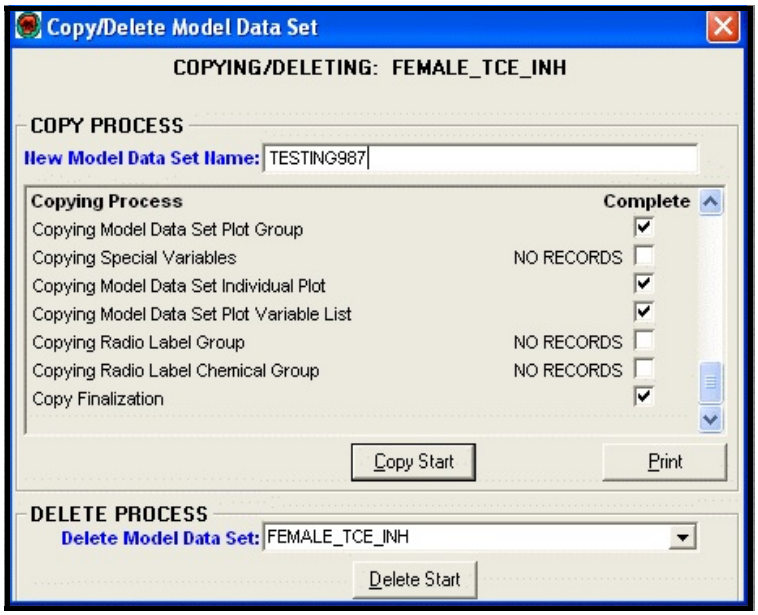
3. Click on the "Copy Start" button.

As each copy process is running, the word "Processing" appears to the right of the process name. When a process is complete, a check mark appears in its "Complete" box. When all the processes are complete, a message box, like the one shown below, appears on top of the window informing you that the MDS was copied successfully.



4. Click on the "OK" button.

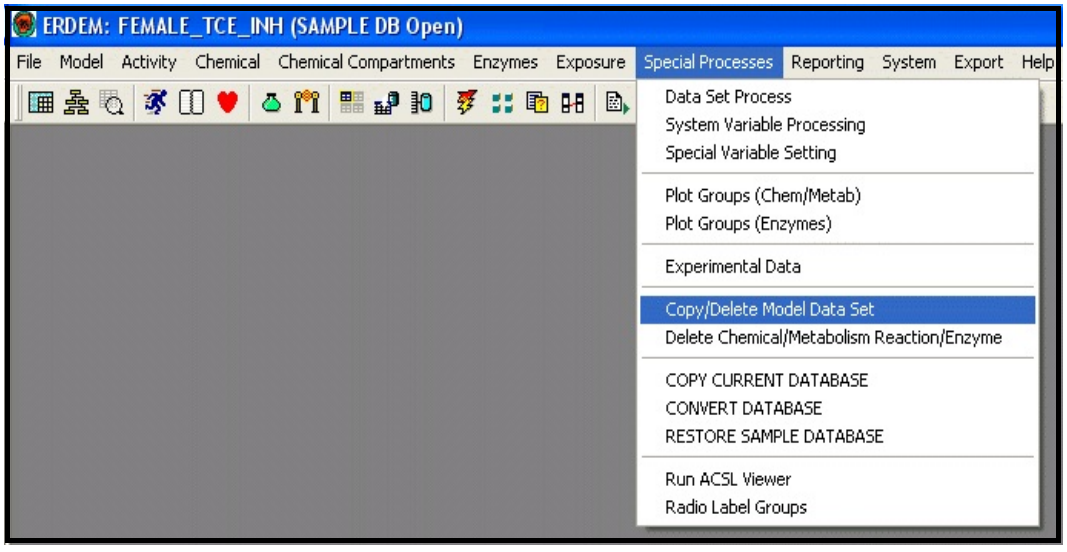
The message box will disappear, revealing the "Copy/Delete Model Data Set" window, as shown below. Boxes will be checked, indicating that copying processes are complete.



3.3.4.2 To Delete an MDS:

From the "Special Processes" Menu

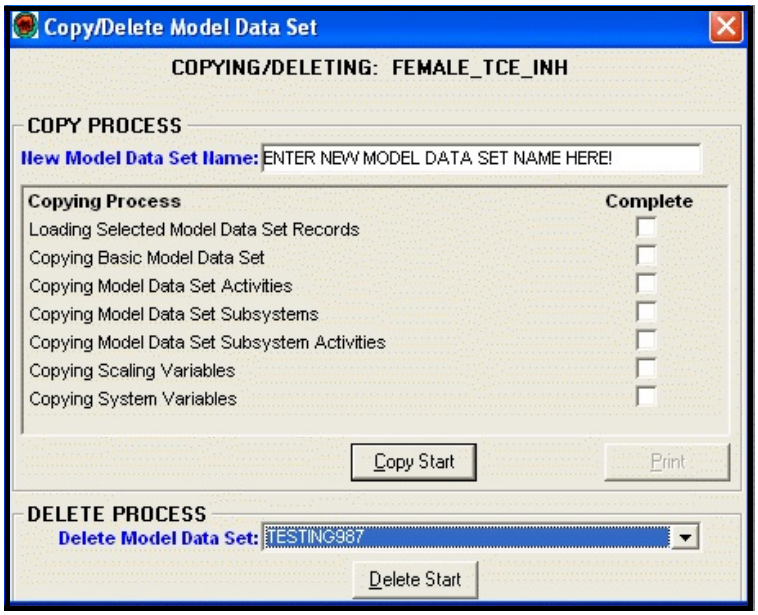
1. Select "Copy/Delete Model Data Set," as shown below.



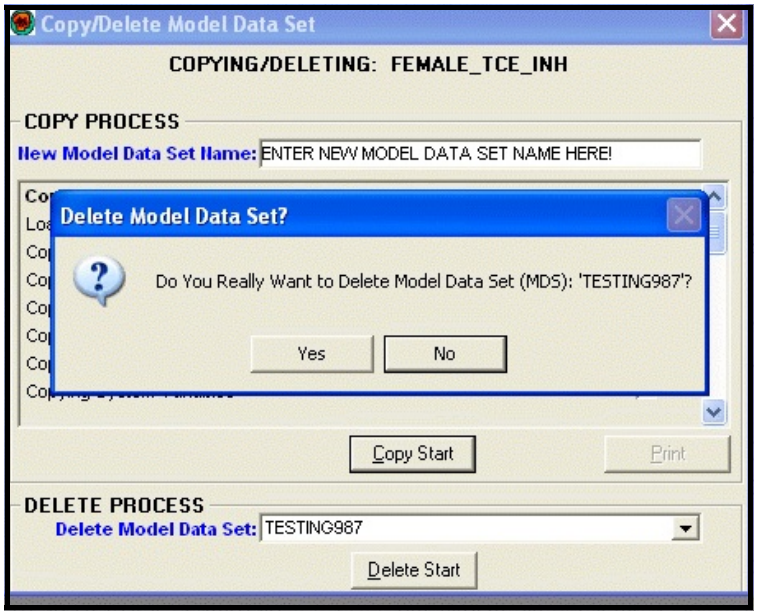
The "Copy/Delete Model Data Set" window will appear, as shown below.

2. **Enter the name of the MDS to be deleted in the "Delete Model Data Set" field.** (In the example below, the MDS to be deleted is "TESTING987".)

3. **Click on the "Delete Start" button.**

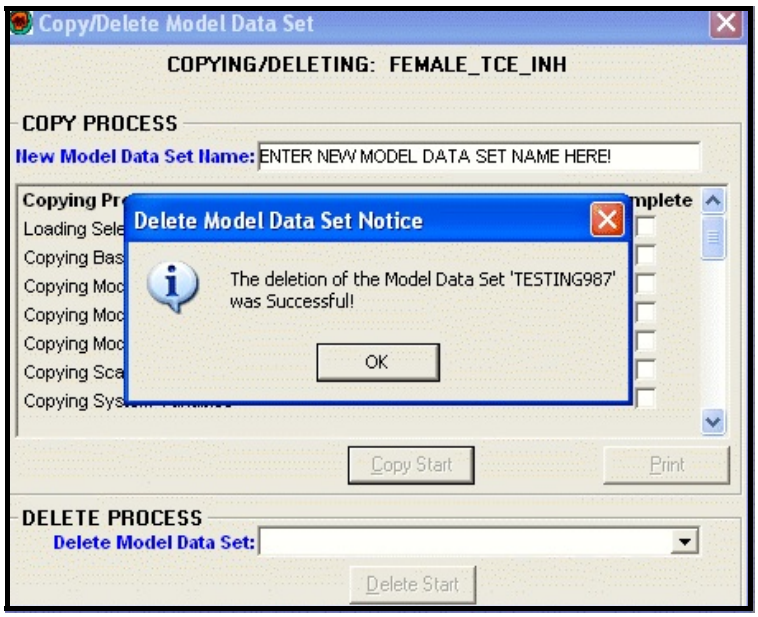


A message will appear, asking "Do You Really Want to Delete Model Data Set (MDS): 'TESTING987'?" (as shown below).



4. **Click on the "Yes" button.**

When the deletion is complete, a message will appear, as shown below, informing you that the deletion was successful.

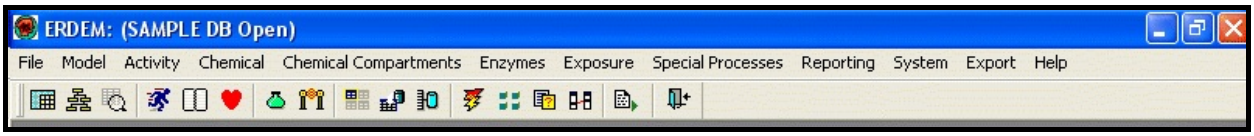


5. Click on the "OK" button.

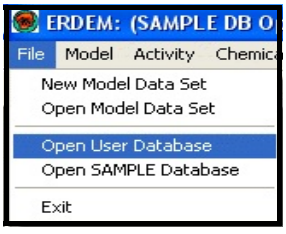
6. Close the "Copy/Delete Model Data Set" window.

3.3.5 Open User Database

When you start the "ERDEM" Front End, the application automatically connects to the "SAMPLE DB" (Database), which is shown in the active title bar in the following illustration.

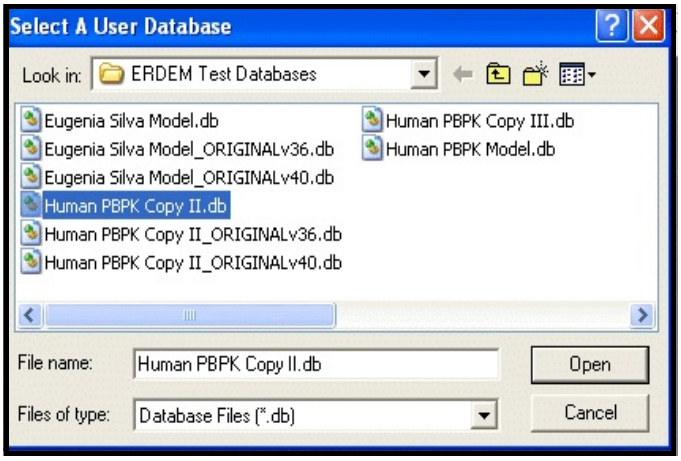


The SAMPLE Database contains carefully prepared and quality assured MDSs that can be exported to produce consistent ERDEM Model run results. These MDSs may be used as examples or templates for developing your own model simulation. They may also be copied, edited, and renamed for your own modeling purposes.



From the "File" menu

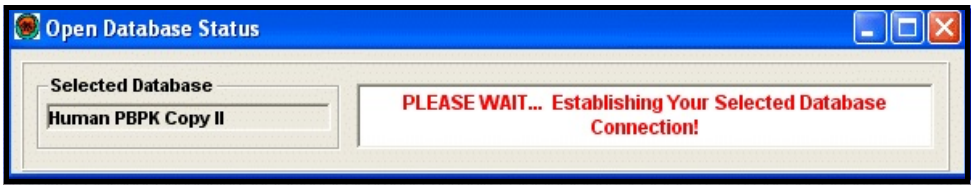
1. **Select "Open User Database," as shown at right.**The "Select A User Database" window appears, as shown below.



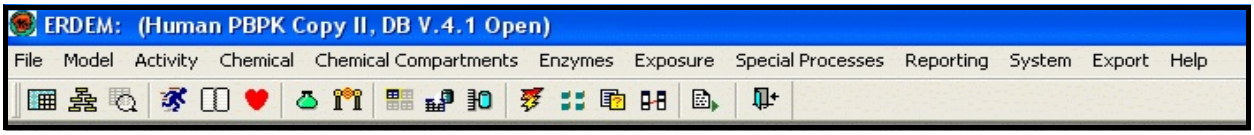
This window allows you to browse to the folder containing the desired user database.

2. **Choose a database and click on the "Open" button.**

The "Open Database Status" window will appear, as shown below.



When the connection is made, the selected database name appears in the active title bar at the top of the screen, as shown below.



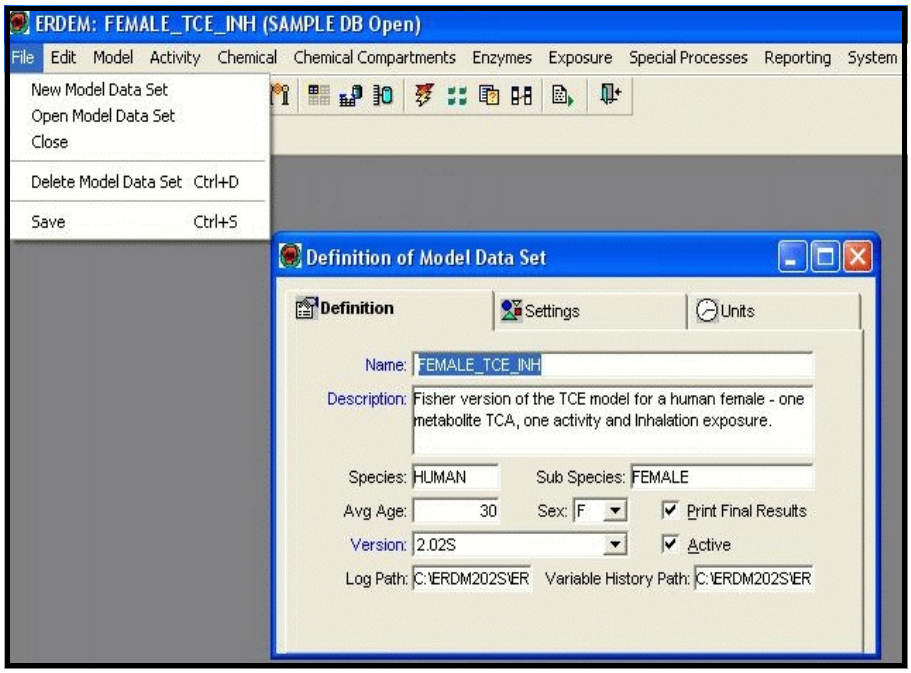
3.3.6 Open SAMPLE Database

From the "File" Menu

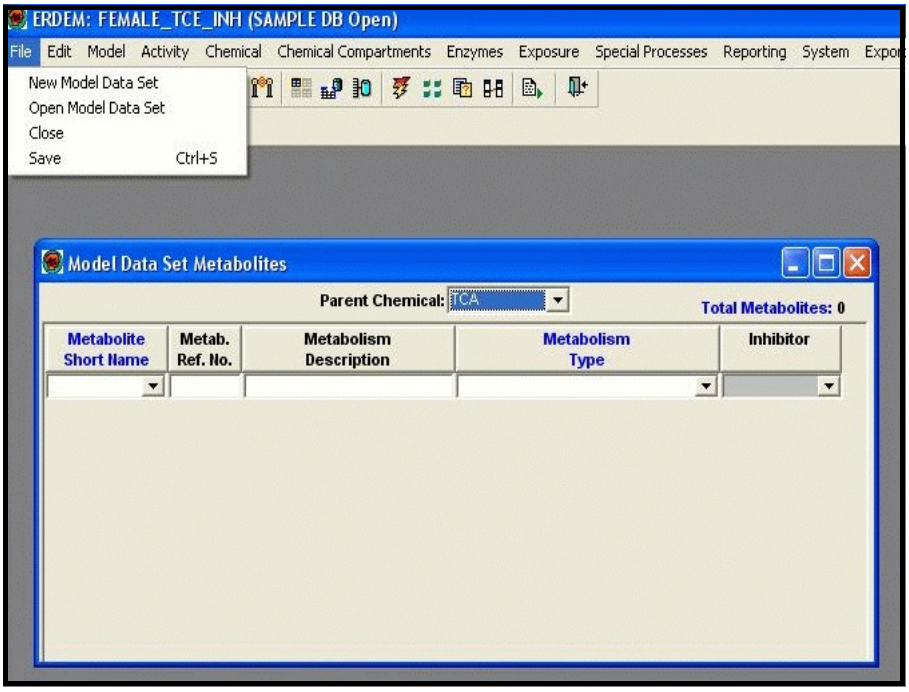
1. **Select "Open SAMPLE Database".**

Note: When an MDS is selected and an ERDEM window is open, the "Open User Database" and the "Open SAMPLE Database" menu options are not available.

In the following example, the MDS is “FEMALE_TCE_INH,” and the “Definition of Model Data Set” window is open. Note that on the “File” menu, the “Open User Database” and “Open SAMPLE Database” options are not available. Note also that “Exit” is not available.



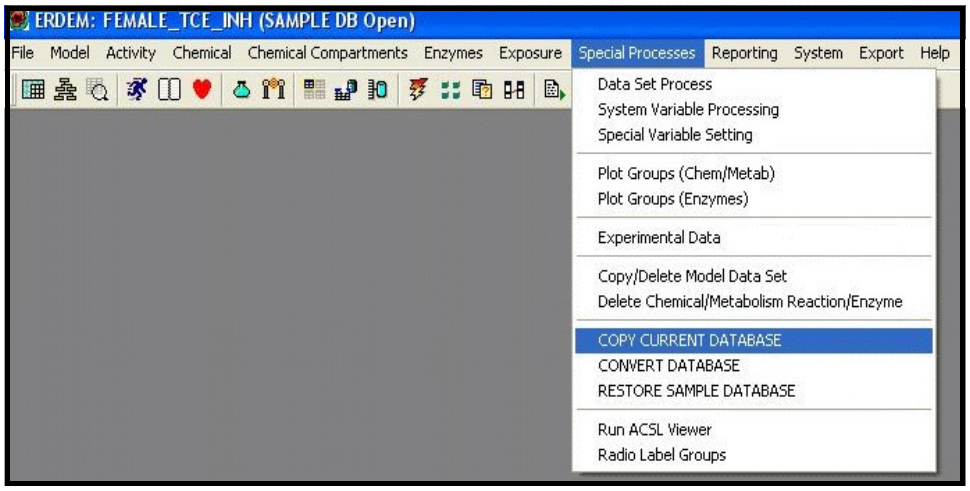
Note: To guard against accidental deletion of a model data set, the “Delete Model Data Set” option is not available when a window other than the Definition of Model Data Set window is open, as shown below.



3.3.7 Special Processes – Copy Current Database

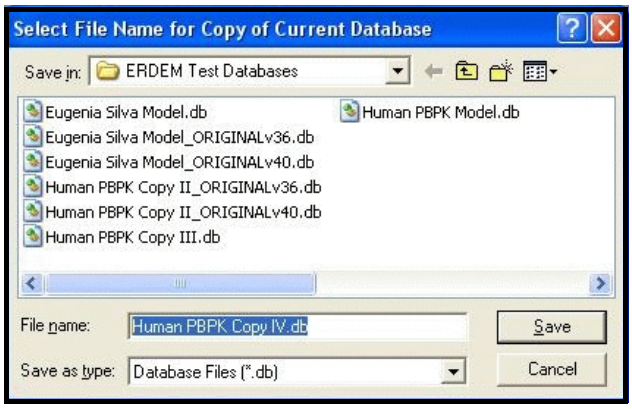
From the "Special Processes" Menu

1. Select "COPY CURRENT DATABASE," as shown below.



Note: The choices "CONVERT DATABASE" and "RESTORE SAMPLE DATABASE" are not available if a database other than the "SAMPLE DB" is open.

The "Select File Name for Copy of Current Database" window opens, as shown at right.

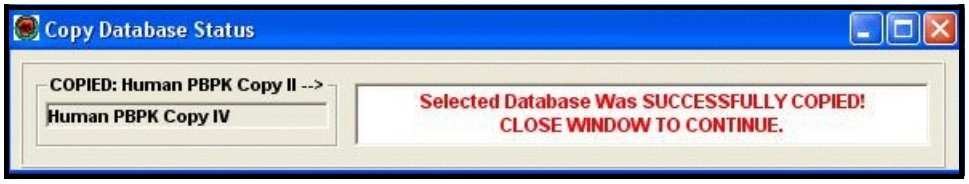


2. Browse to the desired folder for the "Save in" field.

3. Enter the desired File name.

4. To save a copy of the current database, click on the "Save" button.

The following message will appear, informing you that the copy process has been completed.



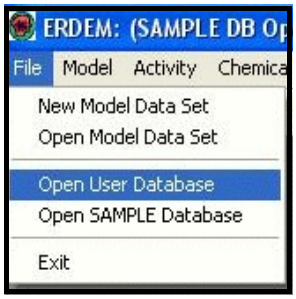
Note: As with the "Open Database" menu options, when an ERDEM window is open the "Copy Current Database" menu option is not available.

3.3.8 Special Processes – Convert Database

Starting with Beta Version 4.0, ERDEM includes enzymes and a new dermal functionality. Because of these new functionalities, databases created with earlier versions of ERDEM must be converted to the new format. This can be done in either of two ways: from the "File" menu or from the "Special Processes" menu. In either method, ERDEM provides prompts to guide you easily through the process.

3.3.8.1 Method One

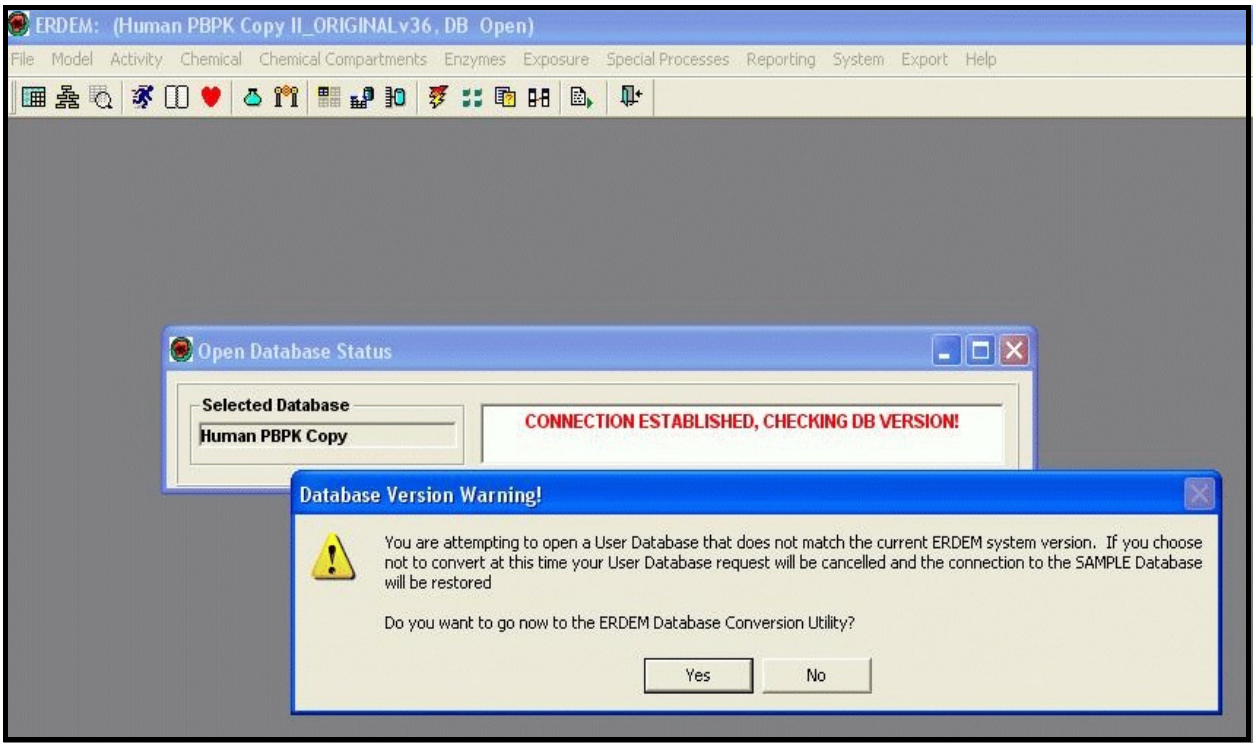
From the "File" Menu



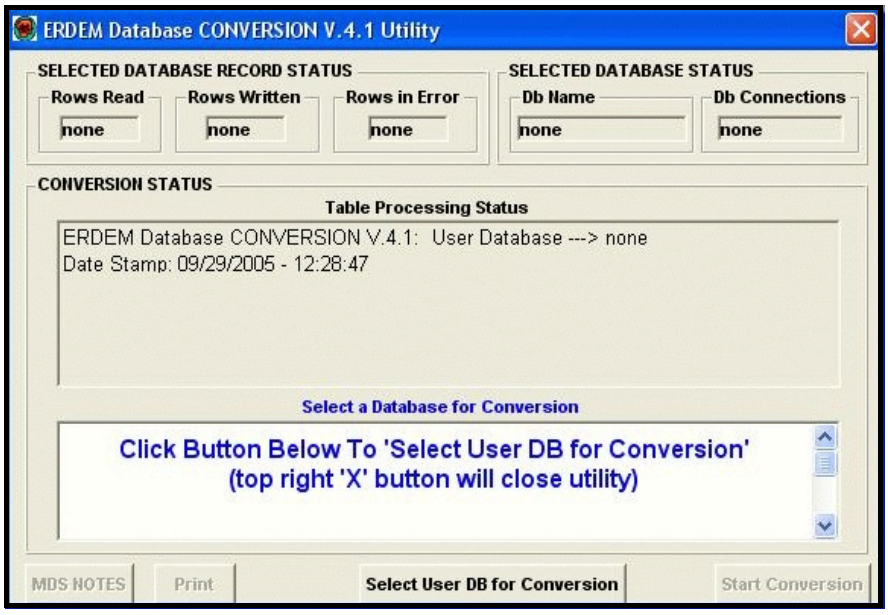
1. Select "Open User Database," as shown at right.

When you select a database, a message will appear informing you that ERDEM is connecting to the database.

If you have selected a database created with an earlier version of ERDEM, a pop-up box will then inform you of that fact, and a second pop-up box will appear asking if you want to go to the "ERDEM Database Conversion Utility," as shown below.



2. If you click on the "Yes" button, the "ERDEM Database CONVERSION V.4.1 Utility" window will appear, as shown below.



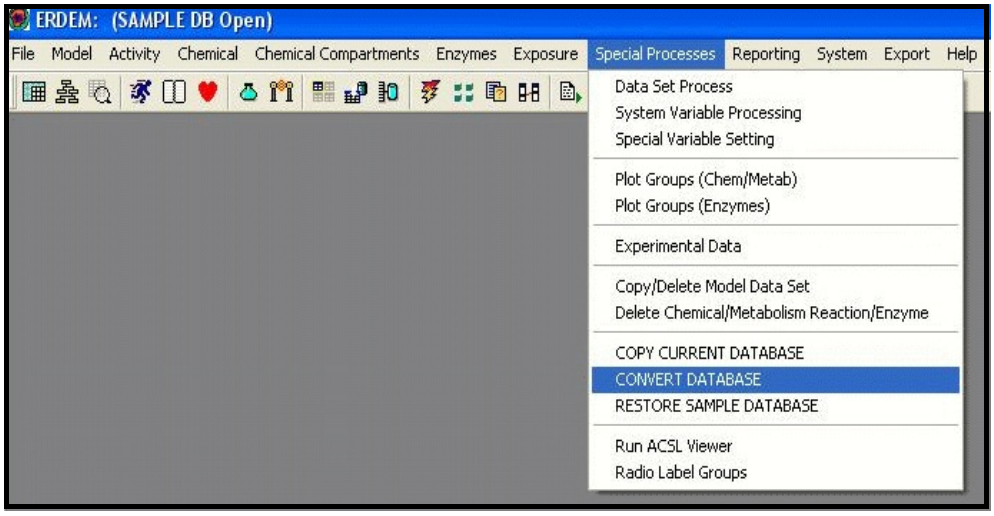
3. From here, proceed as in Method Two, below, beginning with the "ERDEM Database CONVERSION V.4.1 Utility" window.

3.3.8.2 Method Two

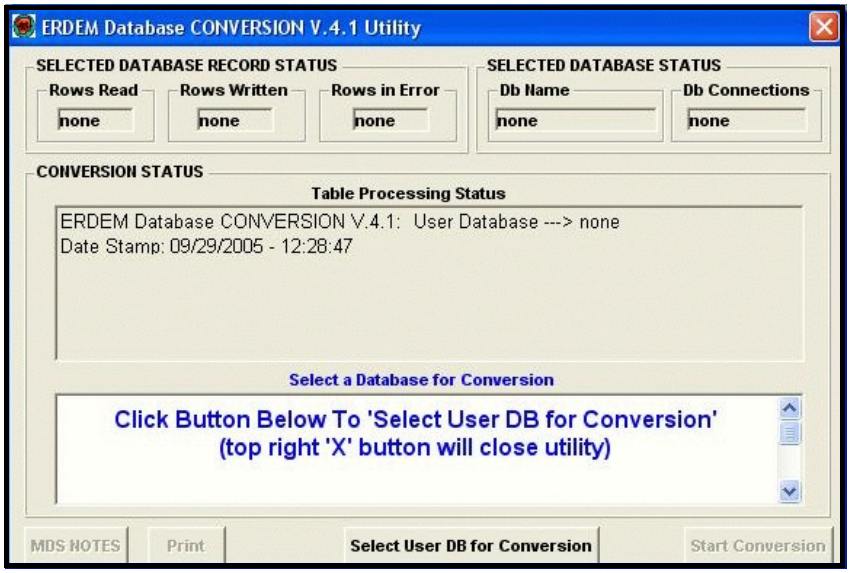
The second method for converting a database is in the "Special Processes" menu, which gives you access to the ERDEM Database Conversion Utility.

From the "Special Processes" Menu

1. Select "CONVERT DATABASE," as shown below.

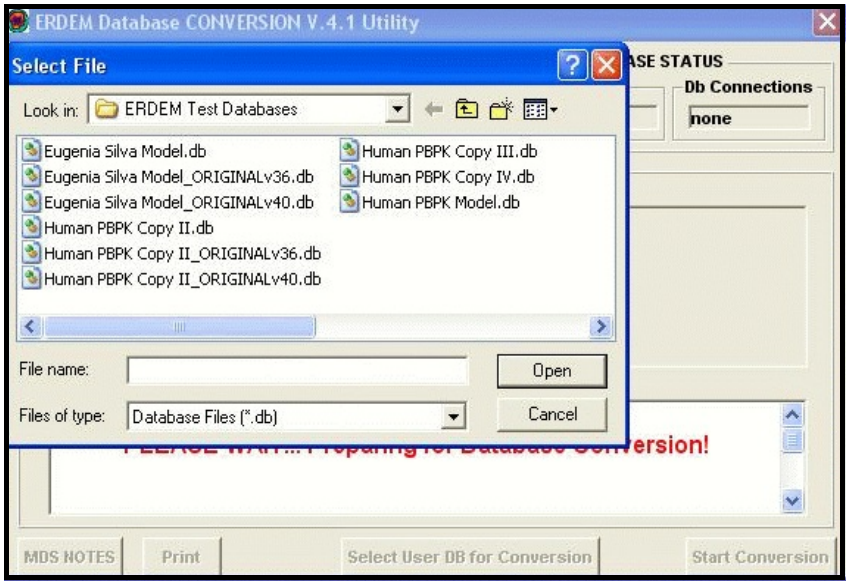


The "ERDEM Database CONVERSION V.4.1 Utility" window will appear, as shown below.



2. Click on the "Select User DB for Conversion" button.

The “Select File” window will appear over the “ERDEM Database CONVERSION V.4.1 Utility” window.

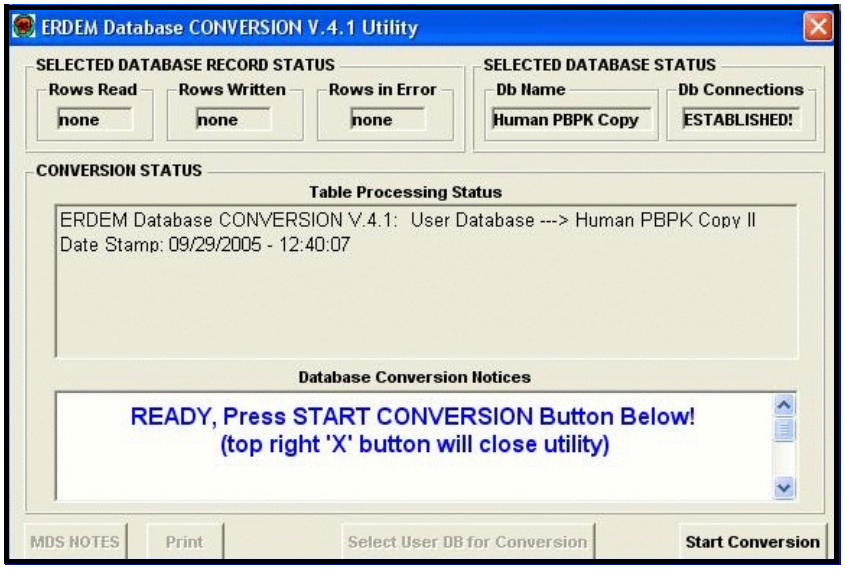


3. Select a file and click on the “Open” button.

ERDEM determines the version of the database to be converted and retains a copy of the database in that version. The new database will have the same name as the original. The backup of the original database will be saved with the naming convention “Userdbname_ORIGINALv36.db,” where “ORIGINALv36” denotes the version (3.6) of the original database. An additional backup with the naming convention “Userdbname_ORIGINALv40.db” will also be saved. The previous illustration shows such files.

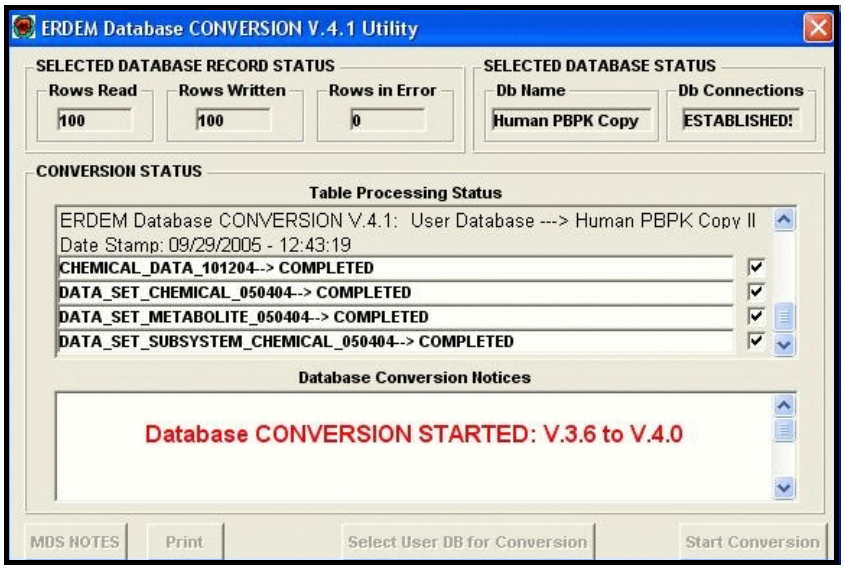
Note:If any errors are encountered during the conversion process, all database conversion changes are returned to their original state, so that no data is lost.

While ERDEM is performing these and other preparatory actions, a series of messages will appear in the “ERDEM Database CONVERSION V.4.1 Utility” window informing you as each is processing. When the “READY, Press START CONVERSION Button Below!” message appears in the “ERDEM Database CONVERSION V.4.1 Utility” window, as shown below, the actual conversion can be started.



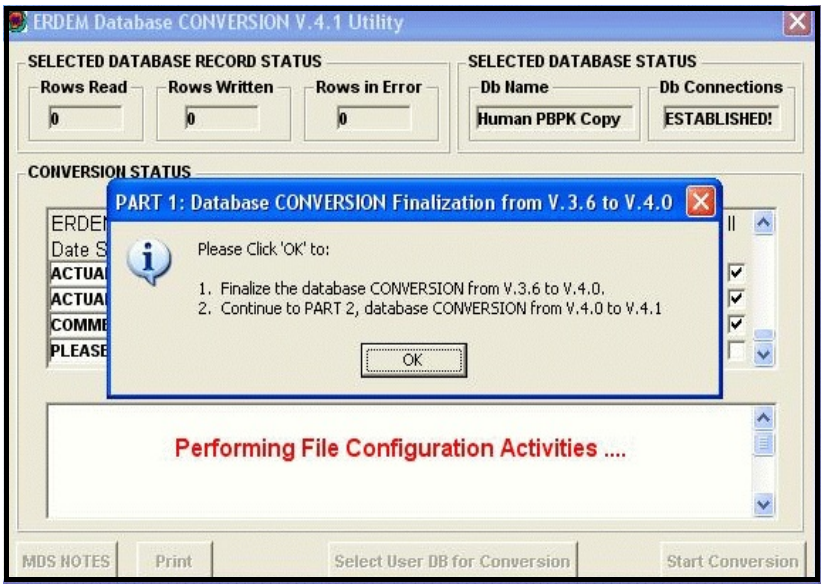
4. **Click on the "Start Conversion" button (located in the lower right corner of the window).**

   The processing information will appear in the "Table Processing Status" window, as shown below.



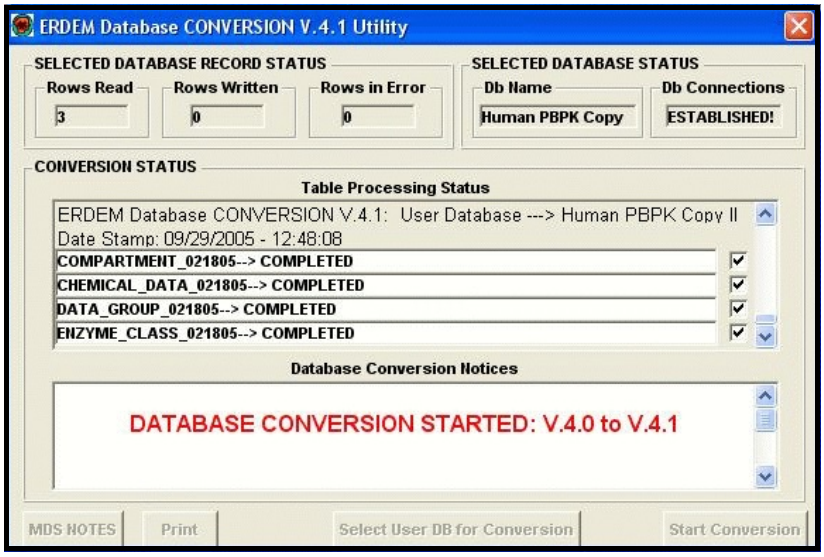
   When the conversion is almost done, a "PART 1: Database CONVERSION Finalization from V.3.6 to V.4.0" pop-up box will appear (see below). Note that if the original database was in version 3.6, the finalization is in two parts: from V.3.6 to V.4.0, and then from V. 4.0 to V.4.1.

Note: If the original database was in version 4.0, the conversion will be completed in a single step.

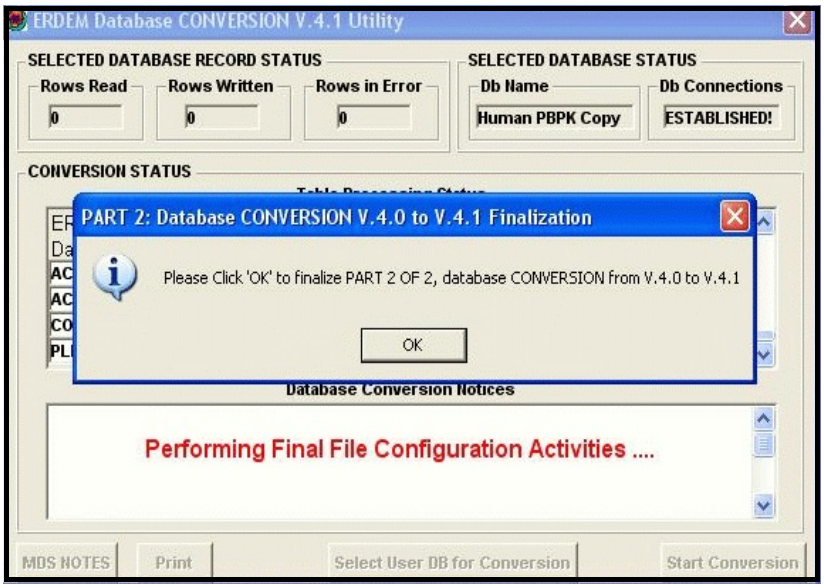


5. Click on the "OK" button.

If you started with a V.3.6 database, the "Database Conversion Notices" portion of the window (see below) would indicate that the conversion from V.4.0 to V.4.1 has started.

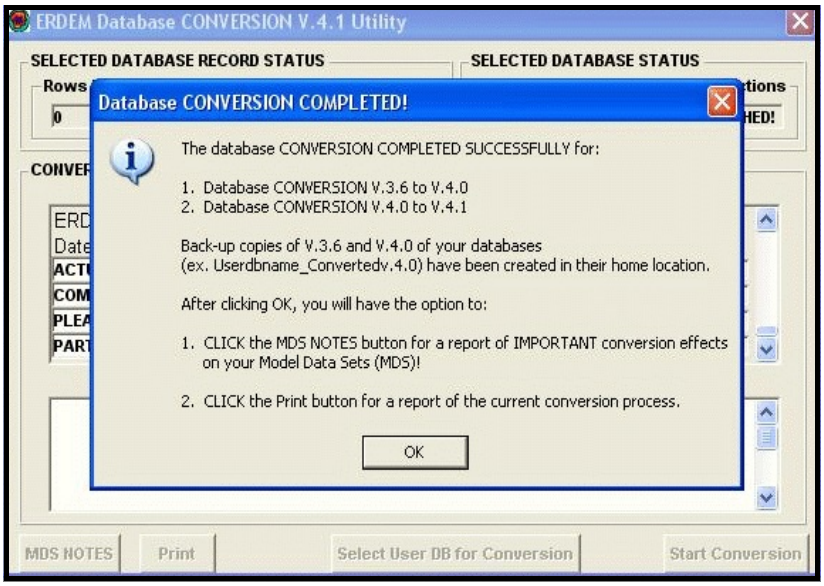


A “Part 2: Database CONVERSION V.4.0 to V.4.1 Finalization” pop-up window will appear, as shown below.



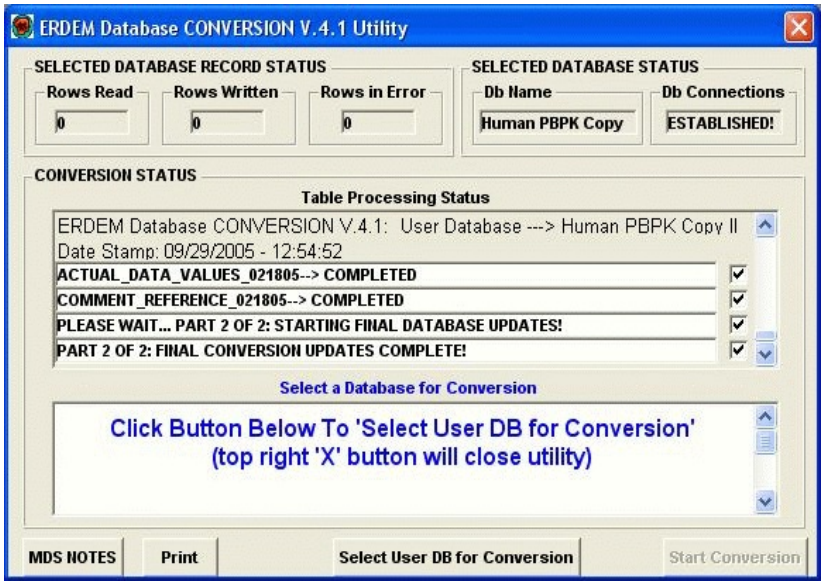
6. Click on the “OK” button.

A “Database CONVERSION COMPLETED!” pop-up window will appear.



7. Click on the “OK” button.

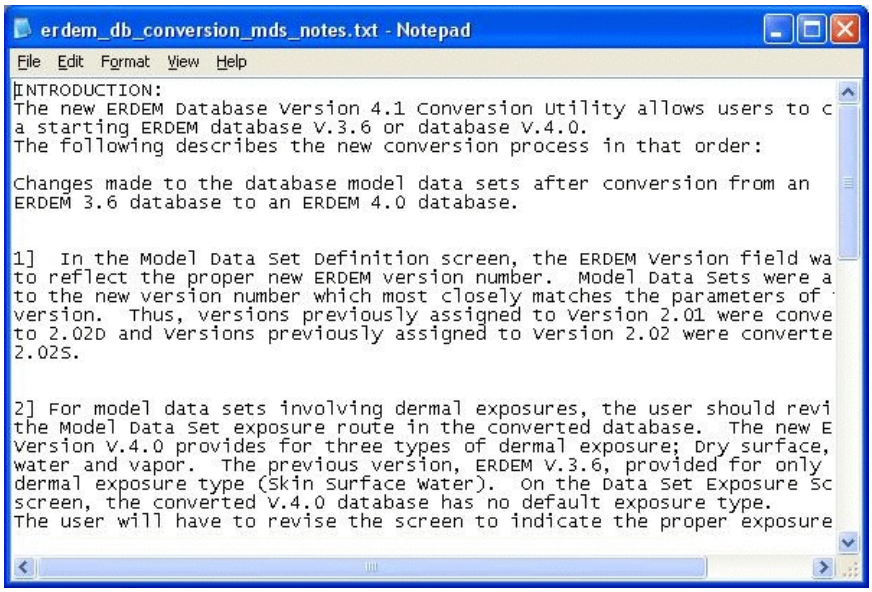
Note that the "MDS NOTES" button and the "Print" button in the lower left corner of the window are now active, as shown below.



8. To obtain a printout of the items in the "Table Processing Status" list, as shown above, click on the "Print" button.

The "MDS NOTES" are comments regarding the important conversion effects on your Model Data Sets.

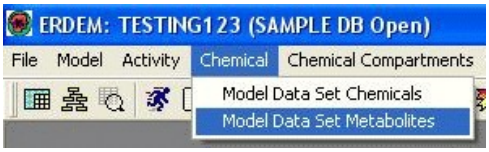
9. To see the "MDS NOTES," click on the "MDS NOTES" button. The notes information will appear in a Notepad window, as shown below.



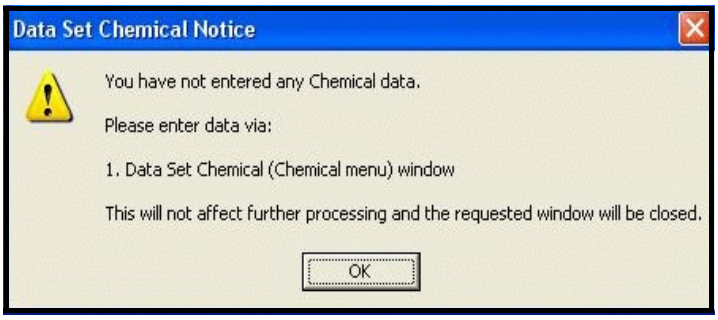
3.4 Maintaining Data Integrity: The ERDEM Data Entry Pipeline

In the EDREM data entry pipeline, before any data can be added or changed, it must pass through each pipeline segment's data validation check. This check proceeds from left to right across the "Main" menu.

Whenever you open a window, the pipeline will validate that the window being requested is part of the next segment in the pipeline and that no data integrity rules have been violated. For example, look at the "Chemical" menu (shown at right), with the "Model Data Set Metabolites" option selected.



If you attempt to enter metabolite data before entering chemical data, you will receive a message reminding you to enter chemical data before entering metabolite data. The message also indicates the menu on which you will find the appropriate window, as shown at right.



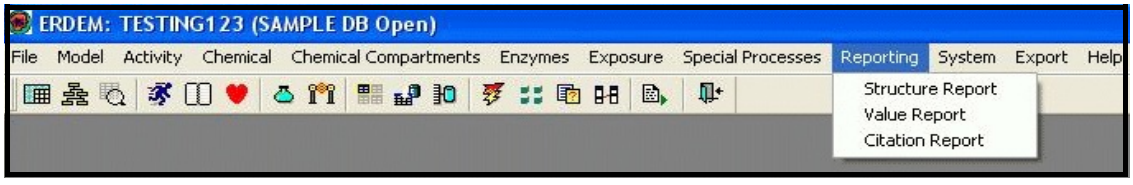
3.4.1 The Pipeline Report

You can easily check the status of the data entry pipeline for the current MDS:

From the "Main" Menu

1. Select "Reporting".

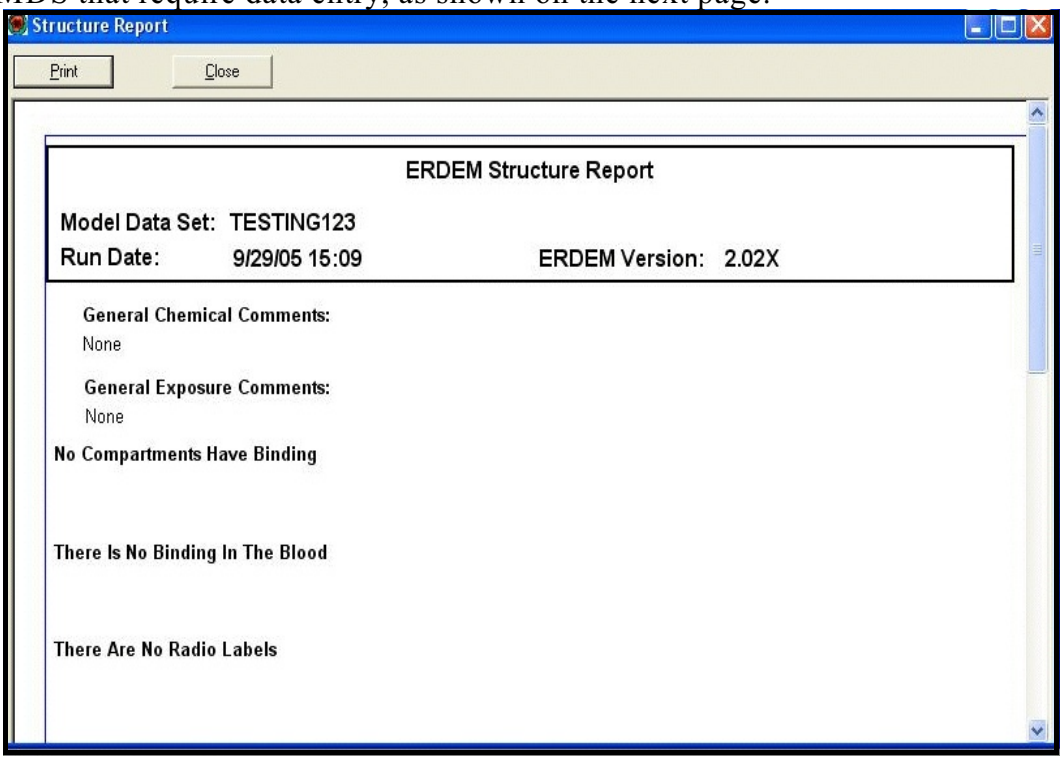
The "Reporting" drop-down menu will appear, as shown below.



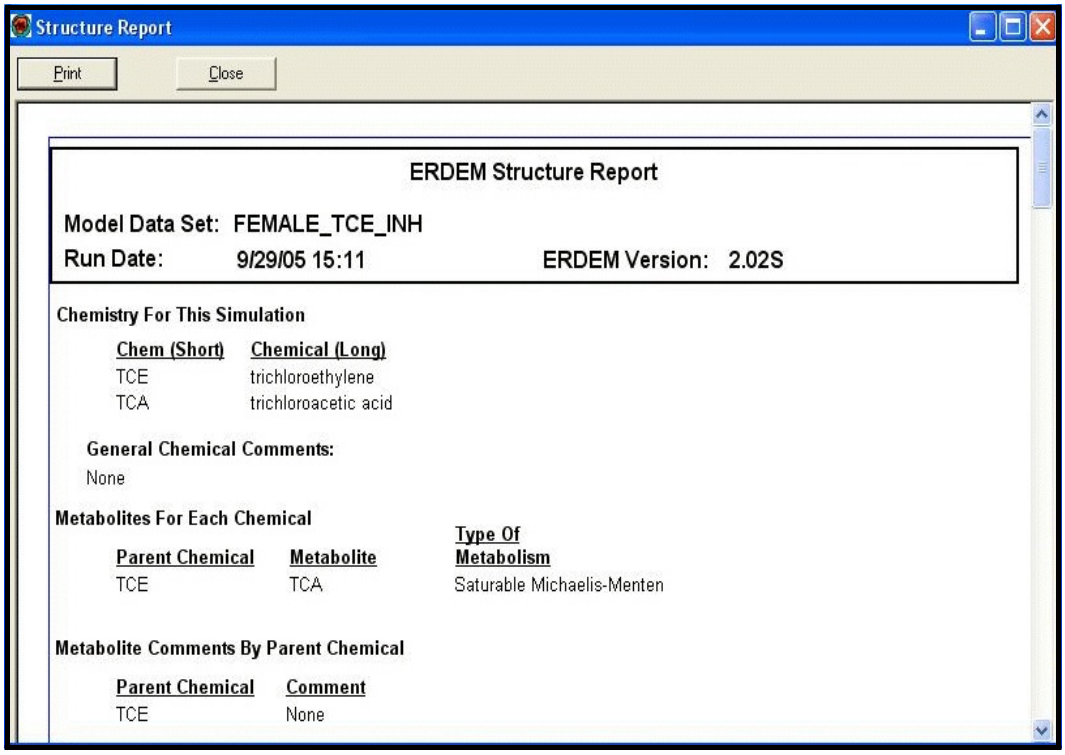
2. Select "Structure Report".

The ERDEM "Structure Report" screen for the current MDS (TESTING123) will appear.

Because this MDS is incomplete, the report will not show information in the parts of the MDS that require data entry, as shown on the next page.



A completed MDS (for example "FEMALE_TCE_INH," as shown below), will contain data in the "ERDEM Structure Report".



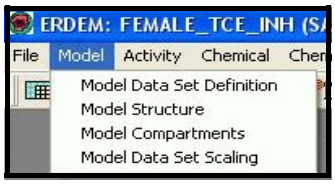
3.5 Editing the Data: Adding, Deleting, Saving

ERDEM data consists of records stored in ERDEM database tables organized primarily according to unique model data sets (MDSs). New data is referred to as data lines or data records. This section covers adding and deleting data lines/records, and saving newly entered data.

Note: In some ERDEM windows, data lines/records cannot be added, inserted, or deleted. This is because these data lines/records are being used for reference purposes only.

From the "Main" Menu

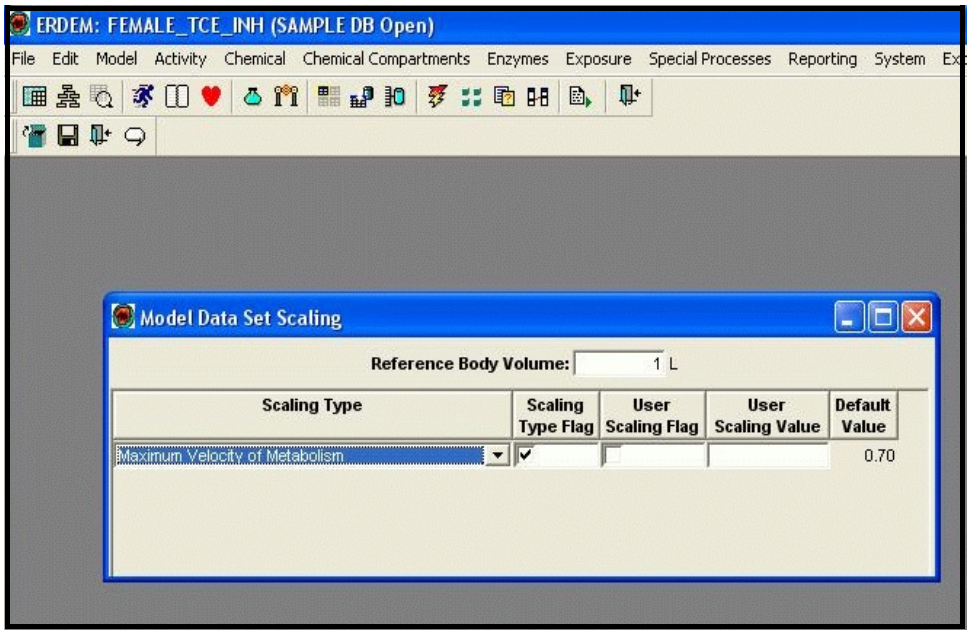
1. Select "Model".



The "Model" menu will appear, as shown at right.

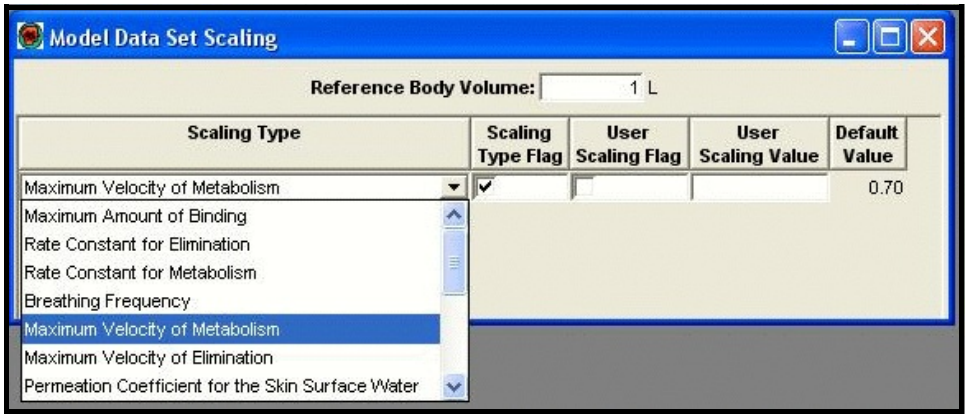
2. Select "Model Data Set Scaling".

The "Model Data Set Scaling" window will appear, as shown below. The selected "Scaling Type" is not applicable for the MDS.



3.5.1 Change An Entry

1. Click on the down arrow under "Scaling type"; a drop-down list will appear, as shown on the following page.

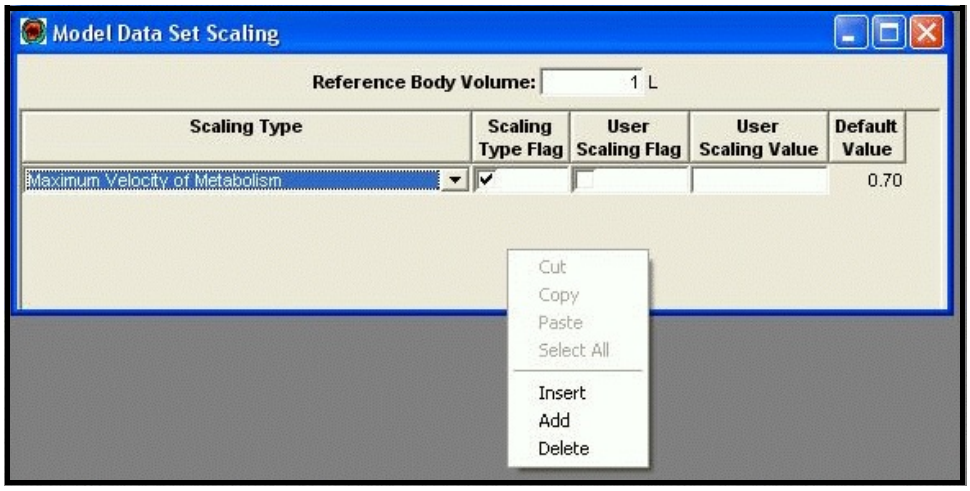


3.5.2 Insert, Add, or Delete a Row

To insert, add, or delete a row:

1. Right-click anywhere in the gray area of the window.

A "Model Data Set Scaling" window will appear, providing options to Insert, Add, or Delete, as shown below.

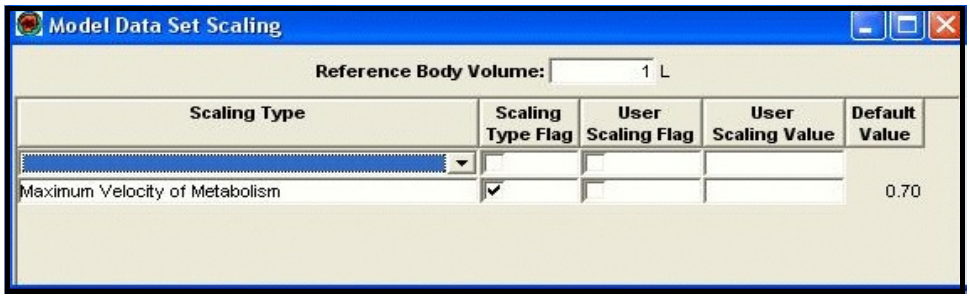


Note that other functions on the pop-up menu (Cut, Copy, Paste, Select All) are grayed out. These functions are not available on the "Model Data Set Scaling" window.

3.5.2.1 To Insert a Row

1. Select the "Insert" option from the pop-up menu.

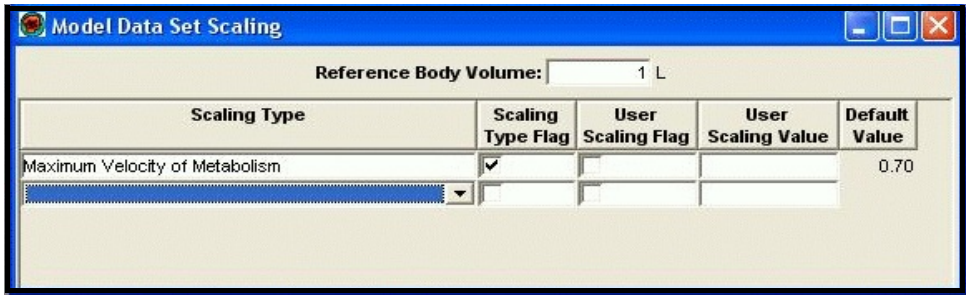
The newly inserted row will appear above the previous row, as shown below.



3.5.2.2 To Add a Row

1. Select the "Add" option from the pop-up menu.

The added row will appear below the previously existing rows, as shown below.

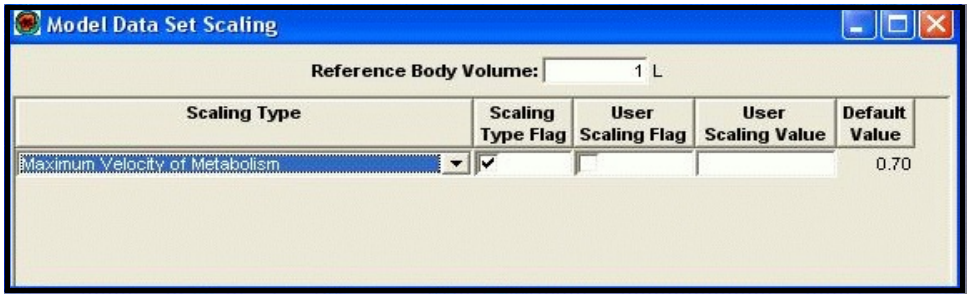


3.5.2.3 To Delete a Row

1. Before deleting the row, confirm that the row to be deleted is active and/or highlighted.

2. Select "Delete" from the pop-up menu.

The row should now be deleted, as shown below.



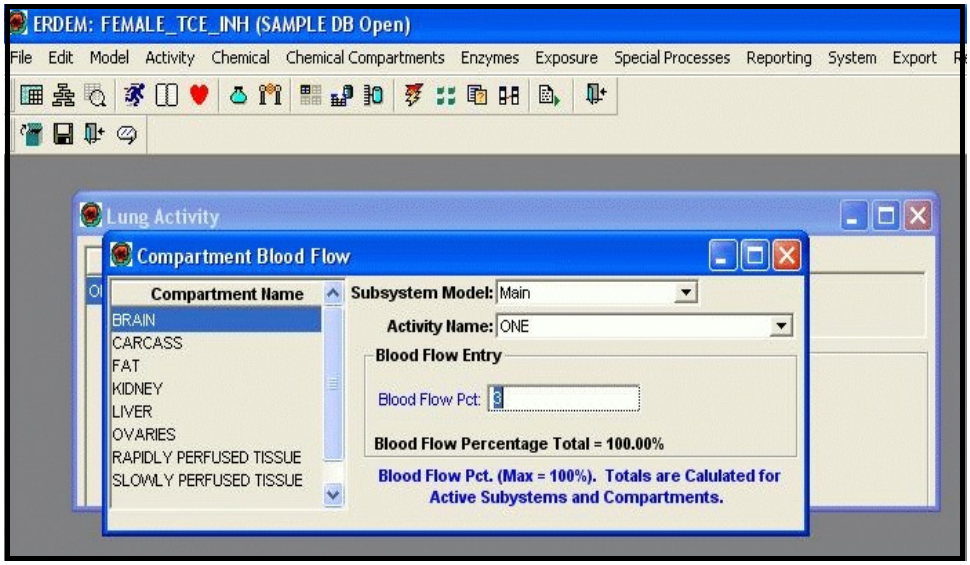
3.5.3 Saving Changes

Changes you have made are not permanent until you save them.

You can save your changes in one of three ways: (1) Click on the *Save* icon (the diskette below the "Main" menu), ***or*** (2) Select "File," "Save" from the "Main" menu, ***or*** (3) Use keystrokes "Ctrl+S".

The Save action applies only to the active window (the window with the bright colored title bar). It does not apply to any windows whose title bars are "ghosted."

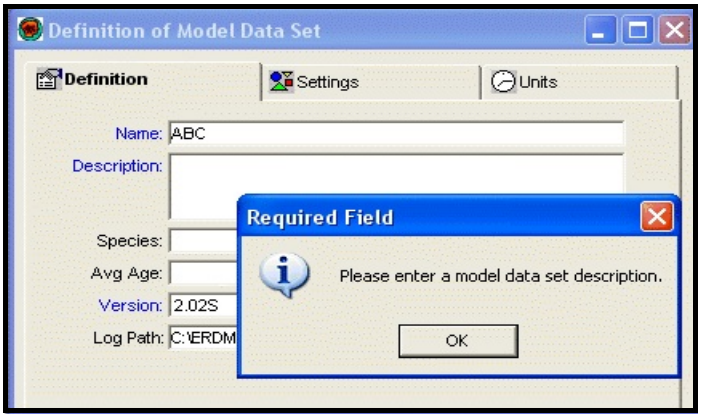
As an example, in the illustration below, "Lung Activity" is the inactive window and "Compartment Blood Flow" is the active window.



3.6 Required Fields and Unavailable Fields

3.6.1 Required Fields

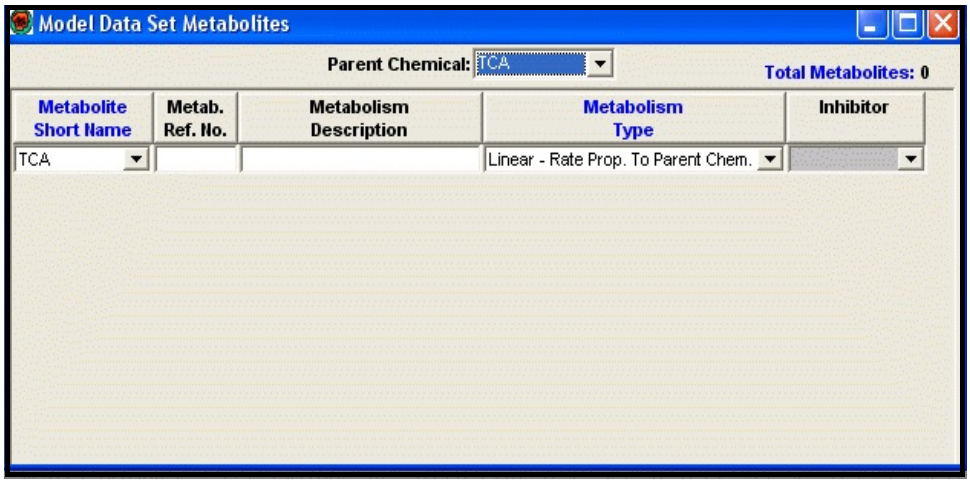
Required fields are fields that must contain data in order for a record to be saved. Required data entry fields have blue field names. If you attempt to save a window before completing all the required fields, you will be prompted to fill in the required field(s), and you will be directed to the appropriate field(s). For example, if you are trying to save a "Definition of Model Data Set" window without entering a description, you will be prompted to fill in the model data set "Description" field, as shown at right.



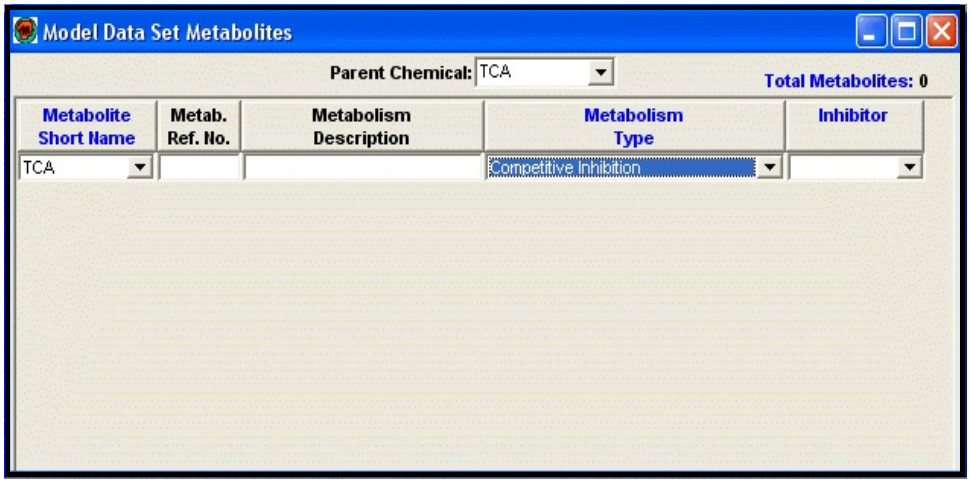
3.6.2 Unavailable Fields

Some data line/record fields are not available, depending on the type of data being entered on the window. When a field is unavailable, the field background color will be gray and the field will not be active for data entry.

For example, the "Model Data Set Metabolites" window (available from the "Chemical" submenu) may, upon opening, show the "Inhibitor" field unavailable, as shown below.



However, if the "Metabolism Type" is changed, the "Inhibitor" field becomes active and data may be entered in it, as shown below.



3.7 Maintaining Productivity: ERDEM Window Features and Shortcuts

The ERDEM Front End has features that can increase your productivity. It allows you to:

- Use non-filtering and filtering dropdowns to view and edit complex chemical data
- Use reference data lists to display and sometimes filter data lines/records
- Track and switch between multiple MDSs
- Get context help for data line/record field definitions

This section will discuss non-filtering and filtering dropdowns. It will also discuss reference data lists. Subsequent sections will discuss switching between MDSs and getting context help.

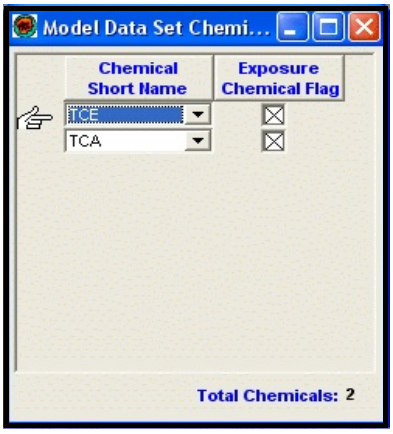
3.7.1 Non-Filtering Dropdowns

ERDEM uses dropdowns to provide lists of selectable data or to filter data lines/records in a window. The following is an idea of how these work:

From the "Main" menu:

1. Select "Chemical", then "Model Data Set Chemicals."

The "Model Data Set Chemicals" window will appear, as shown at right.



2. **Right-click in the gray area of the window to reveal the pop-up editing menu, as shown below in "Illustration 1."**

3. **Click on the "Add" option.**

   A new row appears, as shown below in "Illustration 2."

4. **Click on the down arrow in the new row (or click anywhere in the new row).**

   A dropdown list showing available chemicals will appear, as shown below in "Illustration 3."

5. **Select a chemical to enter into the field.**

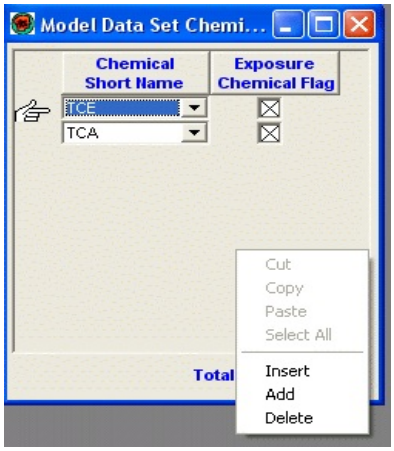


Illustration 1

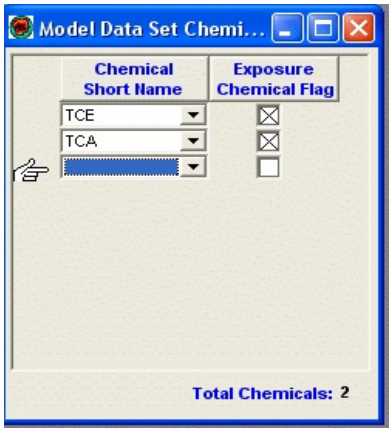


Illustration 2

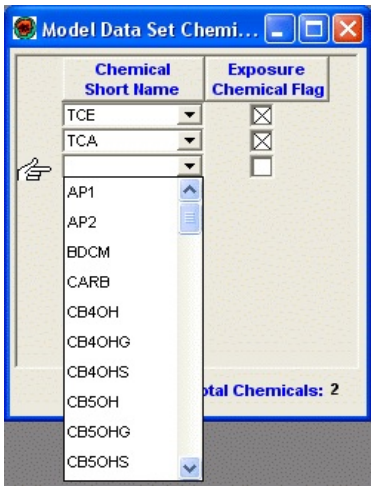


Illustration 3

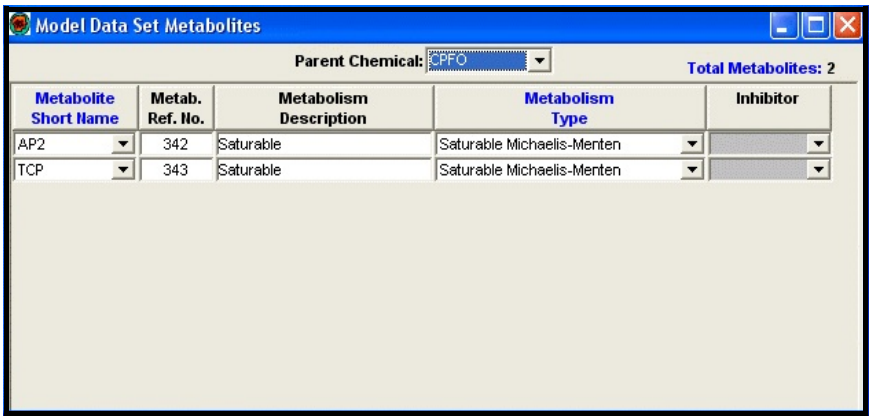
3.7.2 Filtering Dropdowns

Certain ERDEM dropdowns serve to filter the data lines/records. As more and more data is entered along the data entry pipeline, it becomes more and more difficult to view the increasing amounts of data. To alleviate this problem, filtering dropdowns are used to limit the amount of data on the screen at any one time so that you can edit it more easily. The following steps show how filtering dropdowns work:

From the "Main" menu:

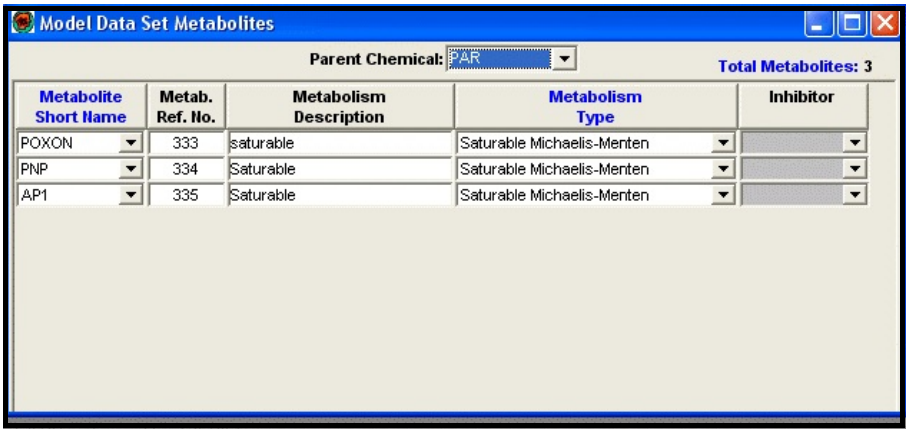
1. **Select "Chemical," and then"Model Data Set Metabolites."**

   The "Model Data Set Metabolites" window will appear, as shown below.

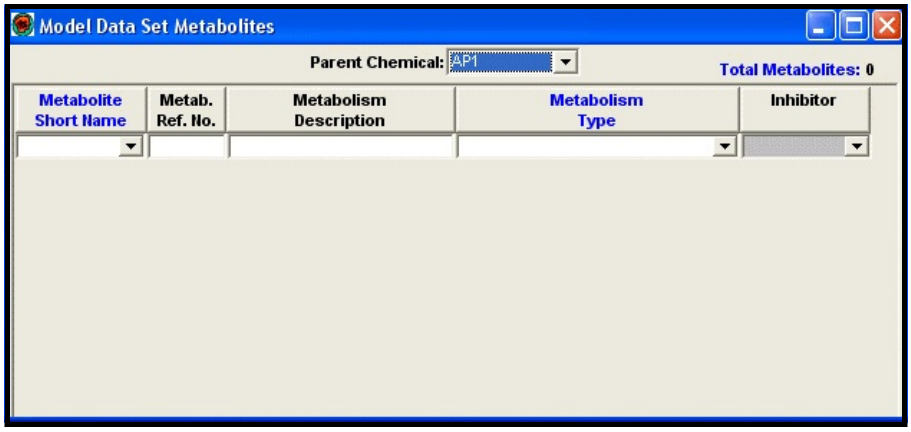


In the example above, the "Parent Chemical" at the top of the window is set to CPFO. The data lines/records displayed are for the metabolites "AP2" and "TCP." These metabolites were entered previously when the filtering dropdown was set to "CPFO".

If you reset the filtering dropdown to "PAR," the related metabolites entered previously for "PAR" will appear, as shown below.



If you reset the filtering dropdown to "AP1", no related metabolites will appear because none have been entered previously, as shown below.

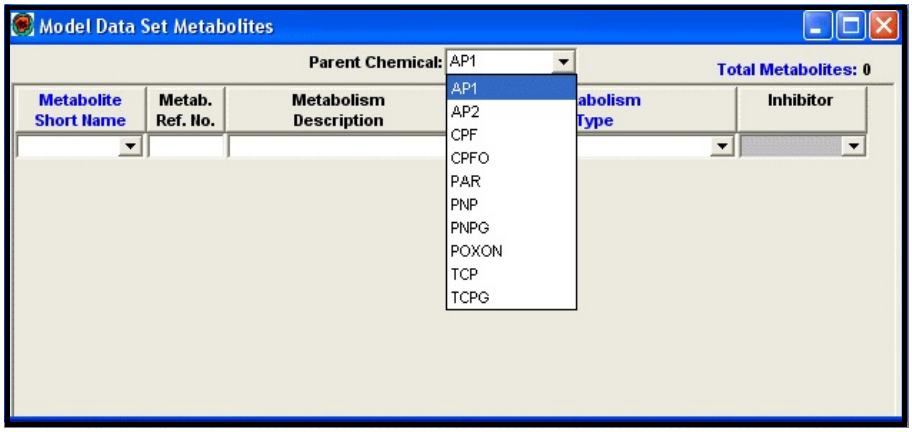


To view the metabolites that have been entered for any parent chemical:

1. **Click on the "Parent Chemical" field down arrow (or click in the field) to display the dropdown list, as shown below.**

2. **With the dropdown list displayed, use the up and down arrow keys to highlight a selection.**

   The window display will change to show the related metabolite rows.



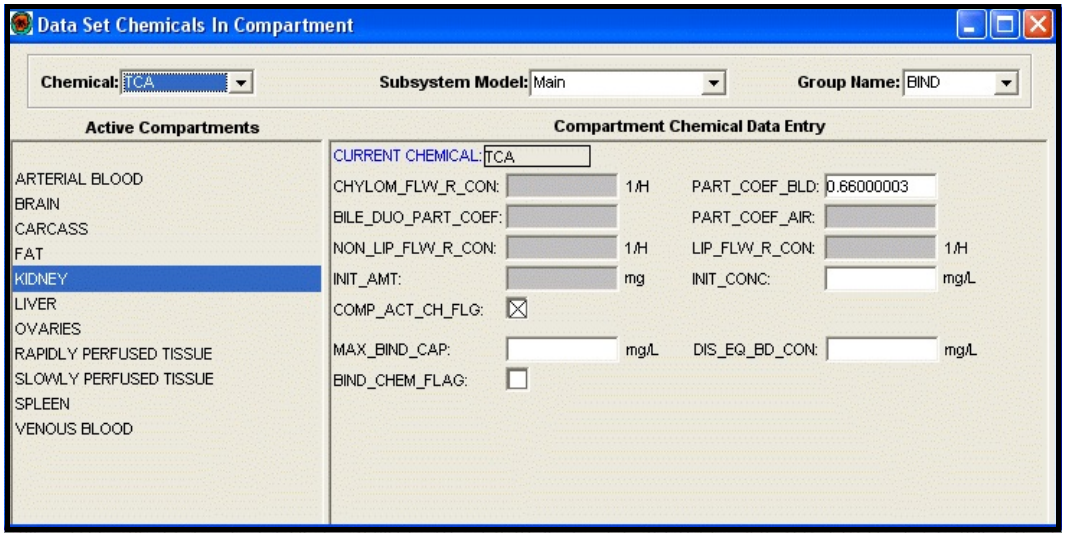
3.7.3 Filtering Dropdowns and Reference Data Lists

Filtering dropdowns can be used in conjunction with reference data lists to filter extremely complex sets of data lines/records.

To see how this feature works, do the following steps -- starting from the "Main" menu:

1. **Select "Chemical Compartments."**

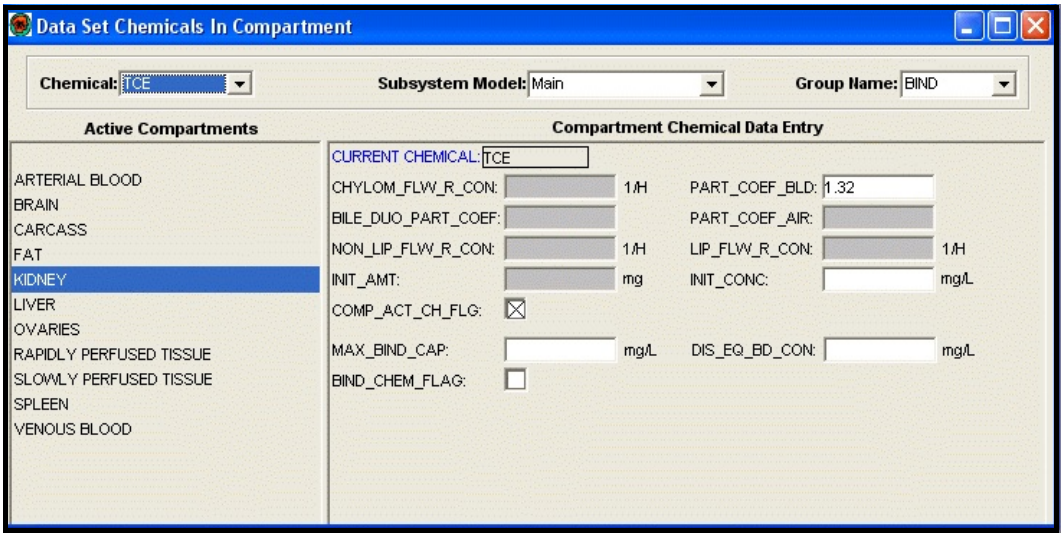
2. **Select "Data Set Chemicals in Compartment."**
   The "Data Set Chemicals in Compartment" window will appear, as shown below.



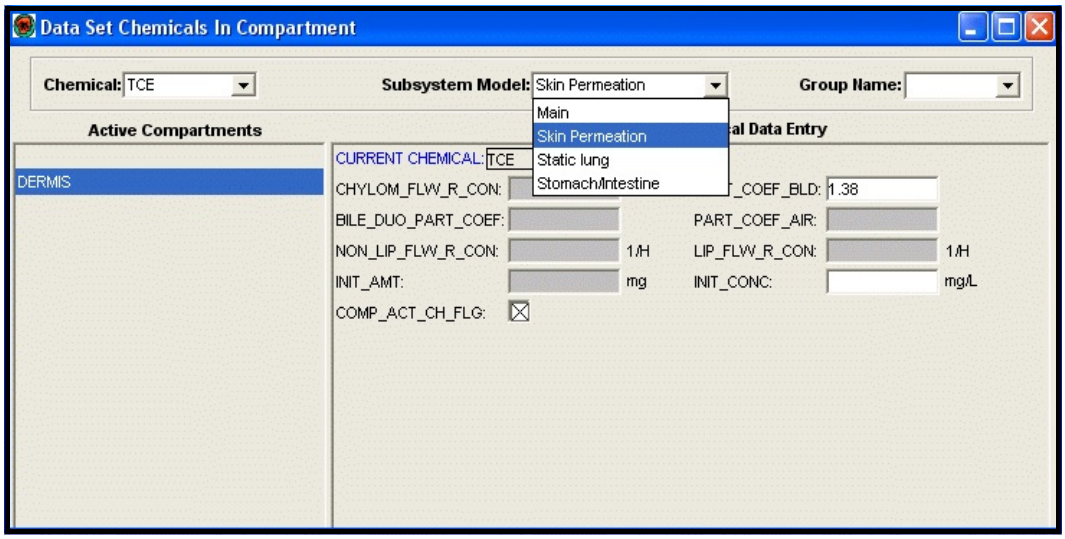
The portion of the window called "Active Compartments" contain an example of a Data List. Data lists, which are used only for reference information or for filtering purposes, cannot be edited. Data lists will be considered in more detail presently.

In the example above, "TCA" is the chemical selected in the "Chemical" field, and "KIDNEY" is selected in the "Active Compartments" section. For these selections, the tissue to venous blood kidney partition coefficient ("PART_COEF_BLD") field value is 0.66000003.

If a different chemical (e.g., "TCE") is selected in the "Chemical field" and "KIDNEY" is selected in the "Active Compartments" section, the value in the "PART_COEF_BLD" field will change accordingly, as shown below.



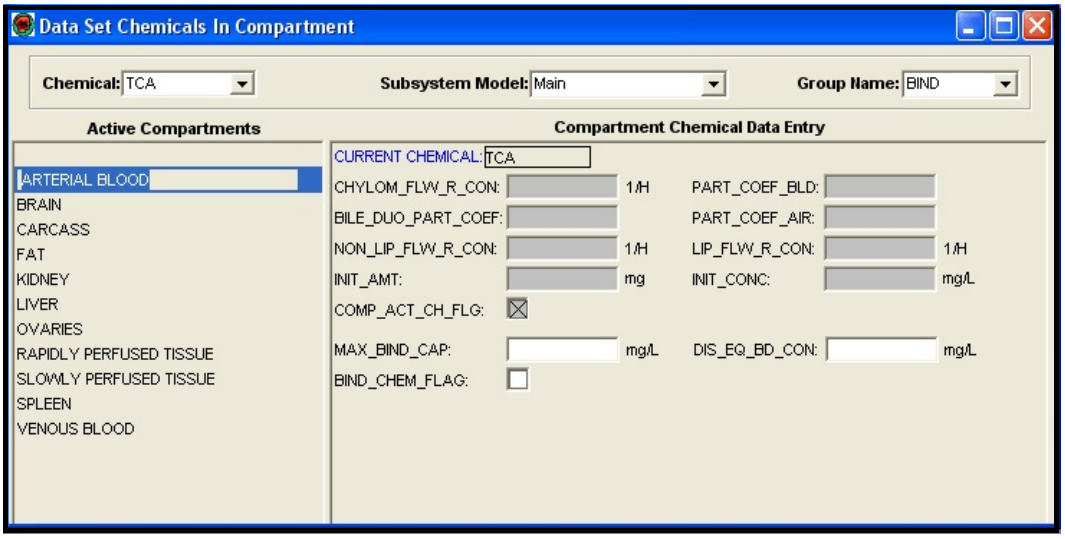
If you select a different "Subsystem Model," the information in the "Active Compartments" and "Compartment Chemical Data Entry" portions of the window changes, as shown below.



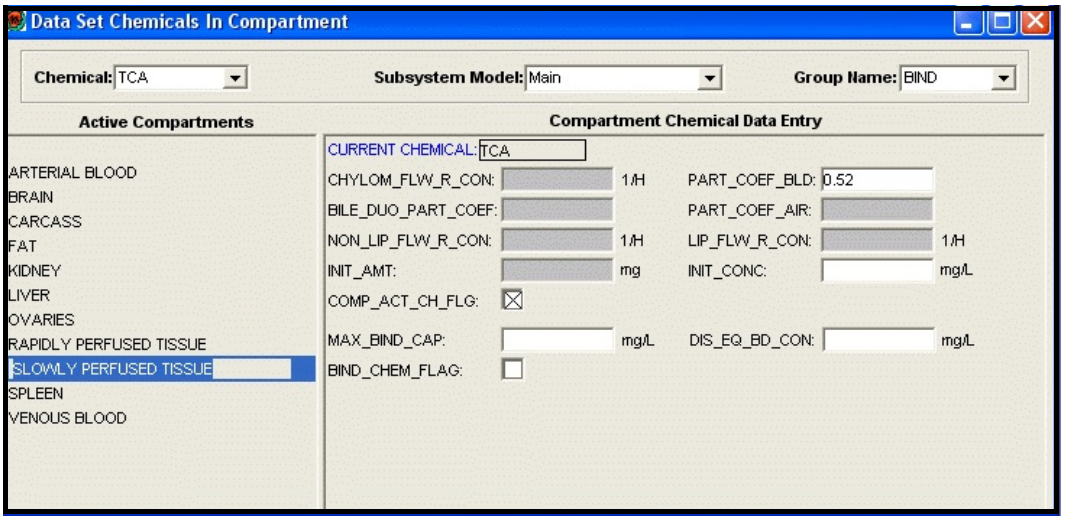
3.7.4 Reference Data Lists

Data lists contain static, non-editable reference information used to display, and sometimes filter, data lines/records.

In the "Data Set Chemicals in Compartment" window (accessed from the "Chemical Compartments" submenu), click on an item in the "Active Compartments" list. Notice that the item name appears in reverse video, with an open area extending to the right of the area of reverse video, as shown below.



Use the up and down arrow keys to view other items in this list. Note that the content and the availability of fields in the "Compartment Chemical Data Entry" portion of the window change as you select different active compartments, as shown at the top of the following page.

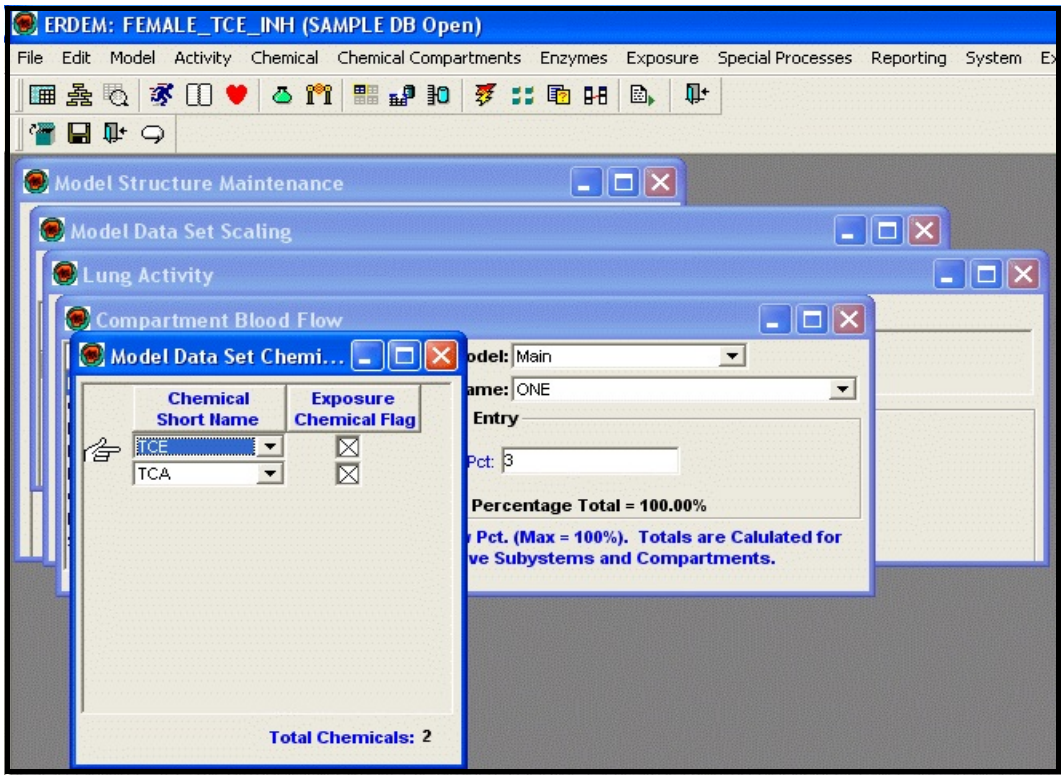


These examples show how the same window can be used to enter, view, and filter large amounts of data in manageable pieces.

3.8 Switching Between Model Data Sets

The ERDEM Front End allows you to easily navigate between multiple sets of MDSs regardless of how many windows you have open or what window you are currently working with.

For example, you might have five windows open at one time. The current window is the one on top – with the brighter colored title bar – as shown below.

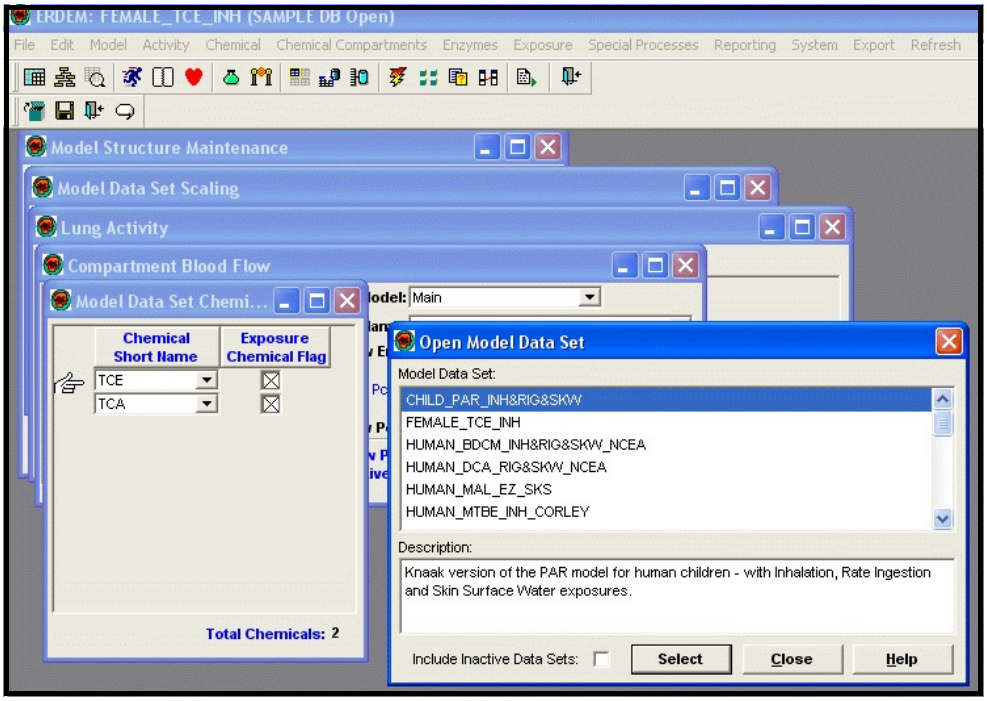


3.8.1 To Switch to Another MDS

From the "Main" Menu

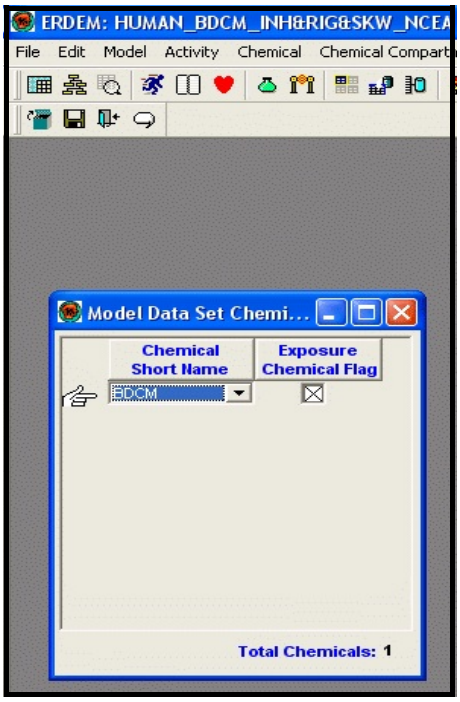
1. Select "File," then "Open Model Data Set".

The "Open Model Data Set" window will appear on top of the other windows, as shown below.



2. Choose the desired MDS, and then click on the "Select" button.

The back window closes and the new MDS information opens in the window that was active, as shown at right.



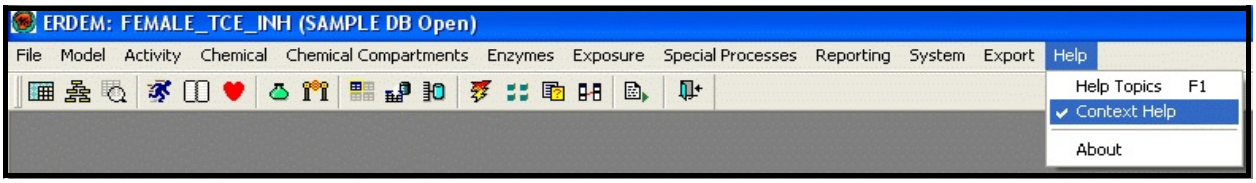
3.9 Using Context Help

On some windows, because of space limitations, data line/record fields must be abbreviated. The context-related help feature allows you to quickly see the definition for a particular field you may not be familiar with.

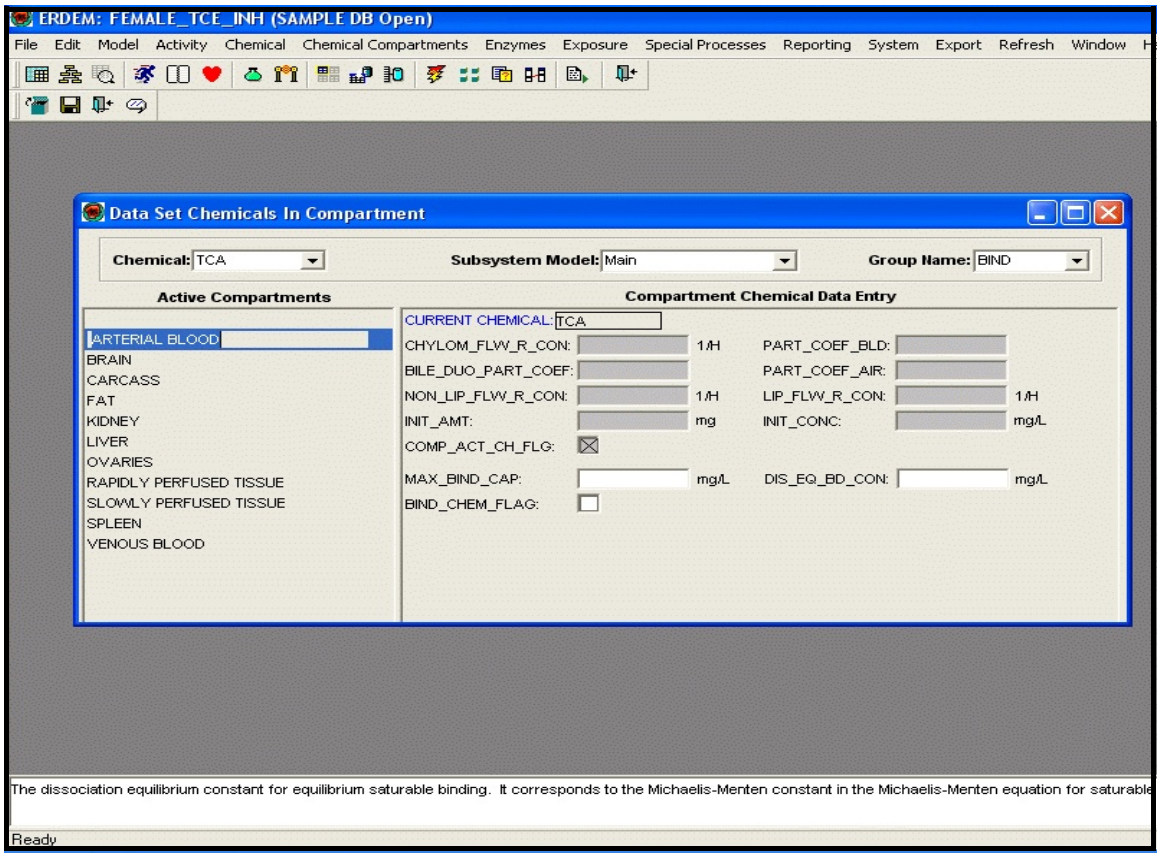
From the "Main" Menu

1. Select "Help," and then "Context Help."

A check mark will appear next to "Context Help" on the "Help" menu, as shown below.



When "Context Help" has been selected, a "Context Help" window will appear at the bottom of the screen, as shown below. The "Context Help" window displays information for whatever data entry field you place the mouse pointer over. In this example, the mouse pointer has been placed over the data entry field for "DIS_EQ_BD_CON," and an explanation of that field appears. If no help is available for a particular field, the message will read "Help is not available for this field or no field has been selected."



As long as it is selected, the "Context Help" window will appear at the bottom of all windows.

3.10 To Turn Off "Context Help"

1. Return to the "Main" menu.

2. Select "Help," then "Context Help."

Section 4

Exporting and Running a Model Data Set

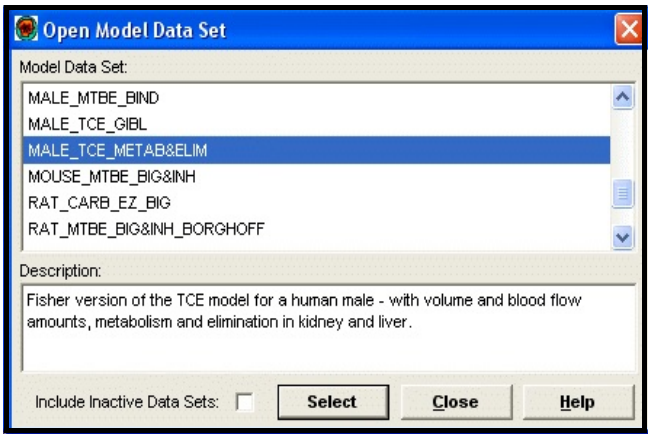
The ERDEM Front End converts your data into a command file format that can be exported to and run by the ACSL/Graphic Modeller (sic) software.

4.1 Preparing the Model Data Set for Export

From the "Main" Menu

1. Select "File," then "Open Model Data Set."

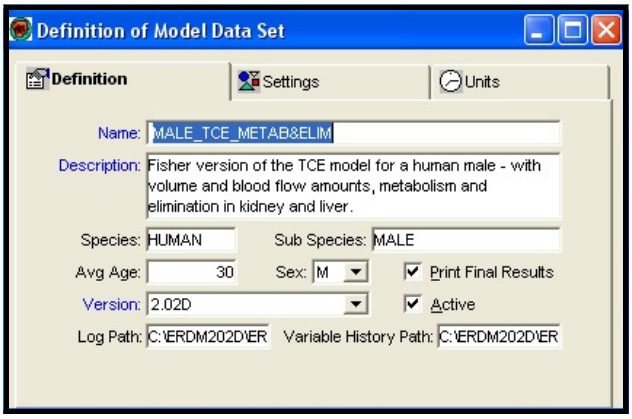
2. Highlight the MDS called "MALE_TCE_METAB&ELIM," then press the "Select" button, as shown at right.



From the "Main" Menu

3. Select "Model," then "Model Data Set Definition."

The "Definition of Model Data Set" window will appear with "MALE_TCE_METAB&ELIM" as the current MDS, as shown at right.



On the "Definition of Model Data Set" window, the "Log Path" and "Variable History Path" should be automatically filled in to match the path where the ERDEM Model was installed. No further action is required.

Note: In the example shown here and on the following pages, the Log Path and Variable History Path were C:\ERDM202D\ERDM202D.log and

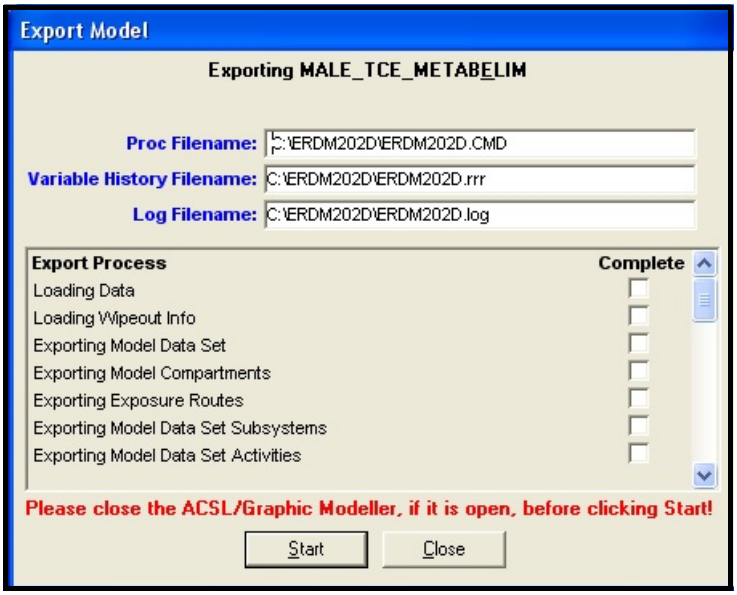
C:\ERDM202D\ERDM202D.rrr, respectively. They may be different for your particular version of the software.

4.2 Exporting the Model Data Set from the ERDEM Database

From the "Main" Menu

1. Select "Export," then "Run Model," as shown below.

The "Export Model" window will appear, as shown below.



Notice the warning above the "Start" and "Close" buttons. If your "ACSL/Graphic Modeller" is open and "Load ACSL" has been selected, the export will experience a file generation conflict until you have closed the Modeller. It is therefore recommended that you close your "ACSL/Graphic Modeller" before proceeding.

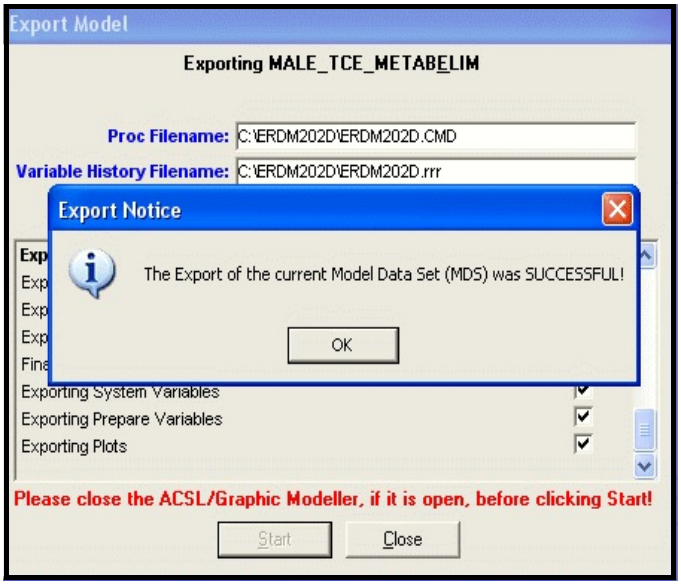
From the "Export Model" Window

2. Set the "Proc Filename" to "C:\ERDM202D\ERDM202D.CMD".

When the Export is completed, the .cmd file will contain the exported current MDS that was entered and saved in the ERDEM Front End database, with the MDS parameters specifically formatted to run in the ERDEM Model.

3. Click on the "Start" button.

As each Export Process is running, the word "processing" appears to the right of the process name. When a process is complete, a check mark will appear in its "Complete" box. When all processes are complete, an "Export Notice" message box will appear informing you that the export was successful, as shown below.



4. Click on the "Export Notice" message box "OK" button.

5. Close the "Export Model" window.

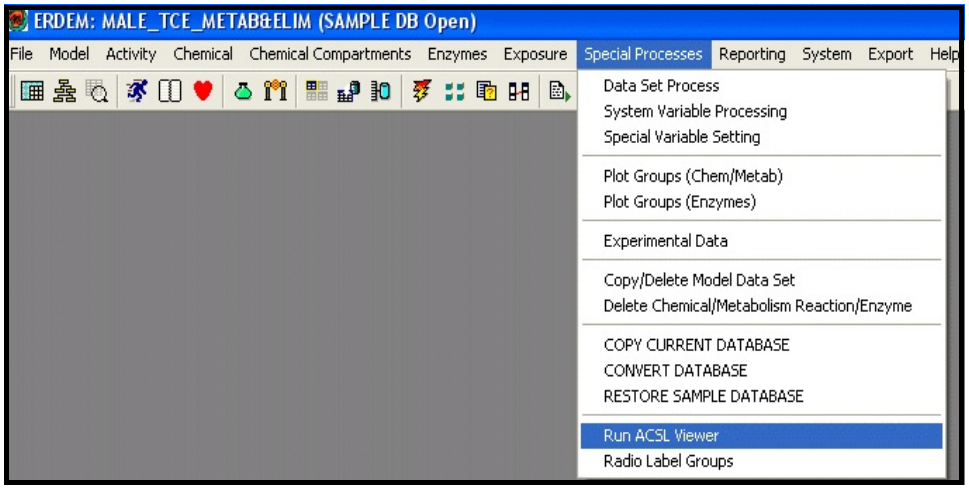
Section 5

Starting the ACSL Viewer and Running the ERDEM Model

5.1 Starting the ACSL Viewer

From the "Main" Menu

1. Select "Special Processes," then "Run ACSL Viewer," as shown below.

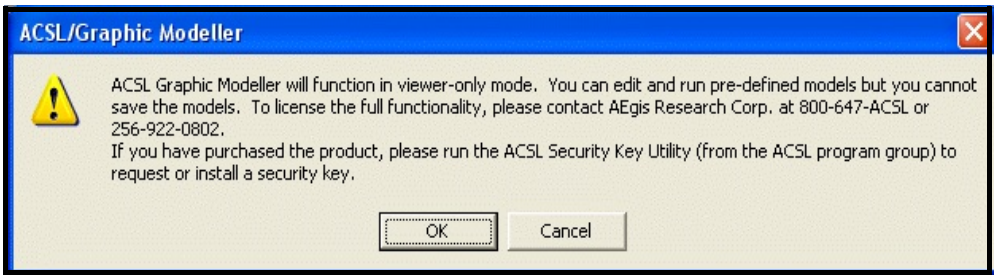


A "Run ACSL Viewer" window will appear, as shown at right.

2. Set the "Default Path" to match the path where the ACSL Viewer was installed, as shown at right.

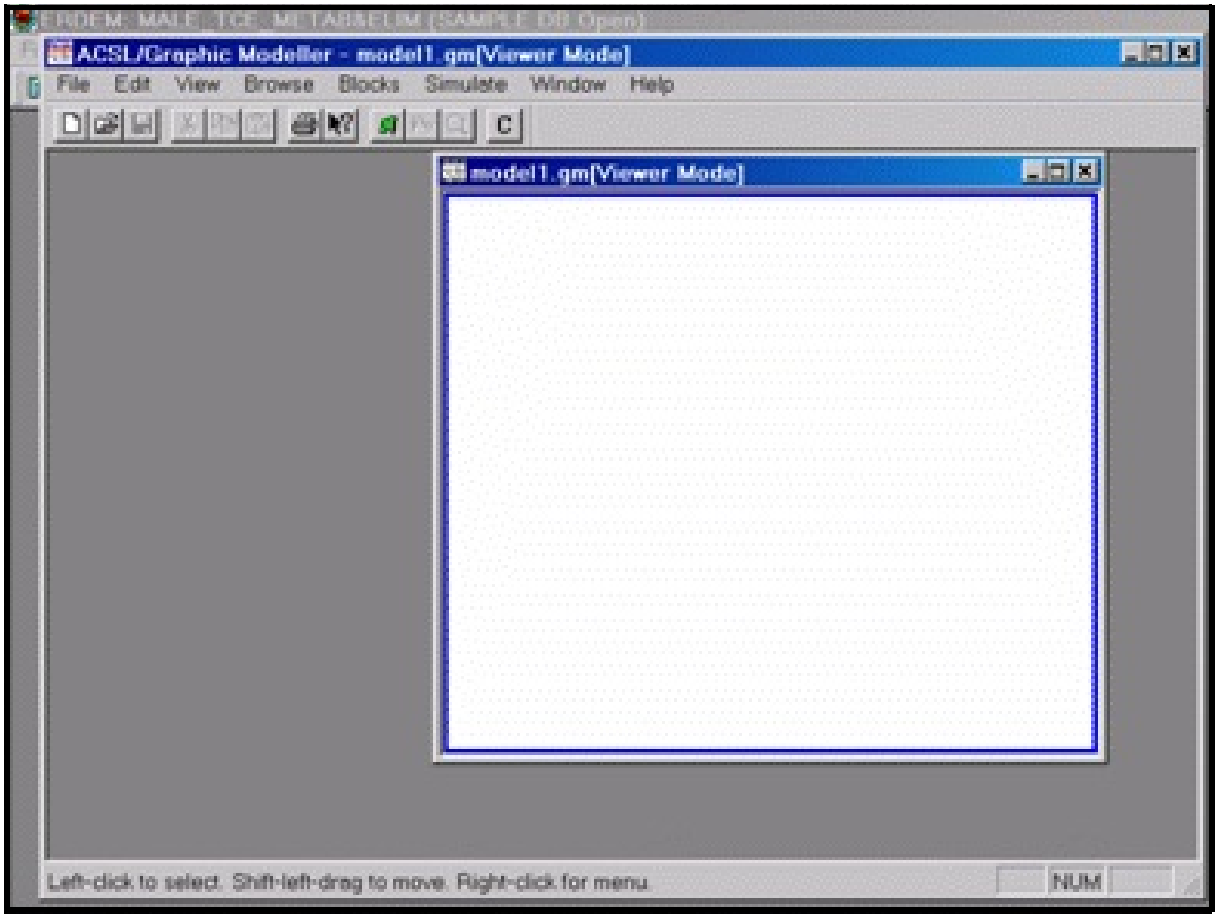
3. Click on the "OK" button.

The "ACSL/Graphic Modeller" (sic) vendor window will appear, as shown on the top of the following page.



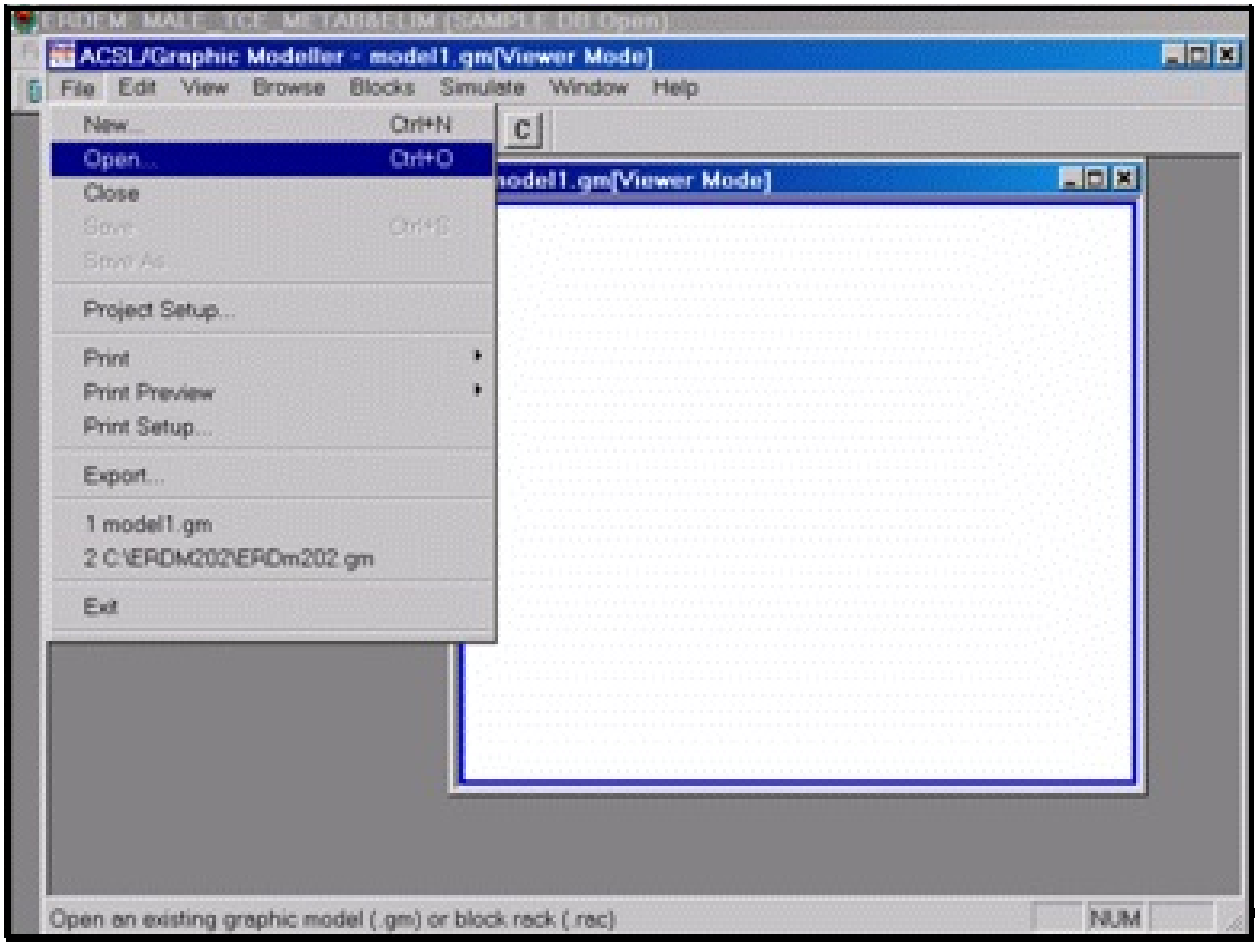
4. Click on the "OK" button for this and any other vendor windows that pop-up until the "ACSL/Graphic Modeller" window appears, showing an inner window called "model1.gm [Viewer Mode]," as shown below.

Note: If this is the first time the *ACSL/Graphic Modeller* has been run, the "Viewer Mode" window may appear minimized on the task bar. If so, click on it and it will open up (as shown below).

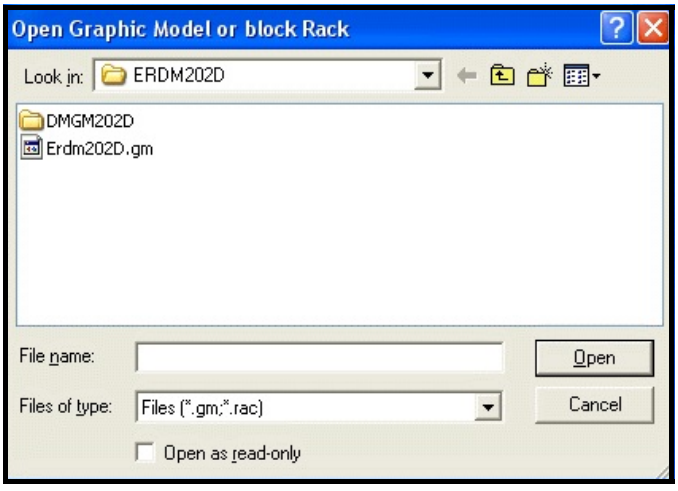


From the “ACSL/Graphic Modeller” Window

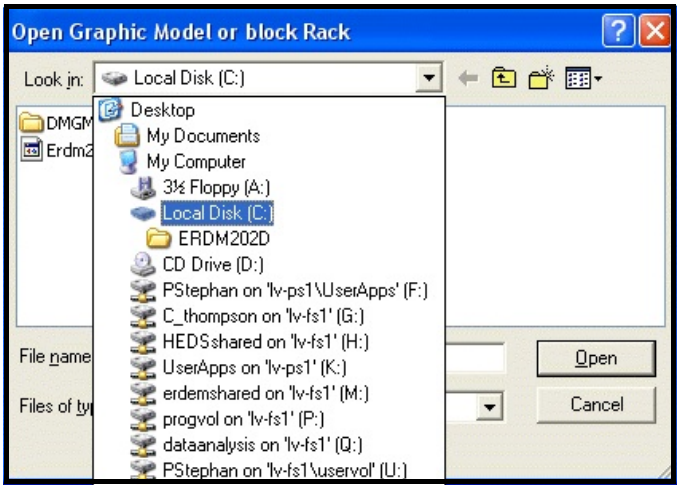
1. Select “File,” then “Open,” as shown below.



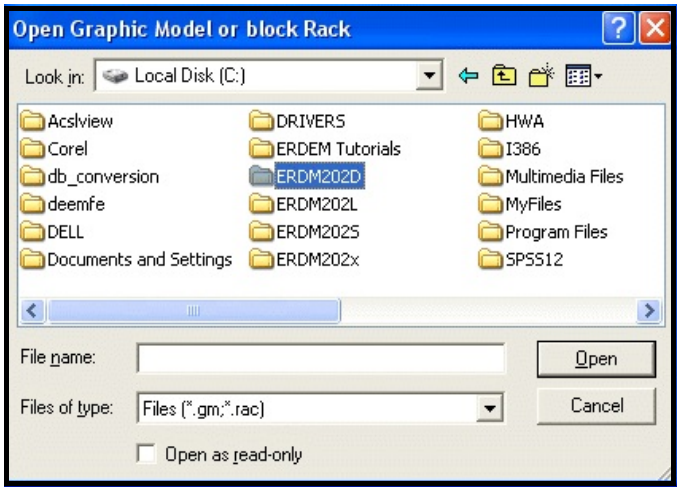
The “Open Graphic Model or block Rack” window will appear, as shown at right.



2. **Click on the down arrow in the "Look in" field (or click anywhere in the field). The directory list will appear, as shown below.**



3. **Select the drive where the software has been installed.**

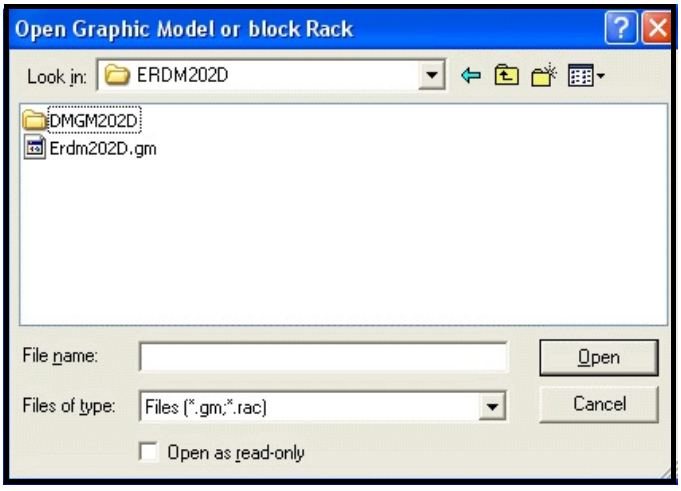


From the Directory That Appears

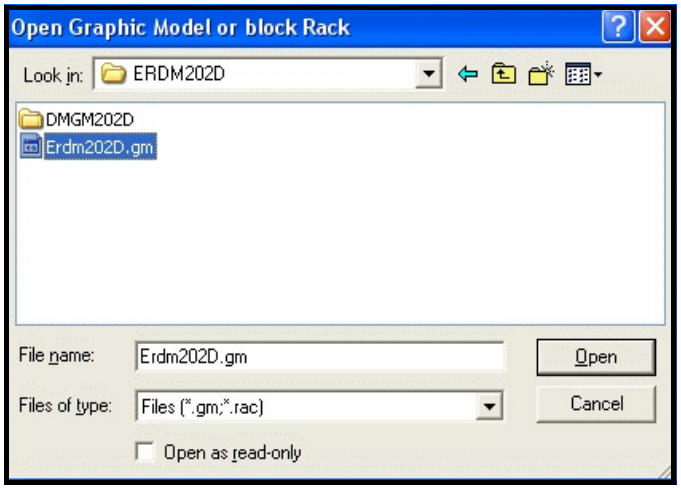
4. **Choose the version you selected in the "Definition of Model Data Set" window (see Section 3.3). (In this case, highlight the file named "ERDM202D".)**

5. **Click on the "Open" button.**

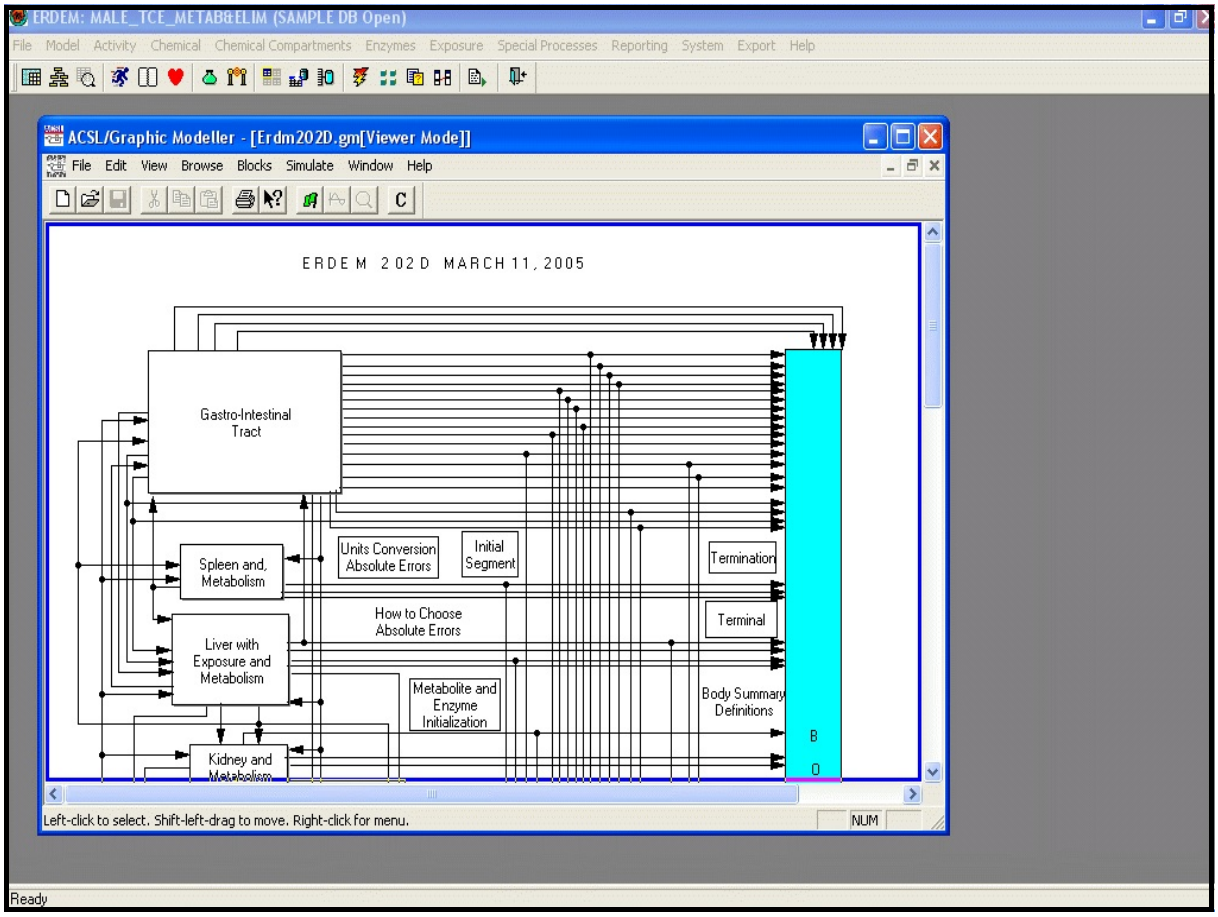
Files that are in the “ERDM202D” directory will appear, as shown below.



6. Select “Erdm202D.gm,” as shown below, then click on the “Open” button.

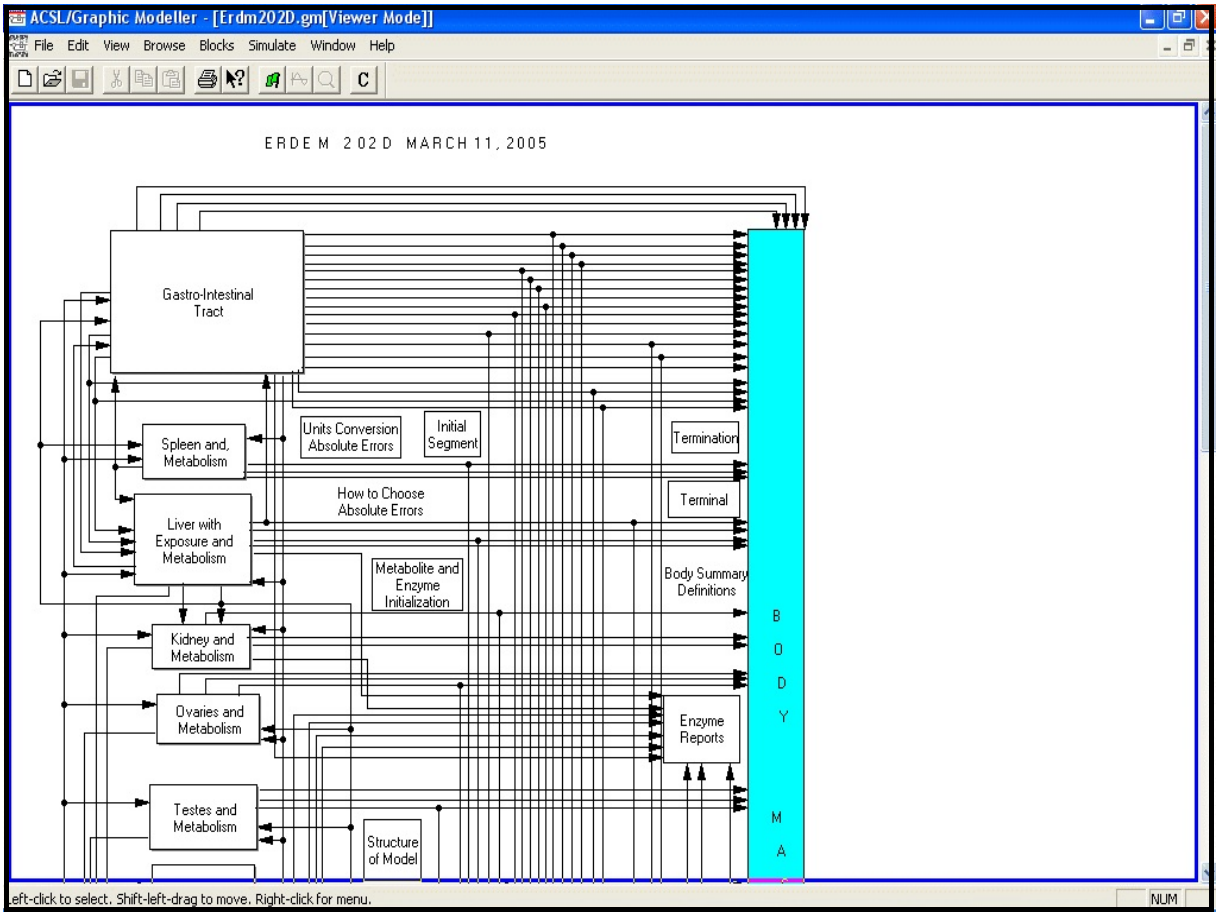


The “ACSL/Graphic Modeller - [Erdm202D.gm [Viewer Mode]]” window will appear, as shown at the top of the following page.

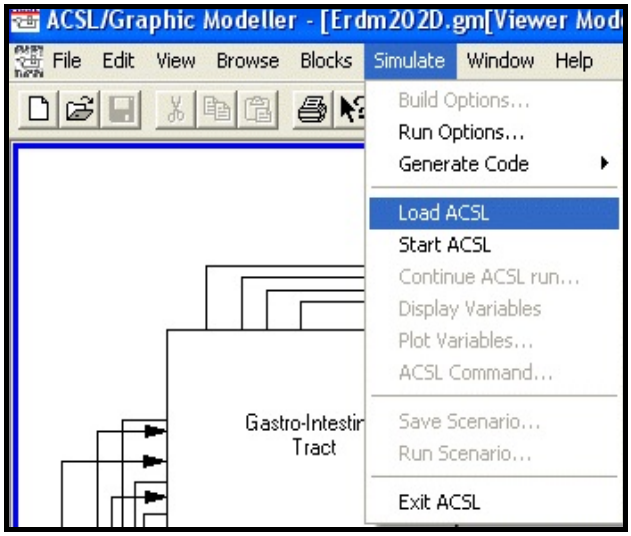


7. Maximize the "ACSL/Graphic Modeller - [Erdm202D.gm [Viewer Mode]]" window (click on the *Maximize* icon (the middle button at the top right corner of the window)).

This will give you a full-screen view of the ERDEM Model, as shown at the top of the next page.



5.2 Running the Model



From the "ACSL/Graphic Modeller" Menu

1. Select "Simulate," then select "Load ACSL," as shown at right.

Two initialization messages will appear and disappear. Then the minimized *ACSL Run Time* icon will appear on the right end of the task bar (bottom of the screen), as shown below.

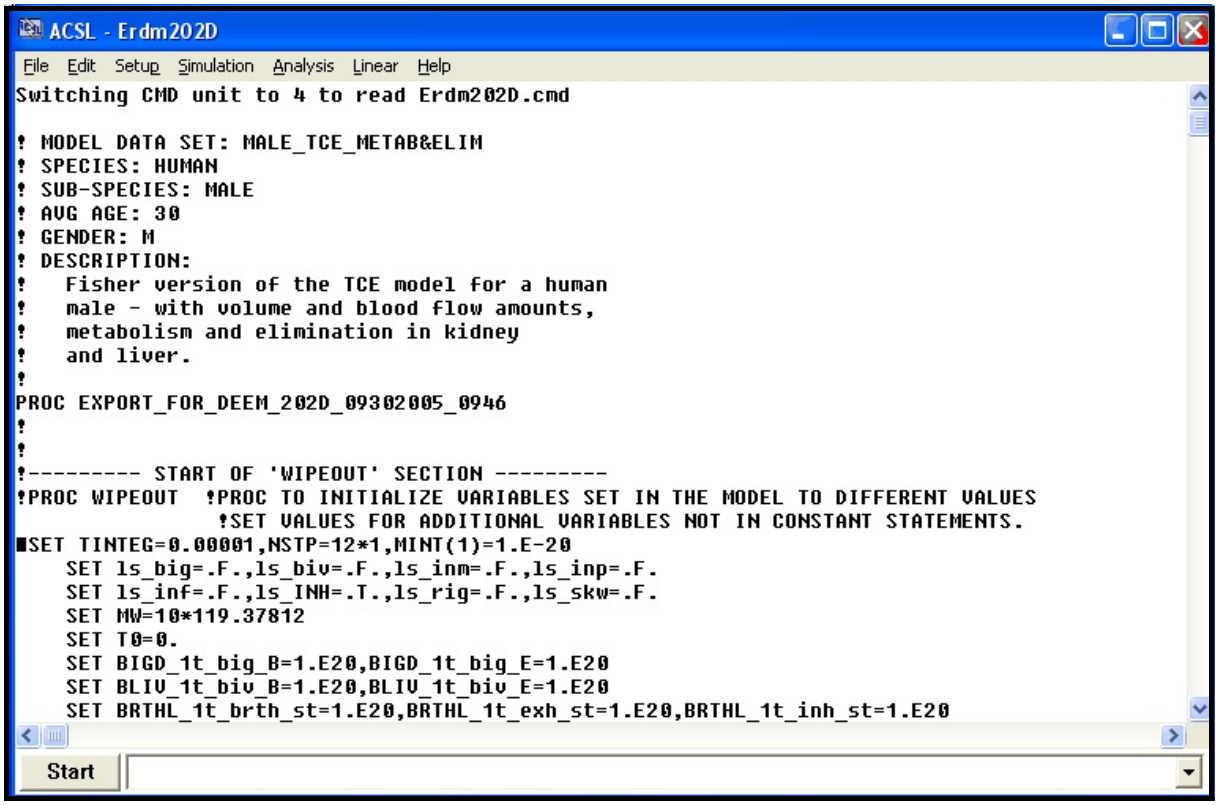
Below is an example of a minimized window from which ERDEM Model runs can be viewed.

To See the Results

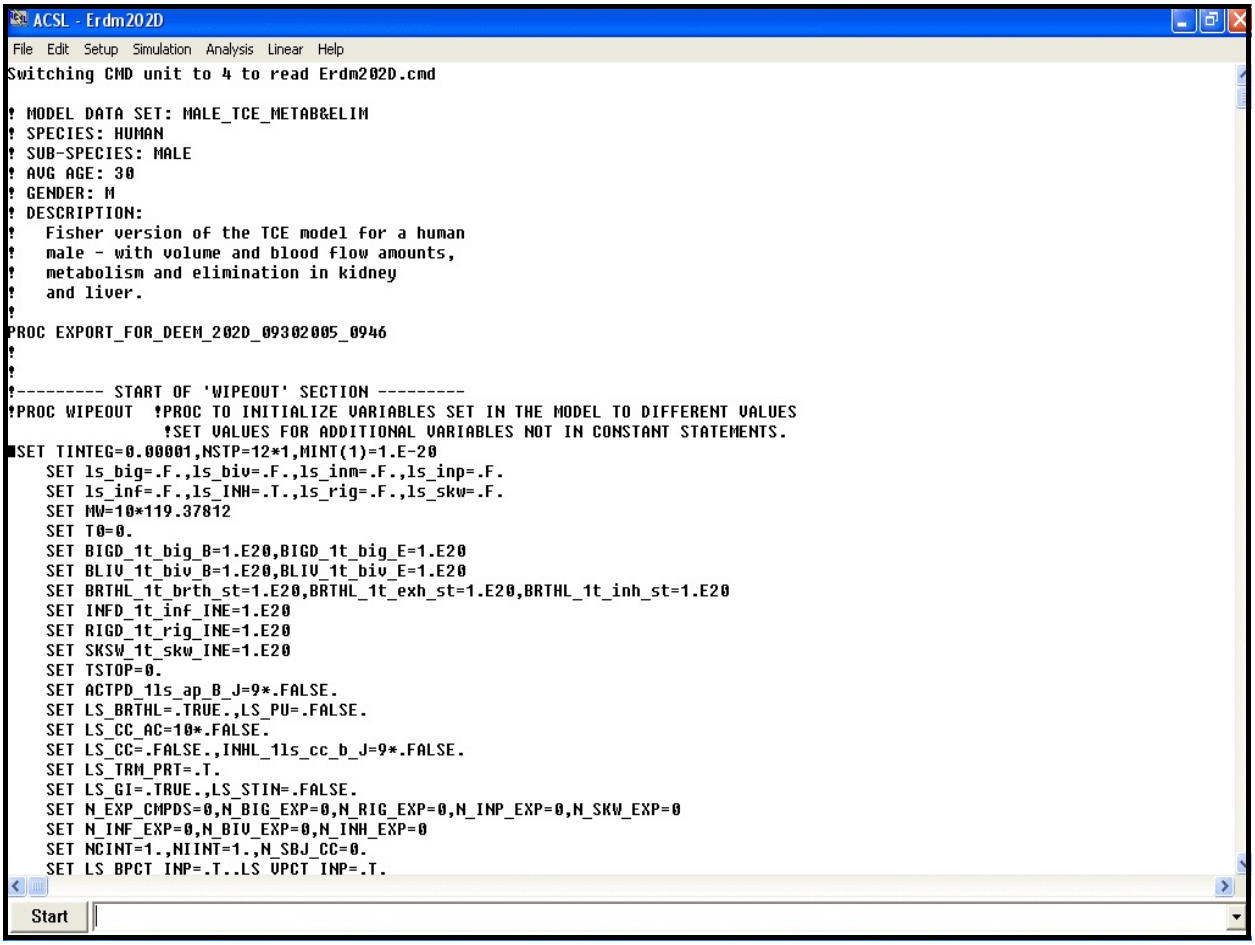
1. Click on the icon.

The results will appear, as shown below.

This window shows the beginning of the command (.cmd) file, the program that runs the model simulation.



You can maximize the window to enhance the view, as shown below.



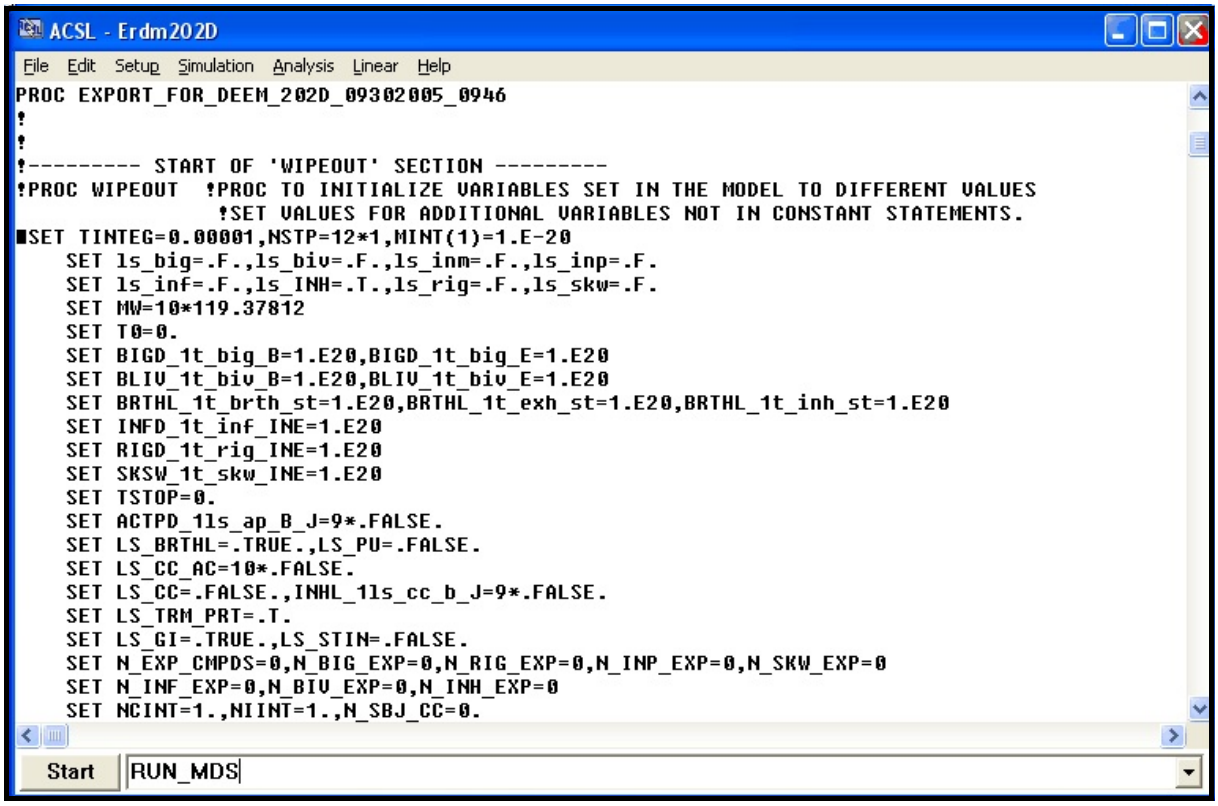
To Stop the Run

1. Click on the “Start” button.

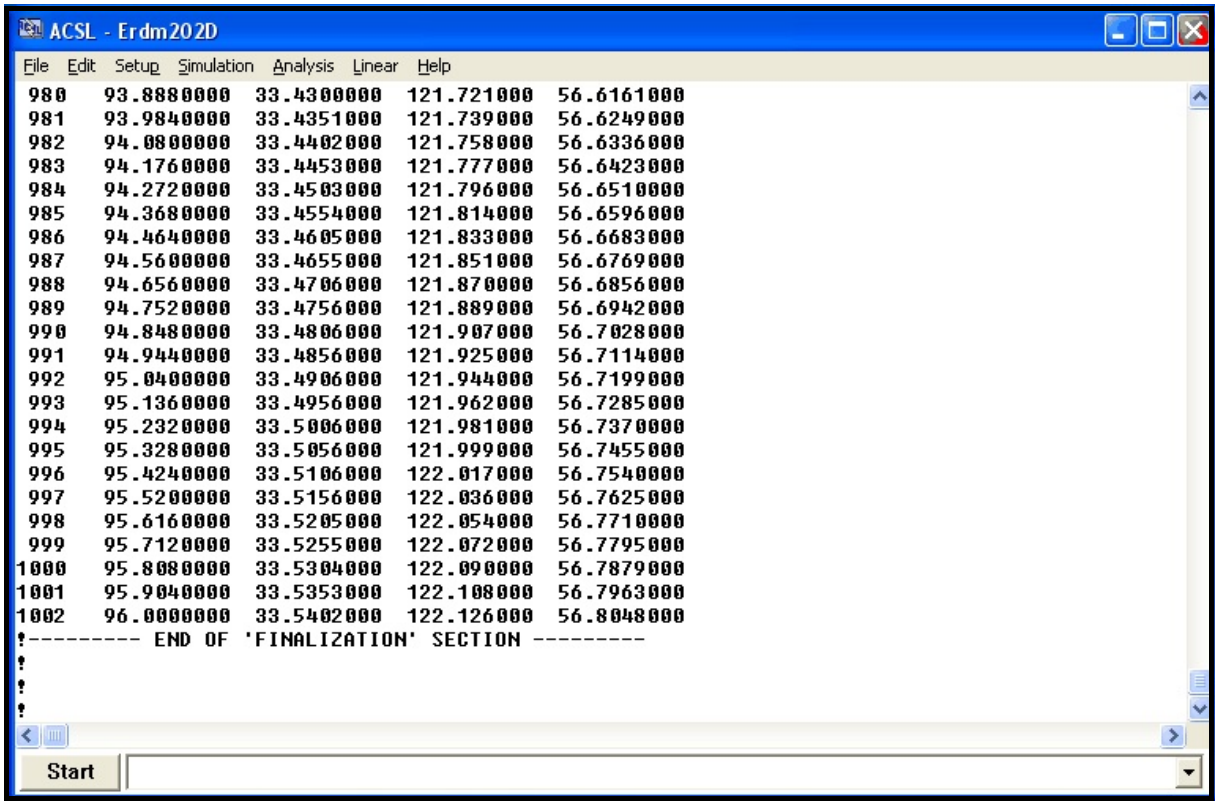
To Run the MDS

1. **Type in: "RUN_MDS" in the field next to the "Start" button (bottom of the window), as shown below.**

2. **Press the "Enter" key.**



The following window shows the .log file. The beginning of the file shows the OUTPUT variables that were previously requested, but not shown in this view. The file then shows the chemical analyses output results by default. At the end of the file, the PRINT variables you requested are displayed, as shown below. At the very end of the file are the words "END OF 'FINALIZATION' SECTION." This indicates that the simulation run for this MDS is complete.



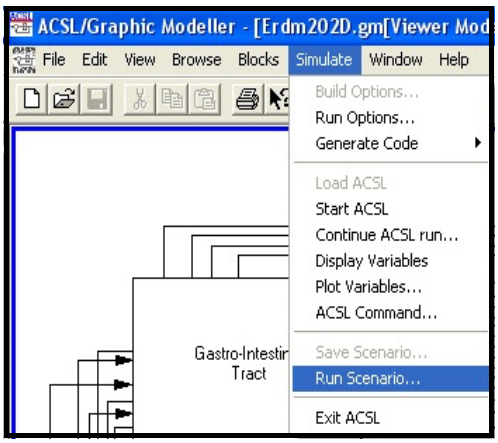
3. Minimize this window.

5.3 Specifying the Scenario

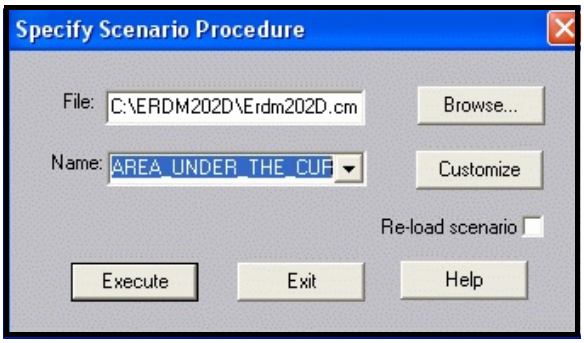
<u>To See Plots</u>

From the "ACSL/Graphic Modeller" menu:

1. Select "Simulate," then "Run Scenario," as shown at right.



The "Specify Scenario Procedure" window will appear, as shown at right.



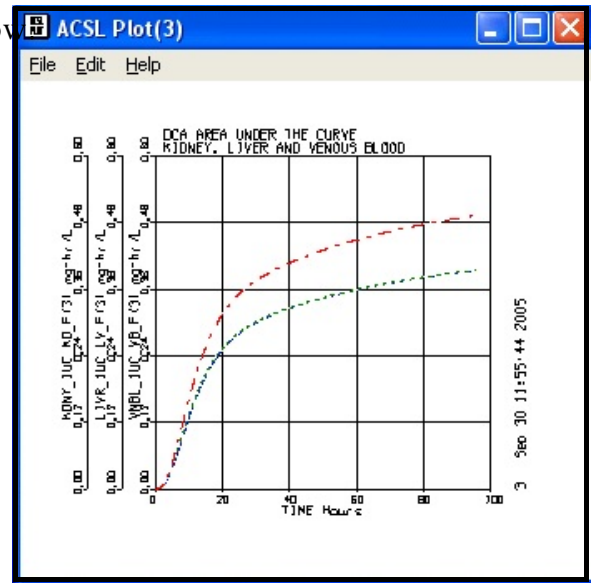
2. Select the desired scenario procedure from the "Name" list.

3. Click on the "Execute" button.

The plots are available for viewing in separate windows.

To view the plots, minimize the active window.

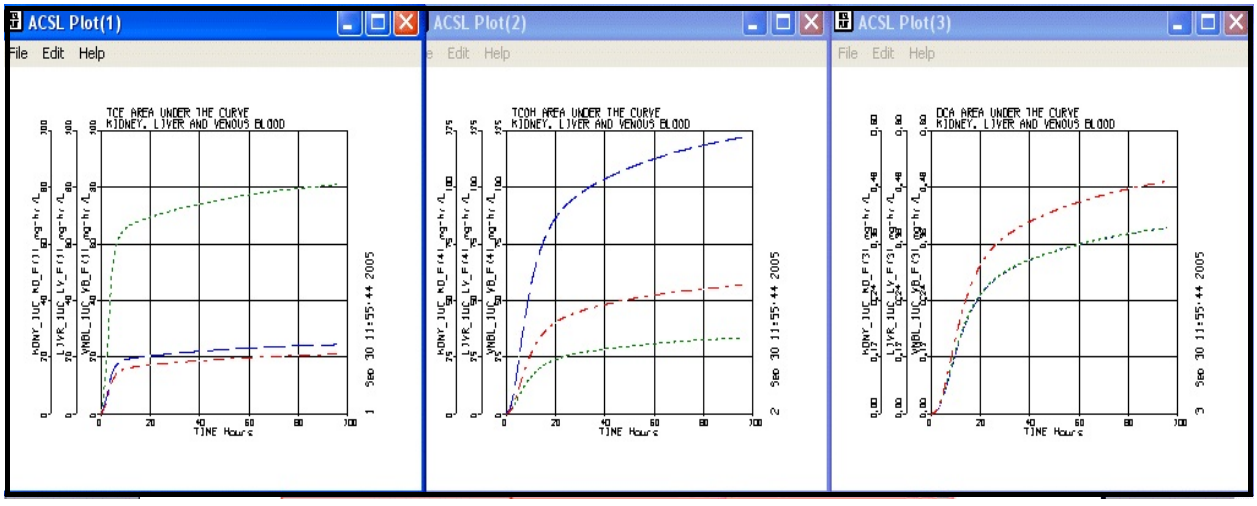
The plots will be "stacked" on top of each other, as shown at right.



To View the Plots Separately

1. Move their windows (click on the colored title bar, hold the mouse button down, and drag the window to another position).

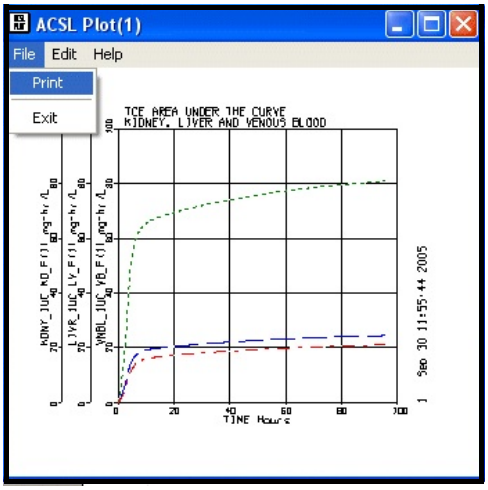
Separated plot windows are shown below. You can also minimize and maximize each plot window.



The plots are also available as minimized window icons on the task bar. In the illustration below, they are the last three to the far right in the lower row.

If you prefer, you can view the plots separately by clicking on the minimized icons.

Note: The plots do not automatically save. To have a record of a plot, you can do one of two things: print it, or save it as a bitmap.



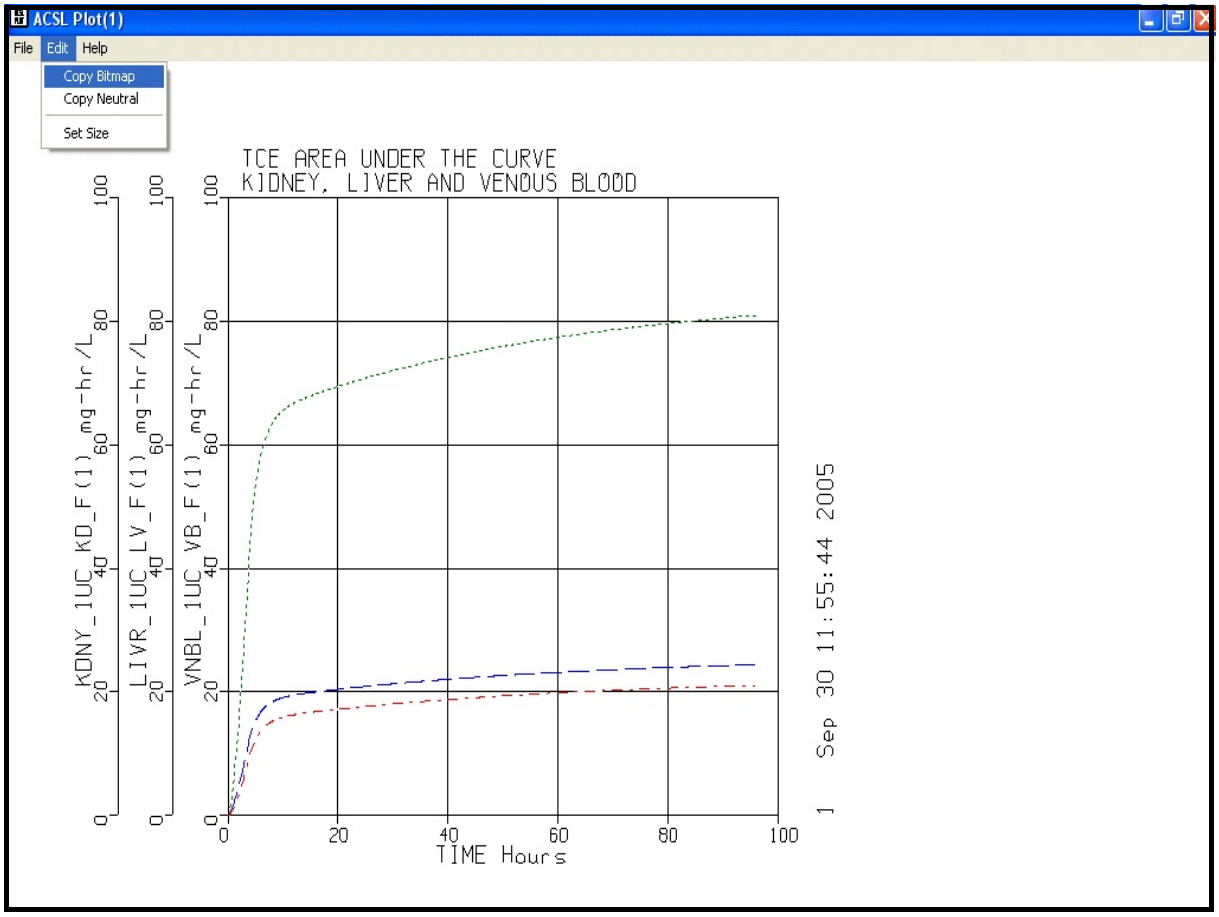
To Print a Plot

1. Select "File," then "Print" from the plot window's menu, as shown at right.

To Save a Plot

1. Maximize the plot window (to full screen).

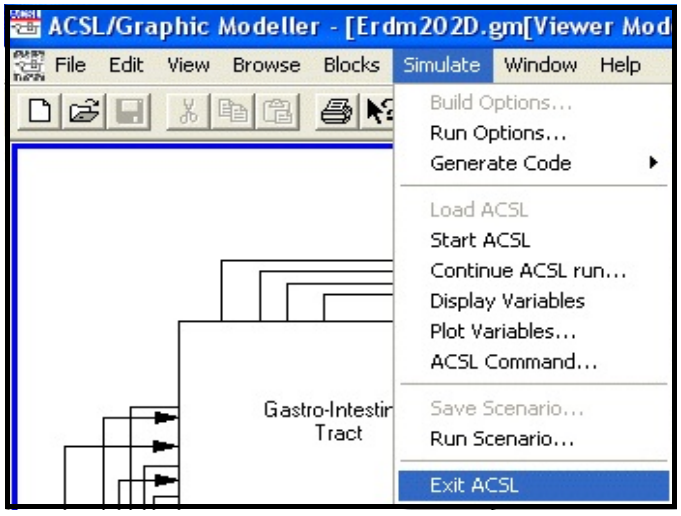
2. Click on "Edit," then "Copy Bitmap" (as shown below) and follow the prompts.



To View Additional Plots

1. **Go back to the beginning of subsection 5.3 and select a different scenario procedure.**

5.4 Exit ACSL



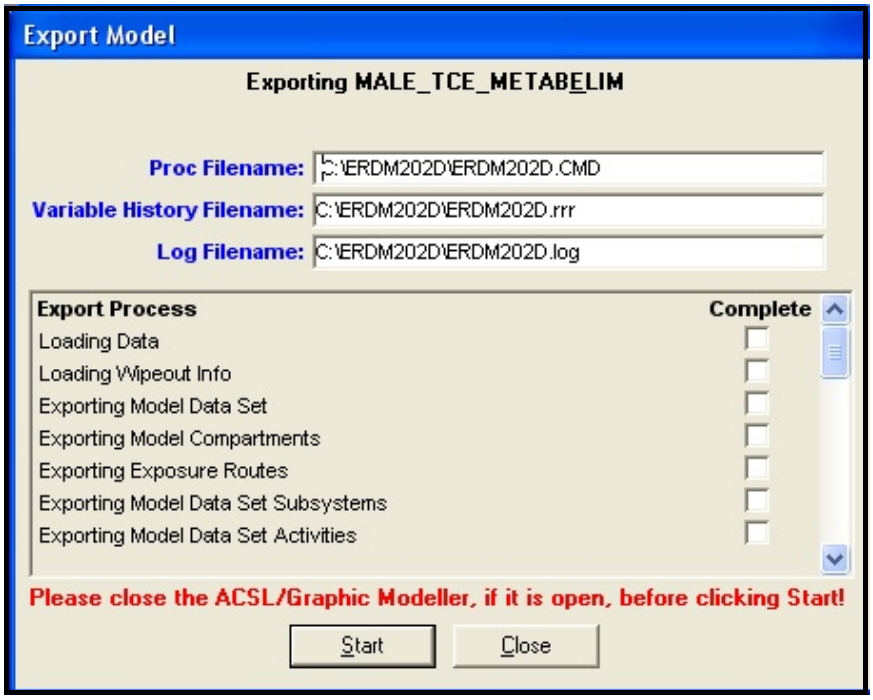
From the "ACSL/Graphic Modeller" Menu

1. **Select "Simulate," then "Exit ACSL," as shown at right.**

   This will close all ACSL windows. It also saves the ".log" file, a record of your MDS simulation run, in the location specified in the "Export Model" window, as previously

shown in subsection 5.2. In addition, it saves the ".CMD" and ".rrr" files identified in the "Export Model" window.

A view of the "Export Model" window, showing the file names, is shown below.



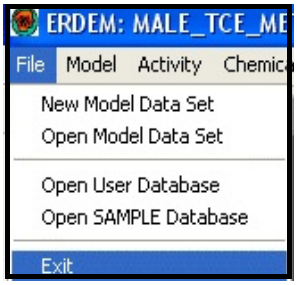
Note: The version used for this demonstration was "ERDEM202D." By default, subsequent model runs using version "ERDM202D" will be saved to the same directory and use the same three file names shown above. If you wish to keep the files from the previous model run, it is recommended that you copy the three files to a different directory and rename them for identification.

5.5 Exit ACSL/Graphic Modeller

1. Select "File," then "Exit" from the menu, *or* click on the red and white "x" at the top right corner of the window.

5.6 Exit ERDEM Front End

1. Select "File," then "Exit," as shown at right, or click on the red and white "x" located at the top right corner of the window.



Section 6

Descriptions of
Exposure Related Dose Estimating Model (ERDEM)

Exposure occurs at the boundary of the body or test system. It is of considerable interest to EPA to limit, reduce and, in specific instances, eliminate exposure. Humans become exposed to chemical and biological substances, physical energy and radiation through the activities they perform routinely in everyday life or occupationally as part of certain policies, practices or procedures. Exposure can occur accidentally as a random event, or during an occupationally related task or as a result of a purposeful action such as a (terrorist) attack.

Humans may become incidentally and unknowingly exposed. Exposure to particles and gasses in the air we breathe may be unavoidable. Dermal contact with surface residues may be unforseen and unrecognizable. Ingestion of particles and residues in food may be unintended and unsuspected. Under certain conditions, exposure can be limited or reduced through education, managerial oversight, regulatory responsiveness, and use of proper personal protection devices (Ness, 1994).

Exposure events in time and space under certain recognizable exposure scenarios may be accomplished more easily for occupationally related exposures where policies, practices and procedures have been established than for those that occur randomly or incidentally. However, regardless of the nature of the exposure, exposure follows along recognized pathways, e.g., inhalation, ingestion, and dermal, and routes, respiratory, oral, and percutaneous.

ERDEM was designed to examine three pathways of exposure, inhalation, ingestion and dermal, and eight routes of entry into the *in silico* test system. Experimental pathways and routes of entry were included (subsection 6.1), along with what might be perceived as naturally occurring unscheduled or not experimentally controlled pathways and routes (subsection 6.2). This approach greatly enhanced the database to include laboratory animal and clinical studies in addition to environmental field studies. For example, enteral administration is represented by intraperitoneal injection (IP) of chemical into the GI tract via the Portal Blood (Liver for the Stomach/Intestine Gastro-Intestinal model).

6.1 Experimental Pathways and Routes of Entry

6.1.1 Intraperitoneal Injection

Intraperitoneal Injections (IP) into the Portal Blood may be given for multiple chemicals for up to nine scenarios starting at time T_{INP_j}, and repeated at the inteT_{INPIT_j}. The amount of chemical to be injected is calculated from the concentration of the chemical times the Body Volume. The amount injected decreases at an exponential rate. All injections start before the simulation start time (T_0). When the scheduled event occurs to start the injection, the amount is calculated as:

$$A_{INP,I_{i,j}} = A_{INPCUR,I_{i,j}} + C_{INP,I_{i,j}} V_B \,, \tag{1}$$

where $A_{INP,CUR,I_{i,j}}$ is the amount remaining to be absorbed from the previous interval. The amount of the ith chemical from the jth exposure remaining to be absorbed is:

$$A_{INP,CUR,J_{i,j}} = A_{INP,J_{i,j}} e^{-MIN(K_{INP,ABS,J_{i,j}} \Delta T, K_{INP,LIM_i})} \tag{2}$$

where, $\Delta T = T - T_{INP,STL,J_j}$, T_{INP,STL,J_j} is the start time for the last IP Injection for th exposure, and MIN is the minimum of the two terms. The amount of the ith chemical remaining to be absorbed for all exposures is:

$$A_{INP,CUR_i} = \sum_{j=1}^{N_{INP,EXP}} A_{INP,CUR,J_{i,j}} \tag{3}$$

and the rate of change of the amount of chemical injected into the Portal Blood is given by:

$$\frac{dA_{INP_i}}{dt} = \sum_{j=1}^{N_{INP,EXP}} K_{INP,ABS,J_{i,j}} A_{INP,CUR,J_{i,j}} \tag{4}$$

At the start of the next injection interval, the IP amount remaining to be absorbed is accumulated for each chemical; the elapsed IP simulation time is reset to zero, and the next injection occurrence is scheduled.

6.1.2 Intramuscular Injection

Parenteral administration is represented by intramuscular injection (IM) in the muscle (Slowly Perfused Tissue). Intramuscular Injections may be given for multiple chemicals

and up to nine scenarios starting at time T_{INM_j}, and repeat at the interT_{INM,TT_j}. The amount of chemical to be injected is calculated from the concentration of the chemical times the Body Volume. The amount injected decreases at an exponential rate. All injections that start before the simulation start time (T_0) and before the simulation end time are scheduled. When the scheduled event occurs, to start the injection the amount is calculated as:

$$A_{INM,J_{i,j}} = A_{INM,CUR,J_{i,j}} + C_{INM,J_{i,j}} V_B. \quad \textbf{(5)}$$

where $A_{INM,CUR,J_{i,j}}$ is the amount remaining to be absorbed from the previous interval. The amount of the ith chemical from the jth exposure remaining to be absorbed is:

$$A_{INM,CUR,J_{i,j}} = A_{INM,J_{i,j}} e^{-MIN(K_{INM,ABS,J_{i,j}}\Delta T, K_{INM,LIM_i})} \quad \textbf{(6)}$$

where $\Delta T = T - T_{INM,STL,J_j}$, T_{INM,STL,J_j} is the start time for the last IM Injection for the jth exp and MIN is the minimum of the two terms. The amount of the ith chemical remaining to be absorbed for all exposures is:

$$A_{INM,CUR_i} = \sum_{j=1}^{N_{INM,EXP}} A_{INM,CUR,J_{i,j}} \quad \textbf{(7)}$$

and the rate of change of the amount of chemical injected into the Slowly Perfused Tissue (muscle) is given by:

$$\frac{dA_{INM_i}}{dt} = \sum_{i=1}^{N_{INM,EXP}} K_{INM,ABS,J_{i,j}} A_{INM,CUR,J_{i,j}} \quad \textbf{(8)}$$

At the start of the next injection interval, the IM amount remaining to be absorbed for each chemical is reset to zero and scheduled for the next injection occurrence.

6.1.3 Intravascular Administration

There are two forms of intravascular administration into the venous blood, Bolus Intravenous Injection or Infusion.

6.1.3.1 Infusion into the Venous Blood

Infusion is the direct insertion of chemical into the venous blood at time T_{INF_j} for a period of time, T_{INF,D_j}, which can be repeated at the interT_{INF,TT_j}. There can be many chemicals

in each infusion, each with its own concentration. The rate of change of the amount of the ith chemical infused into the venous blood versus time is given by:

$$\frac{dA_{INF,VB_i}}{dt} = \sum_{j=1}^{N_{INF}} C_{INF_{i,j}} Q_{INF_j} . \quad (9)$$

The flow rate, Q_{INF_j}, is independent of the chemical. There is one flow rate for each exposure. However, the concentration of the ith chemical in the jth exposure, $C_{INF_{i,j}}$, can be different for each chemical. The total amount of the ith chemical passed to the venous blood by Infusion is:

$$A_{INF,VB_{Ti}} = \int_{To}^{t} \frac{dA_{INF,VB_i}}{dt} dt. \quad (10)$$

6.1.3.2 Bolus Intravenous Injections

Bolus dose Intravenous (IV) Injections start at a given time, T_{BIV_j}, and may be repeated at an input interval, T_{RIG,TT_j}. Bolus dose Intravenous Injections (IVs) injected before simulation start time are not modeled. Those that occur at simulation start time (*T0*) are modeled as true bolus doses into the venous blood. The equation for the initial values for the amount of chemical in the Bolus IV Dose and in the venous blood are given by:

$$A_{BIV_{T0i}} = \sum_{j=1}^{N_{BIG}} A_{BIV_{i,j}} \quad (11)$$

$$A_{VB_{T0i}} = A_{BIV_{T0i}} \quad (12)$$

for the exposures that start at simulation start time. A bolus dose IV that occurs after the simulation start time is simulated with a rate input normally having a time duration of one-quarter of a communication interval or one-quarter of a maximum integration step, whichever is less. The equation for the jth exposure for the ith chemical then takes the form:

$$\frac{dA_{BIV_{i,j}}}{dt} = \frac{A_{BIV_{i,j}}}{T_{BIV_E} - T_{BIV_B}} \quad (13)$$

and for all exposures to the ith chemical at time t:

$$\frac{dA_{BIV_i}}{dt} = \sum_{j=1}^{N_{BIV}} \frac{dA_{BIV_{i,j}}}{dt}. \quad \textbf{(14)}$$

$$A_{BIV_{Ti}} = \int_{To}^{t} \frac{dA_{BIV_i}}{dt}\, dt + A_{BIV_{T0i}} \quad \textbf{(15)}$$

6.1.4 Inhalation Administration

There are two types of inhalation, Open or Closed Chamber Inhalation. Open Chamber Inhalation is assumed.

The subjects in each simulation are in a closed chamber or an open chamber. They cannot be mixed. If the simulation uses an open chamber then:

- If no exposure is defined then the simulation starts with an open chamber with no concentration of chemical.
- There is no change in the concentration of chemical in an open chamber due to exhaled air.
- If one or more open chamber exposures are defined and none are designated the starting exposure then exposure number one is the exposure starting the simulation.
- Any number of chemicals can have a concentration in an Open Chamber exposure.
- The simulation cannot switch in the middle from Open to Closed Chamber Inhalation.

If the simulation uses a closed chamber then:

- There must be a Closed Chamber exposure defined to start the simulation.
- Only one Closed Chamber exposure can be active at once.
- Any number of chemicals can be assigned a concentration for a Closed Chamber exposure.
- The chemicals in the exhaled air change the concentration of each chemical in the closed chamber.
- If Closed Chamber Inhalation is chosen then the whole simulation will be with a closed chamber.
- Open Chamber Inhalation can be approximated with an extremely large closed chamber.

The input concentration for an Open Chamber is in units of parts per million. The input for Closed Chamber Inhalation can be the amount (mass units), or the concentration (units of parts per million). The Open Chamber concentration for the ith chemical in mass per unit volume is calculated from:

$$C_{INH_i} = \sum_{j=1}^{N_{INH,EXP}} C_{AIR,J_{i,j}} C_{AIR,1PPM_i} \quad (16)$$

For Closed Chamber Inhalation the volume of the chamber is required. The volume of the air in the chamber is calculated by subtracting the volume of the number of subjects:

$$V_{CC,GAS_j} = V_{CC_j} - N_{SBJ} V_B \quad (17)$$

If the input into the Closed Chamber is a concentration then it is given in parts per million and converted to mass per unit volume units. But, if the input is an amount, then the amount is converted to concentration by:

$$C_{INH_i} = \frac{A_{CC,J_{i,j}}}{V_{CC,GAS_j}}. \quad (18)$$

There are two types of lung included in ERDEM, static lung and Breathing Lung. These compartments are described in subsections 7.1 and 7.2. The inhalation pathway involves entry through the Open or Closed Chamber static lung or the Breathing Lung.

6.2 Exposure for Bolus Ingestion, Rate Ingestion, Inhalation, and Skin Surface Exposures

Exposure time histories have been implemented in ERDEM for rate ingestion, open chamber Inhalation, and skin surface exposure, but not for bolus dose, or Closed Chamber Inhalation. There can be up to nine time histories for each exposure type (except for skin surface exposure which can have up to five exposures), but only one for each chemical. The time histories may be repeated periodically. Each time history will have a start time and duration interval. Any exposure can be expressed as an exposure time history.

Each exposure route has most of these variables:

- Concentration of chemical in a volume of food, water, or air (usually the dependent variable in a time history);

- Volume of the food, water or air;
- Flow rate - volume per unit time;
- Start time of exposure, duration of exposure, and interval between exposures.

If an exposure starts on or before the simulation start time, then the simulation starts with the exposure in effect. Otherwise, there is an event to start and one to terminate the exposure. There can be overlapping exposures of the same type in most cases (not for Closed Chamber Inhalation exposures). If the exposure is an exposure time history, then only one chemical can be modeled and there can be only one exposure time history of a particular type in any one simulation.

6.2.1 Ingestion Into the Stomach and the Stomach Lumen

If Rate ingestion input is a time history, then time and the amount per unit time (concentration times flow rate) of the chemical are provided. Linear interpolation is used to obtain intermediate values.

6.2.1.1 Bolus Dose Ingestion

Bolus dose ingestion occurs when chemical is taken into the Gastro-Intestinal tract very rapidly; for instance in one big bite or drink (there is no time history input). Bolus dose inputs that occur at simulation start time (T_0) are modeled as true bolus doses. The initial value for the integration in the stomach or stomach lumen is the sum of all exposures that start at simulation start time. The equation is:

$$A_{BIG_{T0i}} = A_{BIG_{T0i}} + \sum_{j=1}^{N_{Big}} C_{BIG_{i,j}} V_{BIG_j} \qquad \textbf{(19)}$$

for all exposures to the ith chemical at time T_0.

Bolus dose inputs with start time T_{BIG_j} that are greater than the simulation start time and before the simulation stop time are simulated by rate inputs that start at the scheduled bolus dose start time with a duration of ¼ of a communication interval, or ¼ of a maximum integration interval, whichever is less. The bolus dose for the jth exposure can be repeated at the input interval, T_{BIG,TT_j}. The approximation of a bolus dose input via a rate input of a relatively short duration produces results very similar to those achieved with an actual bolus dose while allowing a more accurate evaluation of amounts and concentrations via numerical integration. The equation for the jth exposure for the ith chemical then takes the form:

$$\frac{dA_{BIG_{i,j}}}{dt} = \frac{C_{BIG_{i,j}} V_{BIG_j}}{T_{BIG_E} - T_{BIG_B}} \quad (20)$$

and for all exposures to the ith chemical at time t:

$$\frac{dA_{BIG_i}}{dt} = \sum_{j=1}^{N_{BIG}} \frac{dA_{BIG_{i,j}}}{dt}. \quad (21)$$

The variable $A_{BIG_{T0i}}$ is the initial value in the numerical integrations for the total amount of the ith chemical in the bolus dose ingestion, and the amount in the stomach or stomach lumen:

$$A_{BIG_{Ti}} = \int_{To}^{t} \frac{dA_{BIG_i}}{dt} dt + A_{BIG_{T0i}} \quad (22)$$

6.2.1.2 Rate Ingestion

The Rate Ingestion (may be a time history input, see 6.2.1 above) for each exposure starts at a given time, T_{RIG_j}, occurs over a duration of tinT_{RIG,D_j}, and may be repeated at an input interval, T_{RIG,TT_j}. The concentration of the chemical in the food or drink and the flow rate are required inputs. The product results in the rate of change of chemical in the stomach or stomach lumen versus time. Overlapping exposures are allowed. The rate of change of the ith chemical in rate ingestion versus time is given by:

$$\frac{dA_{RIG_i}}{dt} = \sum_{j=1}^{N_{RIG}} C_{RIG_{i,j}} Q_{RIG_j}. \quad (23)$$

Thus there is one flow rate for each exposure. But the concentration of each chemical in the jth exposure may be different. The numerical integration to obtain the total amount of the ith chemical passed to the stomach by Rate Ingestion is:

$$A_{RIG,ST_{Ti}} = \int_{To}^{t} \frac{dA_{RIG_i}}{dt} dt + A_{RIG_{0i}} \quad (24)$$

6.2.2 Inhalation Exposure

If Inhalation exposure input is a time history then time and concentration in Parts Per Million (PPM) of chemical are input (conversion from other units may occur). Linear interpolation is used to obtain intermediate values. The inhalation pathway involves entry through the Open or Closed Chamber static lung or the Breathing Lung. These compartments are described in subsections 7.1 and 7.2.

6.2.3 Dermal Exposure

There are two types of dermal exposure modeled in ERDEM, one for chemicals in an aqueous vehicle, most often a water based diluent, and chemicals as a dried residue or adsorbed onto particles as a dry source.

6.2.3.1 Skin Surface Exposure to a Chemical in an Aqueous Vehicle

Skin Surface exposure due to chemical in an aqueous vehicle may be input as a time history of time, the surface area of the skin (square centimeters) that becomes exposed to the chemical, and the concentration (mass per unit volume) of the chemical in the vehicle. This concentration and area of the skin are used to compute the rate of change of the amount of chemical absorbed. Linear interpolation is used to obtain intermediate values. The skin surface is exposed to chemical in an aqueous vehicle (water) at time T_{SKW_j} for a period of time, T_{SKW,D_j}, which can be repeated at the intT_{SKW,TT_j}. Skin surface (water) exposures progress from a simulation start time and end at a scheduled termination time point. If a fixed scenario is used then the concentration of the ith chemical at the skin surface is found from summing the concentrations from each of the up to five exposure scenarios:

$$C_{SKS_i} = \sum_{j=1}^{N_{SKW,EXP}} C_{SKW,J_{i,j}} \qquad (25)$$

The rate of change of chemical in the epidermis due to the concentration C_{SKS_i} on the skin surface is given by:

$$\frac{dA_{SKW,DR_i}}{dt} = C_{SKS_i} K_{SKS,DR,PRM_i} A_{SK} \, . \qquad (26)$$

6.2.3.2 Skin Surface Exposure to Transfer from a Dry Surface

A chemical exists on a surface represented as a mass per unit area. It is transferred to the skin of a subject represented by a transfer coefficient. A short exposure period would represent a bolus.

The rate of change of chemical on the dermis due to a dry exposure is:

$$\frac{dA_{sks,ex_i}}{dt} = A_{surf_i} K_{sks,rt_i} \tag{27}$$

Integrating this equation gives the total applied dose.

The rate of loss of chemical from the skin surface due to evaporation is given by:

$$\frac{dA_{sks,ev_i}}{dt} = (1.0 - \delta_{wof})\, A_{sks_i} (\delta_{ev1} K_{sks,ev1_i} + \delta_{ev2} K_{sks,ev2_i}) \tag{28}$$

where δ_{wof} = 1 if a wash-off is in progress, and zero otherwise,

δ_{ev1} = 1 if the first evaporation rate constant is active, and zero otherwise,

δ_{ev2} = 1 if the second evaporation rate constant is active and zero otherwise.

The rate that the ith chemical moves from the skin surface into the dermis is given by:

$$\frac{dA_{sks,dr_i}}{dt} = K_{sks,dr,prm_i} A_{sk} C_{sks_i} \tag{29}$$

where

$$C_{sks_i} = \frac{A_{sks_i}}{V_{sk}} \tag{30}$$

If no wash-off is in progress, then the rate of change of the amount of the i^{th} chemical on the skin is given by the rate of application minus the rate of chemical moving into the dermis minus the rate of loss due to evaporation:

$$\frac{dA_{sks_i}}{dt} = \frac{dA_{sks,ex_i}}{dt} - \frac{dA_{sks,dr_i}}{dt} - \frac{dA_{sks,ev_i}}{dt}. \tag{31}$$

If a wash-off is in progress, then:

$$\frac{dA_{sks_i}}{dt} = -\frac{dA_{sks,wof_i}}{dt} \tag{32}$$

where the wash-off is scheduled at time t_{wof} for one time step, Δt, to remove all chemical on the dermis:

$$\frac{dA_{sks,wof_i}}{dt}(t_{wof}) = \frac{A_{sks_i}}{\Delta t}(t_{wof}). \quad \textbf{(33)}$$

6.3 Variable Definitions

Bolus Dose Ingestions

A_{BIG_i} = The amount of the ith chemical in all of the bolus dose Ingestions at time t,

$A_{BIG_{T0i}}$ = The total amount of the ith chemical in the bolus dose at simulation start time,

$C_{BIG_{i,j}}$ = The concentration of the ith chemical in the jth bolus dose,

N_{BIG} = The number of bolus dose Ingestion exposures,

T_{BIG_B} = The time that the bolus dose Ingestion starts,

T_{BIG_E} = The time that the bolus dose Ingestion ends, and

V_{BIG_j} = The volume of the jth bolus dose.

Rate Ingestions

A_{RIG0_i} = The initial value for the ith chemical in the Rate Ingestions,

$A_{RIG,ST_{Ti}}$ = The total amount of the ith chemical passing from Rate Ingestions to the Stomach at time t,

$C_{RIG_{i,j}}$ = The concentration of the ith chemical in the jth Rate Ingestion exposure,

$\frac{dA_{RIG_i}}{dt}$ = The rate of change of the ith chemical in the Rate Ingestions at time t,

N_{RIG} = The number of Rate Ingestion exposures, and

Q_{RIG_j} = The flow rate for the jth Rate Ingestion.

Infusions

$A_{INF,VB_{Ti}}$ = The total amount of the ith chemical in Infusions to venous blood at time t,

$\frac{dA_{INF,VB_i}}{dt}$ = The rate of change of the ith chemical in Infusions versus time at time t,

$C_{INF_{i,j}}$ = The concentration of the ith chemical in the jth Infusion,

Q_{INF_j} = The Infusion flow rate for the jth exposure.

Bolus Dose Intravenous Injection (Bolus IV)

$A_{BIV_{i,j}}$ = The amount of the ith chemical in the jth bolus dose IV,

$A_{BIV_{T0i}}$ = The total amount of the ith chemical in the bolus dose IV at simulation start time,

N_{BIV} = The number of bolus dose IV exposures,

T_{BIV_B} = The time that the bolus dose IV starts,

T_{BIV_E} = The time that the bolus dose IV ends.

Intraperitoneal Injection

$A_{INP,CUR,J_{i,j}}$ = The amount of the ith chemical remaining to be absorbed from the previous interval for the jth IP scenario,

$A_{INP,J_{i,j}}$ = The amount of the ith chemical currently in the IP Injection for the jth scenario,

A_{INP_i} = The amount of the ith chemical currently in the IP Injection,

$C_{INP,J_{i,j}}$ = The concentration of the ith chemical in the IP Injection for the jth scenario,

$\frac{dA_{INP_i}}{dt}$ = The rate of change of the amount of the ith chemical in the IP Injection,

$K_{INP,ABS,J_{i,j}}$ = The first order absorption rate constant for the jth set of IP Injections of the ith chemical,

K_{INP,LIM_i} = The factor to limit the minimum amount of the ith chemical from IP Injections remaining to be absorbed.

V_B = Volume of the Body of each subject.

Intramuscular Injection

$A_{INM,CUR,J_{i,j}}$ = The amount of the ith chemical remaining to be absorbed from the previous interval for the jth IM Injection scenario,

$A_{INM,J_{i,j}}$ = The amount of the ith chemical currently in the IM Injection for the jth scenario,

A_{INM_i} = The amount of the ith chemical currently in the IM Injection,

$C_{INM,J_{i,j}}$ = The concentration of the ith chemical in the IM Injection for the jth scenario,

$\frac{dA_{INM_i}}{dt}$ = The rate of change of the amount of the ith chemical in the IM Injection,

$K_{INM,ABS,J_{i,j}}$ = The first order absorption rate constant for the jth set of IM Injections and the ith chemical,

K_{INM,LIM_i} = The factor to limit the minimum amount of the ith chemical from IM Injections remaining to be absorbed.

Skin Surface Exposure (Water)

A_{SK} = Area of the skin covered by the solution containing the chemical,

$A_{SKW,DR}$ = The amount of the ith chemical that has moved from the skin surface to the Dermis,

$\frac{dA_{SKW,DR_i}}{dt}$ = The rate of change in the amount of the ith chemical moving from the skin surface to the Dermis,

C_{SKS} = The concentration of the ith chemical on the skin surface due to all overlapping exposures,

$C_{SKW,J_{i,j}}$ = The concentration of the ith chemical for the jth exposure on the skin surface,

K_{SKS,DR,PRM_i} = The permeation coefficient for the ith chemical from Skin Surface to Dermis,

Inhalation

$A_{CC,J_{i,j}}$ = The amount of the ith chemical in the jth Closed Chamber,

$C_{AIR,1\ PPM_i}$ = The concentration of ith chemical in air for one part per million at one atmosphere and 25°C. This is used to convert concentration in PPM to mass per unit volume.

$C_{AIR,J_{i,j}}$ = The concentration of the ith chemical in the jth exposure in parts per million.

C_{INH} = The concentration of the ith chemical in inhaled air, units of mass per unit volume.

N_{SBJ} = The number of subjects in the jth Closed Chamber,

V_{CC_j} = The volume of the Closed Chamber for the jth inhalation exposure,

V_{CC,GAS_i} = The volume of the gas in the chamber adjusted for the volume of the subjects.

Section 7

Descriptions of Absorption and Circulation in Model Compartments

ERDEM has the capacity to test spatial and temporal exposure scenarios involving multiple parent compounds, each with multiple metabolites, in a dynamic virtual biological "in silico" system. Individual or collective exposure may be punctuated over time with biological contact occurring randomly or episodically as a series of acute events or multiple chronic events where upon the exposure dose metric enters the "in silico" biological system through recognized portals of entry (U.S. EPA, 1992). Only the absorbed dose, as a portion of the exposure dose, is of interest toxicologically. Consideration of this relationship between exposure dose and absorbed dose begins at the physiological boundaries of exposure, the laryngeal-tracheal system (static or breathing lung), the skin, gastro-intestinal (GI) tract. ERDEM considers these physiological boundaries of exposure separately.

7.1 The Closed Chamber for the Static Lung

The static lung is modeled by finding the rate that the ith chemical in inhaled air is transferred to arterial blood and the rate that chemical in the static lung/arterial blood is transferred to Exhaled Air. The rate of change of the amount of the ith chemical in the Closed Chamber is simply the rate of change of the amount exhaled into the chamber minus the rate of change of the amount inhaled from the chamber by the subjects as represented in equation (34):

$$\frac{dA_{CC_i}}{dt} = NQ_A\left(\frac{C_{PU_i}}{R_{PU,AIR_i}} - C_{INH_i}\right) \quad \textbf{(34)}$$

where N is the number of subjects in the Closed Chamber. In addition, the ith chemical is moving from the venous blood to the static lung, from the static lung to arterial blood, and in the chylomicrons from the Lymph Pool (when the four walled Gastro-Intestinal model is used). Binding of the ith Chemical is modeled in the static lung and is used to reduce the amount of free chemical. The bound chemical does not metabolize and does not pass to the arterial blood. Each of the N_c circulating compounds can metabolize into up to $N_{M,i}$ metabolites. Each metabolite could be the ith chemical. Thus the rates of formation of

each of these metabolites must be added. The equation for the rate of change of the concentration of the ith chemical in the static lung is represented in equation (35):

$$\mathrm{V}_{PU}\frac{dC_{PU_i}}{dt} = Q_B C_{VB,F_i} + Q_A C_{INH_i} - Q_B \frac{C_{PU,F_i}}{R_{PU,AB_i}} + K_{LP,PU_i} A_{LP_i} -$$

$$Q_A \frac{C_{PU_i}}{R_{PU,AIR_i}} - \frac{dA_{PU,B_i}}{dt} - \sum_{j=1}^{N_{M_j}} \frac{dA_{PU,M_{i,j}}}{dt} + \sum_{I_{l,m}=i} \frac{dA_{PU,M_{l,m}}}{dt} \quad (35)$$

where the variable $I_{l,m}$ is the circulating compound that is the mth metabolite of the lth circulating compound. The equations for metabolism are presented in subsection 8.2. Binding and elimination equations are presented below.

7.1.1 Elimination in the Static Lung

There are two types of elimination currently implemented in ERDEM. A linear form in which the
rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the static lung and a saturable Michaelis-Menten form. The linear form is:

$$\frac{dA_{PU,E_i}}{dt} = K_{PU,E_i} A_{PU,F_i} \quad (36)$$

and the saturable form for elimination is:

$$\frac{dA_{PU,E_i}}{dt} = V_{m,PU,E_i} \frac{C_{PU,F_i}}{(K_{mM,PU,E_i} + ABS(C_{PU,F_i}))} \quad (37)$$

7.1.2 Binding in the Static Lung

The binding in the static lung is of the Michaelis-Menten form but the amount of the ith chemical that is bound is calculated rather than the rate. The equilibrium equation is:

$$A_{PU,B_i} = \frac{K_{PU,MxB} C_{PU,F_i}}{(K_{PU,DB_i} + ABS(C_{PU,F_i}))} V_{PU} \quad (38)$$

7.1.3 Calculation of Free Chemical in the Static Lung

The free chemical in the static lung is calculated by subtracting the amount bound from the total amount as follows:

$$A_{PU,F_i} = A_{PU_i} - A_{PU,B_i} \quad (39)$$

7.1.4 Metabolism in the Static Lung

The static lung metabolism equations are the same as those for the Liver given in subsection 8.2.5, except that the equation for the V-Max is given as a function of the Liver value from the equation

$$V_{Mx,PU_{i,j}} = V_{Mx,LV_{i,j}} R_{M,PU,LV_{i,j}} \frac{V_{PU}}{V_{LV}}, \quad (40)$$

where $R_{M,PU,LV_{i,j}}$ is a scaling factor for V-Max in the static lung relative to the Liver for the jth metabolite of the ith chemical.

7.1.5 Arterial Blood and the Static Lung

The equation for arterial blood (AB) is slightly different for the static lung (PU) and the breathing lung. Arterial blood is output from the lung and is input to most of the compartments. The rate of change of the amount of the ith chemical in the arterial blood for the static lung is the rate that chemical is moved into the arterial blood from the static lung minus the rates that the free arterial blood loses chemical to the other compartments (Brain, Carcass, Derma, Fat, Kidney, Liver, Rapidly Perfused and Slowly Perfused Tissue, Spleen, and for the new GI - the Walls of the Stomach, Duodenum, Lower Small Intestine, and the Colon). The equation is:

$$\frac{dA_{AB_i}}{dt} = Q_B \frac{C_{PU,F_i}}{R_{PU,AB_i}} - \sum_{[XX]} \frac{dA_{AB,XX_i}}{dt}, \quad (41)$$

where

$$\frac{dA_{AB,XX_i}}{dt} = Q_{B,XX} C_{AB,F_i}, \quad (42)$$

and [XX] = {BN , CR, DR, FT, KD, LV, RP, SL, SP, SW, DU, SI, and CN}.

7.1.6 Venous Blood Input to the Static Lung

The rate of change of the amount of chemical in the venous blood is given by the rate due to Bolus Intravenous injections and Infusions plus the rate of gain from each compartment minus the rate of loss of free chemical to the static lung. The equation is given by:

$$\frac{dA_{VB_i}}{dt} = \frac{dA_{BIV_i}}{dt} + \frac{dA_{INF_i}}{dt} + \sum_{[YY]} \frac{dA_{YY,VB_i}}{dt} - Q_B C_{VB,F_i} \quad \textbf{(43)}$$

where [YY] = {BN, CR, DR, FT, KD, LV, RP, SL}.

7.2 The Breathing Lung

The breathing lung is modeled with five compartments: Upper Dead Space, Lower Dead Space, Alveoli, Pulmonary Capillaries, and Lung Tissue. In addition, flows for the bronchial artery and the bronchial vein are modeled. Diffusions are modeled for the Alveoli - Pulmonary Capillaries, Alveoli - Lung Tissue, and Pulmonary Capillaries - Lung Tissue interfaces. The system chart for the model using the Breathing Lung is given in Figure 5. Metabolism is modeled in the Lung Tissue. An anatomy chart for the breathing lung model is displayed in Figure 6. Terminology is defined in subsection 7.2.16.

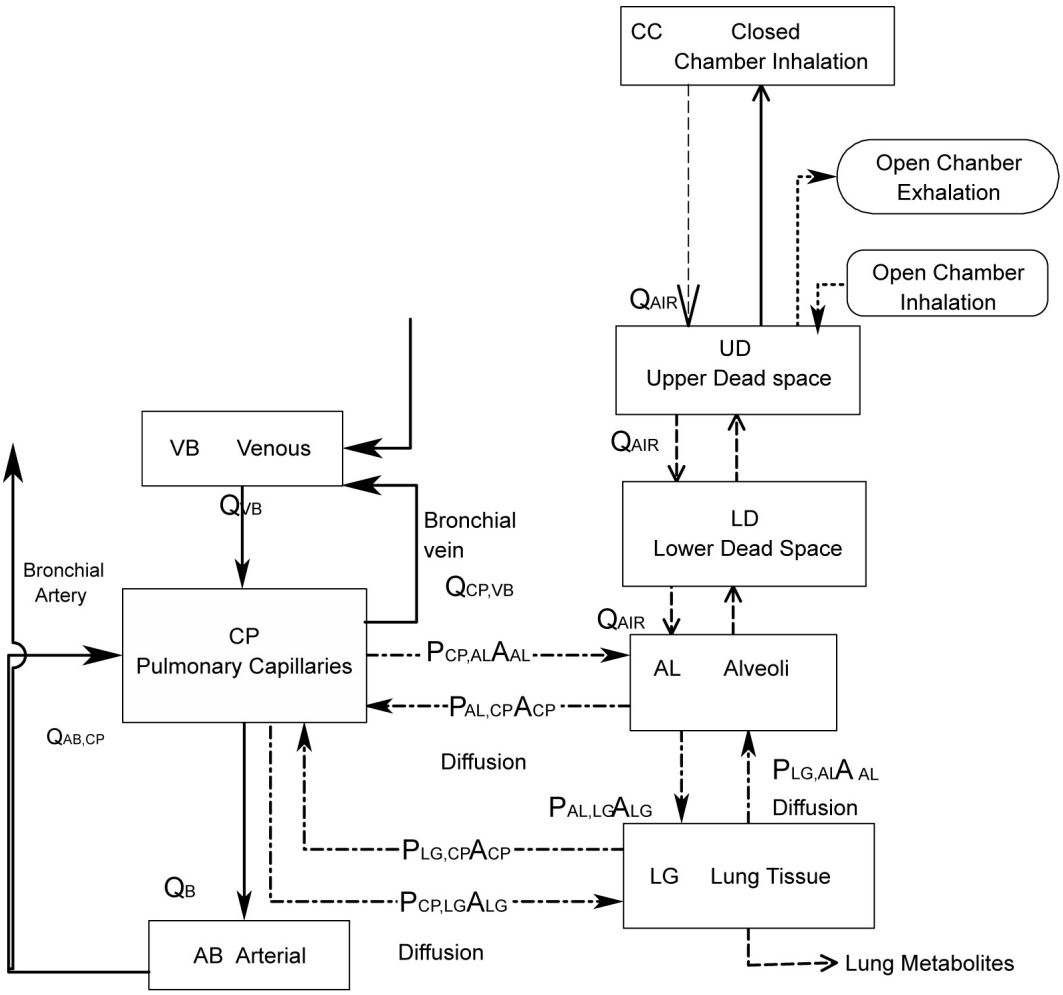


Figure 5. Breathing Lung Model.

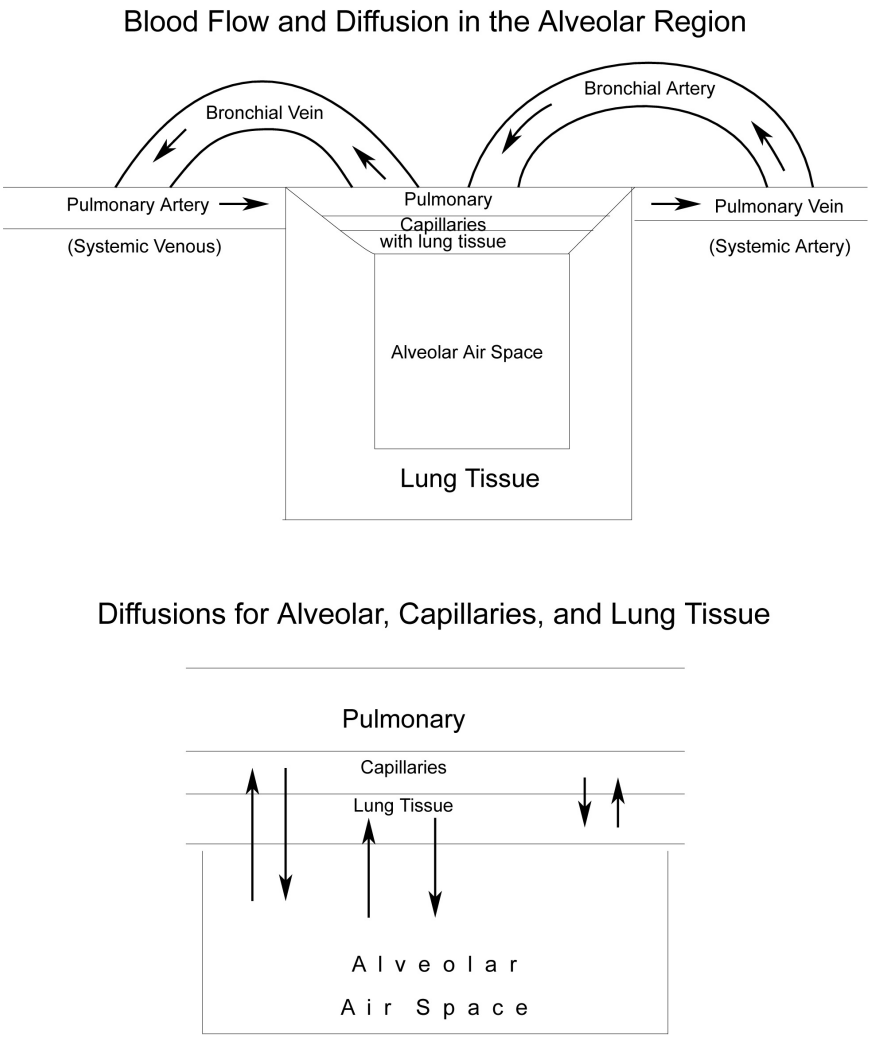


Figure 6. Breathing Lung - Anatomical Description.

7.2.1 Flow of Air in the Breathing Lung

Alveoli volume (V_{AL}) and volumetric flow rate of the air (Q_{AIR}) are calculated from the breathing frequency, F_B, as

$$V_{AL} = V_{FRC} + \frac{V_r}{2}\left[1 - \cos(\Omega t)\right] \tag{44}$$

and,

$$Q_{AIR} = \frac{\Omega}{2} V_r SIN(\Omega t) \tag{45}$$

where

V_{FRC} = Functional residual capacity,
V_T = Tidal volume,
t = Time;

and,

$$\Omega = 2\Pi F_B \tag{46}$$

where F_B is the Breathing Frequency.

The volume of the Alveoli versus time is plotted in Figure 7a and the volumetric flow rate of the air versus time is plotted in Figure 7b.

The breathing cycle consists of one inspiration ($Q_{AIR} \geq 0$) followed by one expiration ($Q_{AIR} < 0$).

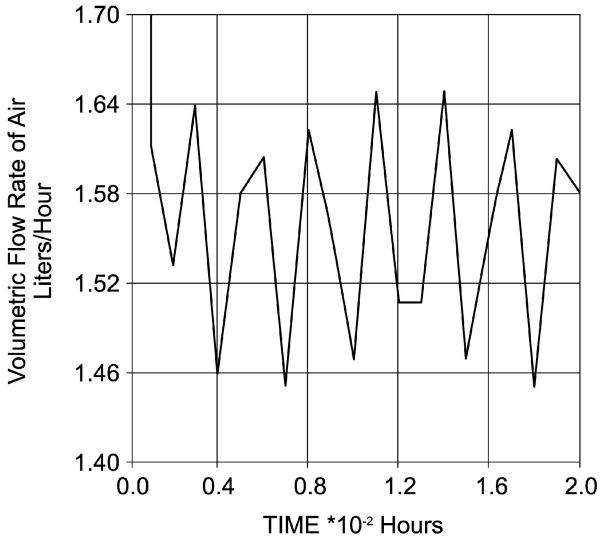


Figure 7a. Alveolar Volume Versus Time.

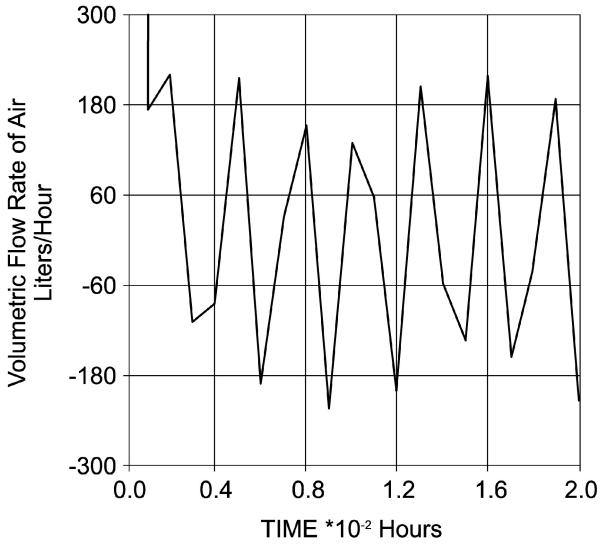


Figure 7b. Breathing Lung Volumetric Flow Rate of Air Versus Time.

7.2.2 Factors to Multiply Terms for Inspiration and Expiration

The direction of air motion reverses from inspiration to expiration during a breathing cycle. The flow rate (Q_{AIR}) is considered positive during inspiration and negative during expiration (equation (45)). The inspiration and expiration terms are combined into one

equation by using multipliers. Each inspiration term in the enclosed equations has the multiplier:

$$I = [1 + SIGN(Q_{AIR})]/2, \quad (47)$$

where

$SIGN(X) = 1$ if $X \geq 0$, and
$SIGN(X) = -1$ if $X < 0$.

Thus

$I = 1$ for $Q_{AIR} \geq 0$, and
$I = 0$ for $Q_{AIR} < 0$.

Every expiration term has the multiplier

$$E = [1 - SIGN(Q_{AIR})]/2, \quad (48)$$

where

$E = 1$ for $Q_{AIR} < 0$, and
$E = 0$ for $Q_{AIR} \geq 0$.

7.2.3 Equation for the Closed Chamber

The closed chamber compartment is shown in the breathing lung system chart (Figure 5). If an open chamber is used then the input concentration is fixed and exhaled air is lost. The rate of change of the amount of the ith chemical in the closed chamber (CC) is:

$$V_{CC} \frac{dC_{CC_i}}{dt} = -N * Q_{AIR} I * C_{CC_i} + N * Q_{AIR} E * C_{UD_i} \quad (49)$$

where inspiration is from the Closed Chamber to the Upper Dead Space and expiration is from the Upper Dead Space to the Closed Chamber. The terms I and E are given by equations (47) and (48) respectively and N is the number of subjects in the Closed Chamber (only one subject is modeled).

7.2.4 Equations for Upper Dead Space

The equation for the rate of change of the ith chemical in the Upper Dead Space is given by:

$$V_{UD}\frac{dC_{UD_i}}{dt} = Q_{AIR}I * C_{INH_i} - Q_{AIR}I * C_{UD_i} + Q_{AIR}E * C_{UD_i} - Q_{AIR}E * C_{LD_i} \quad (50)$$

where C_{INH_i} is the concentration of the ith chemical in inhaled air from either an open or closed chamber, and C_{UD_i} is the concentration of the ith chemical in air exhaled into the closed chamber or lost in an open chamber. The quantities *I* and *E* are the inspiration and expiration coefficients given in equations (47) and (48) respectively. The concentration of the ith chemical in exhaled breath C_{EXH,B_i} is given in equation (71) (see subsection 7.2.13) and is different from C_{UD_i} above.

During inspiration, chemical moves from the air in the chamber to the Upper Dead Space, and from the Upper Dead Space to the Lower Dead Space. Exhaled air moves from the Lower Dead Space to the Upper Dead Space, and from the Upper Dead Space to the Closed Chamber or is lost to exhaled air.

7.2.5 Equations for the Lower Dead Space

The Lower Dead Space exchanges air with the Upper Dead Space and the Alveoli. The equation for the rate of change of the ith chemical in the Lower Dead Space is:

$$V_{LD}\frac{dC_{LD_i}}{dt} = Q_{AIR_i}I * C_{UD_i} - Q_{AIR}I * C_{LD_i} + Q_{AIR}E * C_{LD_i} - Q_{AIR}E * C_{AL_i} \quad (51)$$

where I and E are the inspiration and expiration coefficients from equations (47) and (48) respectively.

During inspiration the ith chemical moves from the Upper Dead Space to the Lower Dead Space, and from the Lower Dead Space to the Alveoli. Exhaled air moves from the Alveoli to the Lower Dead Space, and from the Lower Dead Space to the Upper Dead Space.

7.2.6 The Equation for the Alveoli

The Alveoli exchanges the ith chemical in the air with the Lower Dead Space and exchanges the ith chemical by diffusion with the Pulmonary Capillaries and the Lung tissue. In addition, the volume of the Alveoli varies with time (equation (44)).

The equation for the Alveoli (AL) compartment is written as rate of change of amount:

$$\frac{dA_{AL_i}}{dt} = Q_{AIR}IC_{LD_i} + Q_{AIR}EC_{AL_i} + P_{LG,AL_i}S_{AL}C_{LG,F_i} - P_{AL,LG_i}S_{LG}C_{AL_i} + P_{CP,AL_i}S_{AL}C_{CP,F_i} - P_{AL,CP_i}S_{CP}C_{AL_i}. \quad (52)$$

The concentration of chemical in the Alveoli is found from the amount as

$$C_{AL_i}(t) = \frac{A_{AL_i}(t)}{V_{AL_i}(t)} \tag{53}$$

The first term is the movement of chemical in the air during the breathing cycle with coefficients *I* and *E* given by equations (47) and (48) respectively. The second and third terms represent diffusion of chemical across the membrane from Lung Tissue to Alveoli and vice versa, respectively. The diffusion of chemical from the Pulmonary Capillaries to the Alveoli and back is given by the fourth and fifth terms respectively.

7.2.7 Lung Tissue Equation

The ith chemical in the Lung Tissue compartment diffuses in exchanges with the Alveoli and the Pulmonary Capillaries. Elimination is modeled and the rate of elimination of the ith chemical is subtracted. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the chemical in the Lung Tissue. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$\begin{aligned} V_{LG}\frac{dC_{LG_i}}{dt} &= P_{AL,LG_i}S_{LG}C_{AL_i} - P_{LG,AL_i}S_{AL}C_{LG,F_i} + P_{CP,LG_i}S_{LG}C_{CP,F_i} - \\ &\quad P_{LG,CP_i}S_{CP}C_{LG,F_i} - \frac{dA_{LG,E_i}}{dt} - \sum_{j=1}^{N_{M_j}}\frac{dA_{LG,M_{i,j}}}{dt} + \sum_{I_{l,m}=i}\frac{dA_{LG,M_{l,m}}}{dt} \end{aligned} \tag{54}$$

where the first and second terms show the diffusion of chemical from Alveoli to the Lung Tissue, and vice versa. The third and fourth terms represent the diffusion of chemical from the Lung tissue to the Pulmonary Capillaries and the variable $I_{l,m}$ is the circulating compound that is the *m*th metabolite of the *l*th circulating compound. The equations for metabolism are presented in the attached metabolism report. Binding and elimination equations are presented below.

7.2.7.1 Elimination in the Lung Tissue

There are two types of elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the static lung and a saturable Michaelis-Menten form. The linear form is:

$$\frac{dA_{LG,E_i}}{dt} = K_{LG,E_i}A_{LG,F_i}, \tag{55}$$

and the saturable form for elimination is:

$$\frac{dA_{LG,E_i}}{dt} = V_{m,LG,E_i} \frac{C_{LG,F_i}}{(K_{mM,LG,E_i} + ABS(C_{LG,F_i}))} \quad \textbf{(56)}$$

7.2.7.2 Binding in the Lung Tissue

The binding in the Lung Tissue is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{LG,B_i} = \frac{K_{LG,Mx,B_i} C_{LG,F_i}}{(K_{LG,DB_i} + ABS(C_{LG,F_i}))} V_{LG} \quad \textbf{(57)}$$

7.2.7.3 Calculation of Free Chemical in the Lung Tissue

The free chemical in the Lung Tissue is calculated by subtracting the amount bound from the total amount as follows:

$$A_{LF,F_i} = A_{LG_i} - A_{LG,B_i} \quad \textbf{(58)}$$

7.2.8 Metabolism in the Lung Tissue

The Lung Tissue metabolism equations are the same as those for the Liver given in subsection 8.2, except that the equation for the V-Max is given as a function of the Liver value from equation:

$$V_{Mx,LG_{i,j}} = V_{Mx,LV_{i,j}} R_{M,LG,LV_{i,j}} \frac{V_{LG}}{V_{LV}} \quad \textbf{(59)}$$

where $R_{M,LG,LV_{i,j}}$ is a scaling factor for V-Max in the Lung Tissue for the jth metabolite of the ith chemical.

7.2.9 Equation for the Pulmonary Capillaries

The ith chemical in the Pulmonary Capillary compartment (CP) is moved by diffusions with the Alveoli and the Lung Tissue and with the two input and two output blood flows. The equation is:

$$V_{CP}\frac{dC_{CP_i}}{dt} = Q_{VB}C_{VB,F_i} - Q_{CP,VB}\frac{C_{CP,F_i}}{R_{CP,VB_i}} + P_{AL,CP_i}S_{CP}C_{AL_i} - P_{CP,AL_i}S_{AL}C_{CP,F_i} + P_{LG,CP_i}S_{CP}C_{LG,F_i} - P_{CP,LG_i}S_{LG}C_{CP,F_i} - Q_BC_{CP,F_i} + Q_{B,CP}C_{AB,F_i} \quad (60)$$

The first two terms represent input to the Pulmonary Capillaries from venous blood and output, via the Bronchial Vein, to the venous blood. The third and fourth terms represent the diffusion of chemical in the Alveoli to or from the Pulmonary Capillaries. The next two terms show the diffusion with the Lung tissue. The last two terms are output from the Pulmonary Capillaries to arterial blood via the Cardiac Output, and the input from arterial blood to the Pulmonary Capillaries via the Bronchial Artery. Note that the free ith chemical is used in the venous blood, arterial blood, the Lung Tissue, and the Pulmonary Capillaries.

7.2.10 Binding in the Pulmonary Capillaries

The binding in the Pulmonary Capillaries is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{CP,B_i} = \frac{K_{CP,Mx,B_i}C_{CP,F_i}}{(K_{CP,DB_i} + ABS(C_{CP,F_i}))}V_{CP} \quad (61)$$

7.2.11 Calculation of Free Chemical in the Pulmonary Capillaries

The free chemical in the Pulmonary Capillaries is calculated by subtracting the amount bound from the total amount as follows:

$$A_{CP,F_i} = A_{CP_i} - A_{CP,B_i} \quad (62)$$

7.2.12 Blood Flow for the Breathing Lung

The Cardiac Output Q_B, the sum of all the flows through the Liver, Fat, Kidney, Slowly Perfused Tissue, Rapidly Perfused tissue, Derma, Brain, Pulmonary Capillaries, and Walls of the Full GI is:

$$Q_B = Q_{B,SP} + Q_{B,LV} + Q_{B,CR} + Q_{B,KD} + Q_{B,FT} + Q_{B,SL} + Q_{B,RP} + Q_{B,DR} + Q_{B,BN} + Q_{B,CP} + Q_{PB} \quad (63)$$

where the flow in the Portal Blood of the Full GI is:

$$Q_{PB} = Q_{B,SW} + Q_{B,DU} + Q_{B,SI} + Q_{B,CN}. \quad (64)$$

The blood flow out of the Pulmonary Capillaries (for the Breathing Lung) is equal to the input, thus:

$$Q_B = Q_{VB} + Q_{B,CP} - Q_{CP,VB} \tag{65}$$

The venous blood flow into the Pulmonary Capillaries, Q_{VB}, is:

$$Q_{VB} = Q_{B,SP} + Q_{B,LV} + Q_{B,CR} + Q_{B,KD} + Q_{B,FT} + Q_{B,SL} + Q_{B,RP} + Q_{B,DR} + Q_{B,BN} + Q_{CP,VB} + Q_{PB}. \tag{66}$$

7.2.13 Arterial Blood and the Breathing Lung

The ith chemical in the arterial blood (AB) flows from the Pulmonary Capillaries (CP) and the free chemical flows into the Brain, Carcass, Derma, Fat, Kidney, Liver, Rapidly and Slowly Perfused Tissue, and Spleen. It also flows into the GI Walls - Stomach, Duodenum, Lower Small Intestine, and the Colon. arterial blood flows into the Pulmonary Capillaries via the bronchial artery.

The equation for the arterial blood is expressed in terms of rate of change of amount as (the rates of change for the blood flow through each compartment is calculated as above for the static lung)

$$\frac{dA_{AB_i}}{dt} = Q_B C_{CP,F_i} - \sum_{[XX]} \frac{dA_{AB,XX_i}}{dt}, \tag{67}$$

7.2.14 Venous Blood Input to the Breathing Lung

The ith chemical in the venous blood flows into the Breathing Lung from each of the compartments into the Pulmonary Capillaries (except the new GI Walls, see above). There is also flow of the ith chemical from the Pulmonary Capillaries into the venous blood via the bronchial vein.

The equation for venous blood (VB) must take into account the gain in chemical from the Pulmonary Capillaries via the bronchial vein (the first term). The gain in chemical from the body organs is followed by the term representing the loss of free chemical to the Pulmonary Capillaries. The equation in terms of rate of change of amount is:

$$\frac{dA_{VB_i}}{dt} = Q_{CP,VB} \frac{C_{CP,F_i}}{R_{CP,VB_i}} + \frac{dA_{BIV_i}}{dt} + \frac{dA_{INF_i}}{dt} + \sum_{[YY]} \frac{dA_{YY,VB_i}}{dt} - Q_B C_{VB,F_i} \tag{68}$$

where [YY] = {BN, CR, DR, FT, KD, LV, RP, SL, SP}.

7.2.15 Calculation of Uptake and Chemical in Exhaled Breath

The equations for the breathing lung are discontinuous when the breathing switches from inspiration to expiration. The amount of the ith chemical is recorded at the start and end of inspiration and the difference is taken to get the amount of chemical inhaled during a breath ($A_{INH,B}$). The amount of the ith chemical exhaled during a ($A_{EXH,B}$) is found by recording the amount at the start and end of exhalation and taking the difference. Then the uptake is obtained from:

$$A_{UPB_i} = A_{INH,B_i} - A_{EXH,B_i} \quad \textbf{(69)}$$

The Percent Uptake is:

$$PCT(A_{UPB_i}) = 100\,\frac{A_{UPB_i}}{A_{INH_i}}. \quad \textbf{(70)}$$

The uptake values for the ith chemical only make sense when breathing contaminated air is the only exposure. The average concentration of chemical in exhaled breath is found, using the volume of air flow during exhalation ($V_{TDL}/2$), to be:

$$C_{EXH,B_i} = \frac{A_{EXH,B_i}}{V_{TDL}} \quad \textbf{(71)}$$

7.2.16 Variable Definitions for Breathing Lung

The variables used in the Breathing Lung equations are defined as:

Area Variables

S_{AL} = Area of the Alveoli;
S_{LG} = Area of the Lung Tissue.
S_{CP} = Area of the Pulmonary Arteries;

Variables for the Amount of Chemical

A_{AL_i} = Amount of ith chemical in the Alveoli,
A_{EXH,B_i} = Amount of ith chemical exhaled during a breath;
A_{INH,B_i} = Amount of ith chemical inspired during a breath;
A_{UPB_i} = Amount of ith chemical in uptake in one breath.

Variables for the Concentration of Chemical

C_{AL_i} = Concentration of ith chemical in the Alveoli;
C_{CC_i} = Concentration of ith chemical in the Closed Chamber;

C_{CP_i} = Concentration of ith chemical in the Pulmonary Capillaries;
C_{CP,B_i} = Concentration of bound ith chemical in the Pulmonary Capillaries;
C_{CP,F_i} = Concentration of free ith chemical in the Pulmonary Capillaries;
C_{EXH,B_i} = Concentration of ith chemical in exhaled breath;
C_{INH_i} = Concentration of ith chemical in the inhaled air;
C_{LD_i} = Concentration of ith chemical in the Lower Dead Space;
C_{LG_i} = Concentration of ith chemical in the Lung Tissue;
C_{LG,B_i} = Concentration of bound ith chemical in the Lung Tissue;
C_{LG,F_i} = Concentration of free ith chemical in the Lung Tissue;
C_{UD_i} = Concentration of ith chemical in the Upper Dead Space;

Variables for the Coefficients for Inspiration and Expiration

I = Coefficient for inspiration terms, see equation 47;
E = Coefficient for expiration terms, see equation 48.

Variables for the Binding in the Pulmonary Capillaries

K_{CP,DB_i} = Equilibrium binding constant for the ith chemical in the Pulmonary Capillaries corresponding to the Michaelis-Menten constant.
K_{CP,MxB_i} = Maximum amount of binding for the ith chemical in the Pulmonary Capillaries corresponding to V-Max in the Michaelis-Menten equation.

Variable for the Number of Subjects

N = Number of subjects in the closed chamber.

Variables for the Permeation Coefficients

P_{AL,CP_i} = Alveoli to Pulmonary Capillaries permeation coefficient for the ith chemical;
P_{AL,LG_i} = Alveoli to Lung Tissue permeation coefficient for the ith chemical;
P_{CP,AL_i} = Pulmonary Capillaries to Alveoli permeation coefficient for the ith chemical;
P_{CP,LG_i} = Pulmonary Capillaries to Lung Tissue permeation coefficient for the ith chemical;
P_{LG,AL_i} = Lung Tissue to Alveoli permeation coefficient for the ith chemical;
P_{LG,CP_i} = Lung Tissue to Pulmonary Capillaries permeation coefficient for the ith chemical.

Variables for Volumetric Flow rates

Q_{AIR} = Volumetric flow rate of air during the breathing process;
Q_B = Cardiac Output (L/H) from current model;

$Q_{B,CP}$ = Volumetric flow rate of chemical from arterial blood to the Pulmonary Capillaries;

$Q_{CP,VB}$ = Volumetric flow rate of the chemical from Pulmonary Capillaries to venous blood.

Q_{VB} = Venous blood flow rate.

Variable for the Partition Coefficients

R_{CP,VB_i} = Pulmonary Capillaries to venous blood partition coefficient for the ith chemical.

7.3 Equations for the Four Compartment Gastro-Intestinal (GI) Simulation

The basic abridged Gastro-Intestinal (GI) Model has a Stomach and Intestine (Figure 8) with Rate and Bolus Ingestion into the Stomach, flow from the Stomach to the Intestine and from the Intestine to Intestinal Elimination. In addition, there is flow from the Spleen, the Stomach and the Intestine to the Liver via Portal Blood. There is no Bile flow from the Liver to the Intestine and no Lymph flow or pool. Arterial blood is an input only to the Liver, not the Stomach or the Intestine.

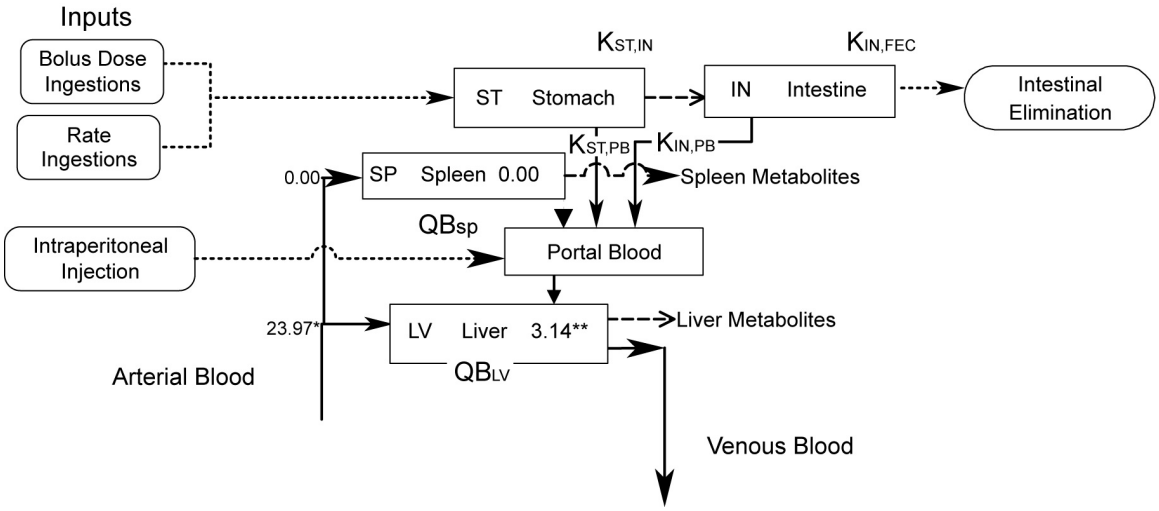


Figure 8. Stomach/Intestine Gastro-Intestinal Model.

In the Full unabridged GI model (Figure 9), the terminology and the compartments are changed from the basic abridged Gastro-Intestinal (GI) Model. The variable names used in ERDEM and the variables used in these equations are given in tables by compartment. The equations are written for a more general case where there are a number of circulating compounds.

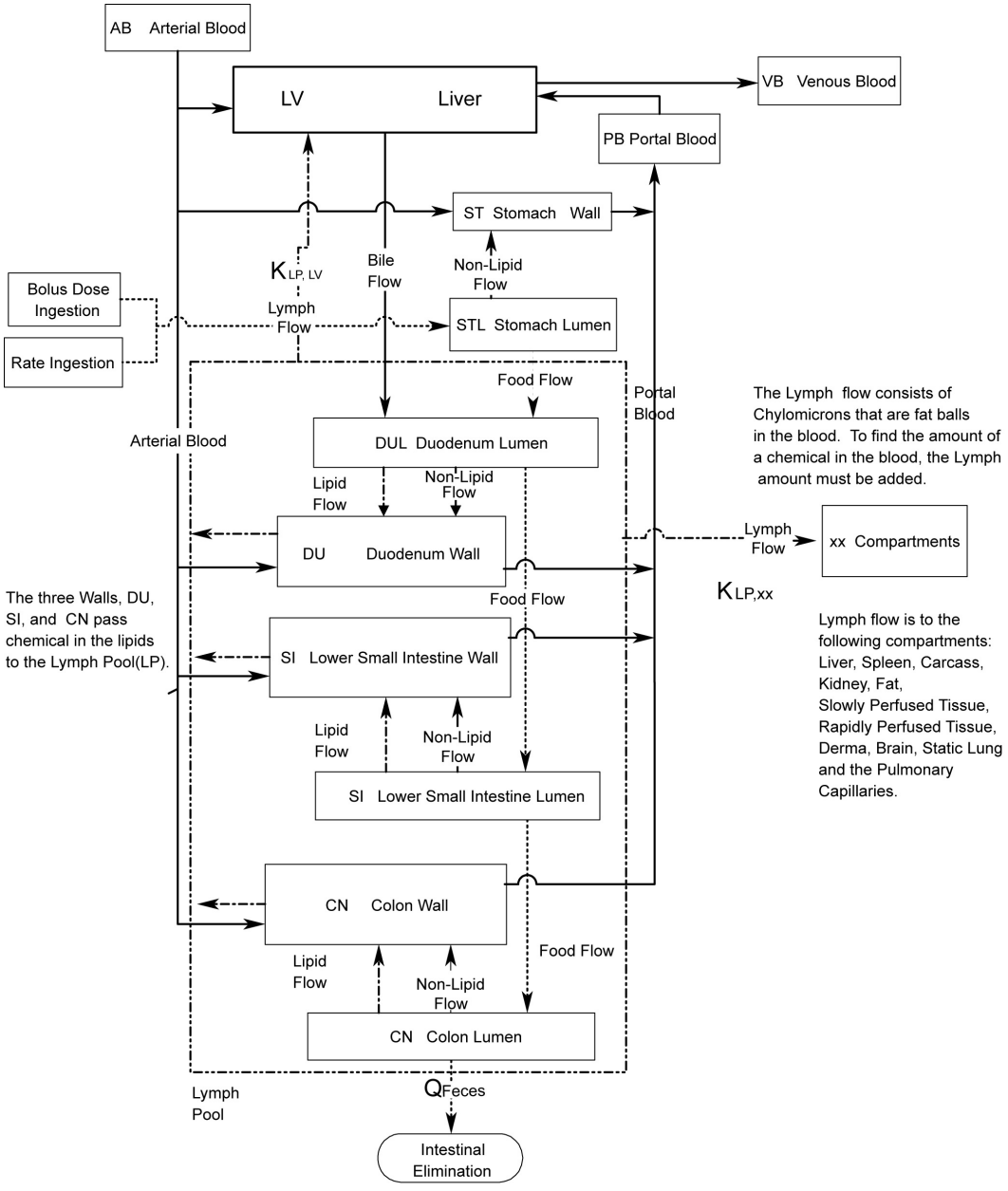


Figure 9. Full Gastro-Intestinal Tract Model.

There are eight compartments and four sections. Each section consists of a Wall and a Lumen. The wall of the Stomach is designated SW and the lumen is STL. In a similar manner the designations for the Duodenum are DU and DUL for the Duodenum Luman, for the Lower Small Intestine, SI and SIL, and for the Colon, CN and CNL.

Arterial blood flows into the Liver and the wall of each section. Bile flows from the Liver to the Duodenum. Food flows from the Stomach through the other three sections to the Feces. Portal Blood (PB) flows from the Stomach, Duodenum, Lower Small Intestine, and the Colon Walls to the Liver. There is a Non-Lipid (NL) flow from the Lumens to the Walls of these four compartments.

There is chylomicron flow from the Lymph Pool to the Brain, Carcass, Derma, Kidney, Liver, Fat, Rapidly Perfused Tissue, Slowly Perfused Tissue (Muscle), and the Spleen. In addition there is chylomicron flow to the static lung and to the Pulmonary Capillaries of the Breathing Lung. Lipid absorption occurs from the Lumen to the Wall for each of the Duodenum, Lower Small Intestine and the Colon as well as from the respective Walls to the Lymph Pool. And of course there is flow from the Liver to the venous blood. Metabolism is modeled in the walls of the Stomach, Duodenum, Lower Small Intestine and the Colon.

7.3.1 Flow Through the Stomach Wall

The mass balance input equation for the ith circulating chemical in the Stomach Wall (SW) enters from the arterial blood, non-lipid flow from the Stomach Lumen, and metabolites of other chemicals which represent the ith chemical. The outputs go to the Portal Blood as parent compound and metabolites. The terminology in ERDEM indicates flow as subscripts from the left to the right entering a compartment. The equation is:

$$V_{SW}\frac{dC_{SW_i}}{dt} = Q_{B,SW}(C_{AB_i} - \frac{C_{SW_i}}{R_{SW,PB_i}}) + K_{NL,SW_i}A_{STL_i} - \sum_{j=1}^{N_{M_i}}\frac{dA_{SW,M_{i,j}}}{dt} + \sum_{I_{l,m}=i}\frac{dA_{SW,M_{l,m}}}{dt}, \quad (72)$$

where

N_M = the number of metabolites of the ith chemical,

$I_{l,m}$ = the circulating compound that is the *m*th metabolite of the *l*th circulating compound, and

C_{AB} = the concentration of the ith chemical in the arterial blood.

The variables for the Stomach Wall are given in Table 1.

Table 1. Variables for the Stomach Wall

Variable in Documents	Variable in ERDEM (for the Stomach Wall)	Description
$\frac{dA_{SW,M_{i,j}}}{dt}$	STME_1DA_SW_M(I,J)	The rate of formation of the jth Stomach Wall metabolite of the ith chemical.
C_{SW_i}	STWL_1C_SW(I)	The concentration of the ith chemical in the Stomach Wall.
$V_{SW}\frac{dC_{SW}}{dt}$	STWL_1DA_SW(I)	The rate of change of the amount of the ith chemical in the Stomach Wall.
$Q_{B,SW}$	QB_SW	The volume rate of Arterial Blood flow through the Stomach Wall.
R_{SW,PB_i}	STWL_1R_SW_PB(I)	The partition coefficient for the ith chemical moving from the Stomach Wall to Portal blood.
V_{SW}	STWL_1V_SW	The volume of the Stomach Wall.

7.3.2 Flow Through the Stomach Lumen

The flow of the ith chemical through the Stomach Lumen (with no delay currently implemented) is due to input from Rate Ingestion or bolus dose, and output food flow into the Duodenum and Non-Lipid absorption into the Stomach Wall,

$$V_{STL}\frac{dC_{STL_i}}{dt} = \frac{dA_{RIG_i}}{dt} + \frac{dA_{BIG_i}}{dt} - Q_{F,STL}C_{STL_i} - K_{NL,SW_i}A_{STL_i} \quad \textbf{(73)}$$

where

$\frac{dA_{BIG_i}}{dt}$ = the rate of change of the amount of the ith chemical in the bolus dose, and

$\frac{dA_{RIG_i}}{dt}$ = the rate of change of the amount of the ith chemical in the Rate Ingestion.

The data for the Stomach Lumen is given in Table 2.

Table 2. Stomach Lumen Variables

Variable in Documents	Variable in ERDEM (for the Stomach Lumen)	Description
A_{STL_i}	STLM_1A_STL(I)	The amount of the ith chemical in the Stomach Lumen.
C_{STL_i}	STLM_1C_STL(I)	The concentration of the ith chemical in the Stomach Lumen.
$V_{STL}\frac{dC_{STL_i}}{dt}$	STLM_1DA_STL(I)	The rate of change of the amount of the ith chemical in the Stomach Lumen.
$Q_{F,STL}$	STLM_1QF_STL_DUL	The volume rate of food flowing through the Stomach Lumen to the Duodenum.
K_{NL,SW_i}	STLM_1K_STL_SW_NL(I)	The rate constant for the amount of the ith chemical in Non-Lipid flow from the Stomach Lumen to the Stomach Wall,
V_{STL}	STLM_1V_STL	The volume of the Stomach Lumen.

7.3.3 Flow Through the Duodenum Wall

The rate of change of the ith chemical in the Duodenum Wall is due to input from arterial blood, Lipids from the Lumen, Non-lipids absorbed from the Lumen, and metabolites from chemicals which are the ith chemical. The ith chemical is output by flow from the Duodenum Wall to the Lymph Pool and the Portal Blood, as well as metabolized chemical. The equation for the Duodenum Wall is given by:

$$V_{DU}\frac{dC_{DU_i}}{dt} = Q_{B,DU}(C_{AB_i} - \frac{C_{DU_i}}{R_{DU,PB_i}}) + K_{NL,DU_i}A_{DUL_i} + K_{DU,LP_i}(A_{DUL_i} - A_{DU_i}) - \sum_{j=1}^{N_{M_i}}\frac{dA_{DU,M_{i,j}}}{dt} + \sum_{l_{l,m}=i}\frac{dA_{DU,M_{l,m}}}{dt}, \quad (74)$$

where Table 3 presents the variables for the Duodenum Wall.

Table 3. Variables for the Duodenum Wall

Variable in Documents	Variable in ERDEM (for the Duodenum Wall)	Description
A_{DU_i}	DUWL_1A_DU(I)	The amount of the ith chemical in the Duodenum Wall.
$\frac{dA_{DU,M_{ij}}}{dt}$	DUME_1A_DU_M(I,J)	The rate of change of the amount of the jth Duodenum metabolite of the ith chemical.
C_{DU_i}	DUWL_1C_DU(I)	The concentration of the ith chemical in the Duodenum Wall.
$V_{DU}\frac{dC_{DU_i}}{dt}$	DUWL_1DA_DU(I)	The rate of change of the amount of the ith chemical in the Duodenum Wall.
K_{DU,LP_i}	DUWL_1K_DU_LP(I)	The rate constant for the ith chemical in Lipids moving from the Duodenum Lumen to the Wall, and from the Wall to the Lymph Pool.
$Q_{B,DU}$	QB_DU	The volume rate of Arterial Blood flow through the Duodenum Wall.
R_{DU,PB_i}	DUWL_1R_DU_PB(I)	The partition coefficient for the ith chemical moving from the Duodenum Wall to Portal blood.
V_{DU}	DUWL_1V_DU	The volume of the Duodenum Wall.

7.3.4 Flow Through the Duodenum Lumen

The rate of change of the ith chemical in the Duodenum Lumen is determined by the rate that food enters from the Stomach Lumen and exits to the Lower Small Intestine Lumen as well as output by absorption to the Stomach Wall. In addition the Bile from the Liver flows in and Lipid flows out to the Wall. The equation for the rate of change of the ith chemical in the Duodenum Lumen is:

$$V_{DUL}\frac{dC_{DUL_i}}{dt} = Q_{F,STL}C_{STL_i} + Q_{BL,DUL_i}\frac{C_{LV_i}}{R_{BL,DUL_i}} - K_{DU,LP_i}A_{DUL_i} - K_{NL,DU_i}A_{DUL_i} - Q_{F,DUL}C_{DUL_i} \quad \textbf{(75)}$$

where

C_{LV_i} = the concentration of the ith chemical in the Liver,

Q_{BL,DUL_i} the volumetric flow rate of Bile from the Liver to the Duodenum Lumen for the ith chemical, and

R_{BL,DUL_i} the partition coefficient for the ith chemical Bile flow from the Liver to the Duodenum Lumen.

The other variables for the Duodenum Lumen are given in Table 4:

Table 4. Duodenum Lumen Variables

Variable in Documents	Variable in ERDEM (for the Duodenum Lumen)	Description
A_{DUL_i}	DULM_1A_DUL(I)	The amount of the ith chemical in the Duodenum Lumen.
C_{DUL_i}	DULM_1C_DUL(I)	The concentration of the ith chemical in the Duodenum Lumen.
$V_{DUL}\frac{dC_{DUL_i}}{dt}$	DULM_1DA_DUL(I)	The rate of change of the amount of the ith chemical in the Duodenum Lumen.
$Q_{F,DUL}$	DULM_1QF_DUL	The volume rate of food flowing through the Duodenum Lumen to the Small intestine.
K_{NL,DU_i}	DULM_1K_DUL_DU_NL(I)	The rate constant for the amount of the ith chemical in Non-Lipids moving from the Duodenum Lumen to the Duodenum Wall.
V_{DUL}	DULM_1V_DUL	The volume of the Duodenum Lumen.

7.3.5 Flow Through the Lower Small Intestine Wall

The ith chemical is input to the Lower Small Intestine Wall (SI) from the arterial blood, in Lipids from the Lumen, and Non-Lipid absorption from the Lumen. The output of the ith chemical is to Portal blood, and Lipids to the Lymph Pool. The equation for the Lower Small Intestine Wall is:

$$V_{SI}\frac{dC_{SI_i}}{dt} = Q_{B,SI}\left(C_{AB_i} - \frac{C_{SI_i}}{R_{SI,PB_i}}\right) + K_{NL,SI_i}A_{SIL_i} + K_{SI,LP_i}\left(A_{SIL_i} - A_{SI_i}\right) - \sum_{j=1}^{N_{M_i}}\frac{dA_{SI,M_{i,j}}}{dt} + \sum_{l_{l,m}=i}\frac{dA_{SI,M_{l,m}}}{dt}, \quad (76)$$

where Table 5 contains the variables for the Lower Small Intestine Wall.

Table 5. Variables for the Lower Small Intestine Wall

Variable in Documents	Variable in ERDEM2.01 (for the Lower Small Intestine Wall)	Description
A_{SI_i}	SIWL_1A_SI(I)	The amount of the ith chemical in the Lower Small Intestine Wall.
C_{SI_i}	SIWL_1C_SI(I)	The concentration of the ith chemical in the Lower Small Intestine Wall.
$V_{SI}\frac{dC_{SI_i}}{dt}$	SIWL_1DA_SI(I)	The rate of change of the amount of the ith chemical in the Lower Small intestine Wall.
K_{SI,LP_i}	SIWL_1K_SI_LP(I)	The rate constant for the ith chemical in Lipids moving from the Lower Small Intestine Lumen to the Wall, and from the Wall to the Lymph Pool.
$Q_{B,SI}$	QB_SI	The volume rate of Arterial Blood flow through the Lower Small Intestine Wall.
R_{SI,PB_i}	SIWL_1R_SI_PB(I)	The partition coefficient for the ith chemical moving from the Lower Small Intestine Wall to Portal blood.
V_{SI}	SIWL_1V_SI	The volume of the Lower Small Intestine Wall.

7.3.6 Flow Through the Lower Small Intestine Lumen

For the Lower Small Intestine Lumen, the ith chemical is input in the food from the Duodenum Lumen and output via the food to the Colon. The ith chemical is also output in the Lipids to the Wall and absorption of Non-Lipids to the Wall. The equation for the Lower Small Intestine Lumen is given by

$$V_{SIL}\ \frac{dC_{SIL_i}}{dt} = Q_{F,DUL}C_{DUL_i} - K_{SI,LP_i}A_{SIL_i} - K_{NL,SI_i}A_{SIL_i} - Q_{F,SIL}C_{SIL_i} \quad \textbf{(77)}$$

where the variables for the Lower Small Intestine Lumen are given in Table 6.

Table 6. Lower Small Intestine Lumen Variables

Variable in Documents	Variable in ERDEM (for the Lower Small Intestine Lumen)	Description
A_{SIL_i}	SILM_1A_SIL(I)	The amount of the ith chemical in the Lower Small Intestine Lumen.
C_{SIL_i}	SILM_1C_SIL(I)	The concentration of the ith chemical in the Lower Small Intestine Lumen.
$V_{SIL}\frac{dC_{SIL_i}}{dt}$	SILM_1DA_SIL(I)	The rate of change of the amount of the ith chemical in the Lower Small Intestine Lumen.
$Q_{F,SIL}$	SILM_1QF_SIL	The volume rate of food flowing through the Lower Small Intestine Lumen to the Colon.
K_{NL,SI_i}	SILM_1K_SIL_SI_NL(I)	The rate constant for the amount of the ith chemical in Non-Lipids moving from the Lower Small Intestine Lumen to the Lower Small Intestine Wall.
V_{SIL}	SILM_1V_SIL	The volume of the Lower Small Intestine Lumen.

7.3.7 Flow Through the Colon

The input to the Colon Wall (SI) is the ith chemical from the arterial blood, the Lipids from the Lumen, and the Non-Lipid absorption from the Lumen. The output is to Portal Blood and Lipids to the Lymph Pool. The equation for the Colon Wall is:

$$V_{CN}\frac{dC_{CN_i}}{dt} = Q_{B,CN}(C_{AB_i} - \frac{C_{CN_i}}{R_{CN,PB_i}}) + K_{NL,CN_i}A_{CNL_i} + K_{CN,LP_i}(A_{CNL_i} - A_{CN_i}) - \sum_{j=1}^{N_{M_i}}\frac{dA_{CN,M_{i,j}}}{dt} + \sum_{I_{l,m}=i}\frac{dA_{CN,M_{l,m}}}{dt}, \quad (78)$$

where the variables for the Colon Wall are presented in Table 7.

Table 7. Variables for the Colon Wall

Variable in Documents	Variable in ERDEM (for the Colon Wall)	Description
A_{CN_i}	CNWL_1A_CN(I)	The amount of the ith chemical in the Colon Wall.
C_{CN_i}	CNWL_1C_CN(I)	The concentration of the ith chemical in the Colon Wall.
$V_{CN}\frac{dC_{CN_i}}{dt}$	CNWL_1DA_CN(I)	The rate of change of the amount of the ith chemical in the Colon Wall.
K_{CN,LP_i}	CNWL_1K_CN_LP(I)	The rate constant for the ith chemical in Lipids moving from the Colon Lumen to the Wall, and from the Wall to the Lymph Pool,
$Q_{B,CN}$	QB_CN	The volume rate of Arterial Blood flow through the Colon Wall.
R_{CN,PB_i}	CNWL_1R_CN_PB(I)	The partition coefficient for the ith chemical moving from the Colon Wall to Portal blood.
V_{CN}	CNWL_1V_CN	The volume of the Colon Wall.

7.3.8 Flow Through the Colon Lumen

For the Colon Lumen, the input is the ith chemical in the food from the Lower Small Intestine Lumen, and the output is the ith chemical in the lipids to the Wall, the absorption of chemical in the Non-Lipids to the Wall, and Feces elimination.

The equation for the Colon Lumen is given by:

$$V_{CNL}\frac{dC_{CNL_i}}{dt} = Q_{F,SIL}C_{SIL_i} - K_{CN,LP_i}A_{CNL_i} - K_{NL,CN_i}A_{CNL_i} - Q_{CNL,FEC}C_{CNL_i} \quad \textbf{(79)}$$

where Table 8 contains variable definitions for the Colon Lumen.

Table 8. Colon Lumen Variables

Variable in Documents	Variable in ERDEM (for the Colon Lumen)	Description
A_{CNL_i}	CNLM_1A_CNL(I)	The amount of the ith chemical in the Colon Lumen.
C_{CNL_i}	CNLM_1C_CNL(I)	The concentration of the ith chemical in the Colon Lumen.
$V_{CNL}\frac{dC_{CNL_i}}{dt}$	CNLM_1DA_CNL(I)	The rate of change of the amount of the ith chemical in the Colon Lumen.
$Q_{CNL,FEC}$	CNLM_1QF_CNL_FEC	The volumetric rate of excretion from the Colon to the feces for the ith chemical
K_{NL,CN_i}	CNLM_1K_CNL_CN_NL(I)	The rate constant for the amount of the ith chemical in Non-Lipids moving from the Colon Lumen to the Colon Wall.
V_{CNL}	CNLM_1V_CNL	The volume of the Colon Lumen.

7.3.9 Flow Through the Lymph Pool

The ith chemical is input to the Lymph Pool from the Wall of the Duodenum, Lower Small Intestine and Colon. The ith chemical is output to the Brain, Carcass, Derma, Kidney, Liver, Fat, Rapidly Perfused Tissue, Slowly Perfused Tissue and the Spleen from the chylomicrons in the Lymph Pool. The ith chemical in the chylomicrons is also passed to the static lung and the Pulmonary Capillaries (Breathing Lung). The chemical in the Lipids is passed from the Lumen to the Wall of these compartments and from the Wall to the Lymph Pool. The equation is:

$$\begin{aligned}\frac{dA_{LP_i}}{dt} = {} & K_{LP,DU_i}A_{DU_i} + K_{LP,SI_i}A_{SI_i} + K_{LP,CN_i}A_{LP_i} - K_{LP,BN_i}A_{LP_i} - K_{LP,CR_i}A_{LP_i} - \\ & K_{LP,DR_i}A_{LP_i} - K_{LP,FT_i}A_{LP_i} - K_{LP,KD_i}A_{LP_i} - K_{LP,LV_i}A_{LP_i} - K_{LP,RP_i}A_{LP_i} - \\ & K_{LP,SL_i}A_{LP_i} - K_{LP,SP_i}A_{LP_i} - K_{LP,CP_i}A_{LP_i} - K_{LP,PU_i}A_{LP_i}\end{aligned} \quad \textbf{(80)}$$

where the variables for the Lymph Pool are defined in Table 9.

Table 9. Variables for the Lymph Pool

Variable in Documents	Variable in ERDEM (for the Lymph Pool)	Description
A_{LP_i}	LPYL_1A_LP(I)	The amount of the ith chemical in the Lymph Pool.
$\frac{dA_{LP_i}}{dt}$	LPYL_1DA_LP(I)	The rate of change of the amount of the ith chemical in the Lymph Pool.
K_{LP,BN_i}	LPYL_1K_LP_BN(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Brain.
K_{LP,CR_i}	LPYL_1K_LP_CR(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Carcass.
K_{LP,DR_i}	LPYL_1K_LP_DR(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Derma.
K_{LP,FT_i}	LPYL_1K_LP_FT(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Fat.
K_{LP,KD_i}	LPYL_1K_LP_KD(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Kidney.
K_{LP,LV_i}	LPYL_1K_LP_LV(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Liver.
K_{LP,RP_i}	LPYL_1K_LP_RP(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Rapidly Perfused Tissue.
K_{LP,SL_i}	LPYL_1K_LP_SL(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Slowly Perfused Tissue.
K_{LP,SP_i}	LPYL_1K_LP_SP(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Spleen.
K_{LP,CP_i}	LPYL_1K_LP_CP(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Pulmonary Capillaries.
K_{LP,PU_i}	LPYL_1K_LP_PU(I)	The rate constant for flow in the Lipids from the Lymph Pool to the Static Lung.

The amount of the ith chemical in the venous blood is given by:

$$A_{VB_i} = A_{VB_i} + A_{LP_i}\,, \tag{81}$$

where A_{VB_i} = the amount of the ith chemical in the venous blood.

7.3.10 Portal Blood and Bile Flow

The volumetric flow rate of the Portal Blood is determined by the flows from each of the compartment Walls (Stomach, Duodenum, Lower Small Intestine, and the Colon) and from the Spleen. This flow is a constant in this implementation. The value is given by:

$$Q_{PB,LV} = Q_{B,ST} + Q_{B,DU} + Q_{B,SI} + Q_{B,CN} + Q_{B,SP} \quad (82)$$

and the rate of change of the amount of the ith chemical in Portal Blood is given by the contributions from the Walls of the GI, the rate that chemical passes from the Spleen (SP) and the rate of injection of chemical from Intraperitoneal Injection (INP). The ith chemical is passed from the Portal Blood to the Liver:

$$\frac{dA_{PB_i}}{dt} = Q_{B,SW}\frac{C_{SW_i}}{R_{SW,PB_i}} + Q_{B,DU}\frac{C_{DU_i}}{R_{DU,PB_i}} + Q_{B,SI}\frac{C_{SI}}{R_{SI,PB_i}} + Q_{B,CN}\frac{C_{CN_i}}{R_{CN,PB_i}} + Q_{B,SP}\frac{C_{SP_i}}{R_{SP,PB_i}} + \frac{dA_{INP_i}}{dt} - Q_{PB,LV}C_{PB_i} \quad (83)$$

where the Portal Blood variables are presented in Table 10.

Table 10. Variables for the Portal Blood

Variable in Documents	Variable in ERDEM (for the Portal Blood)	Description
A_{PB_i}	PRBL_1A_PB(I)	The amount of the ith chemical in the Portal Blood.
C_{PB_i}	PRBL_1C_PB(I)	The concentration of the ith chemical in the Portal Blood.
$\frac{dA_{PB_i}}{dt}$	PRBL_1DA_PB(I)	The rate of change of the amount of the ith chemical in the Portal Blood.
$Q_{PB,LV}$	Q_PB	The volumetric Portal Blood flow rate.

7.3.11 Flow in the Liver Compartment and Bile Flow to the Duodenum Lumen

In the Liver the ith chemical is (1) output from the Liver to venous blood, (2) contained in the Bile flow to the Duodenum Lumen, (3) eliminated by some process to be defined, and (4) metabolized to other compounds (metabolites). Input of the ith chemical is from (1) Intraperitoneal Injection, (2) the arterial blood, (3) the Walls of the Stomach, Duodenum, Lower Small Intestine and Colon via Portal blood, and (4) metabolites which are the same chemical (resulting from metabolism of any of the circulating compounds). The rate of change of the ith chemical in the Bile flowing to the Duodenum from the Liver is given by:

$$\frac{dA_{BL_i}}{dt} = Q_{BL}\frac{C_{LV_i}}{R_{BL,DUL_i}} \quad (84)$$

and the rate of change of the ith chemical in the Liver is:

$$V_{LV}\frac{dC_{LV_i}}{dt} = Q_{B,LV}(C_{AB_i} - \frac{C_{LV,F_i}}{R_{LV,VB_i}}) + Q_{PB,LV}(C_{PB_i} - \frac{C_{LV,F_i}}{R_{LV,VB_i}}) - \frac{dA_{LV,E_i}}{dt} + K_{LP,LV_i}A_{LP_i} - Q_{BL}\frac{C_{LV,F_i}}{R_{BL,DUL_i}} - \sum_{j=1}^{N_{M_i}}\frac{dA_{M,LV_{i,j}}}{dt} + \sum_{I_{C,l,m}=i}\frac{dA_{M,LV_{l,m}}}{dt} \quad (85)$$

where the variables for the Liver and Bile flow are presented in Table 11.

Table 11. Variables for the Liver and Bile

Variable in Documents	Variable in ERDEM (for the Liver and Bile)	Description
A_{BL_i}	LIVR_1A_BL(I)	The amount of the ith chemical in the Bile.
C_{LV_i}	LIVR_1C_LV(I)	The concentration of the ith chemical in the Liver.
C_{LV,F_i}	LIVR_1C_LV_F(I)	The concentration of Free ith chemical in the Liver.
$\frac{dA_{BL_i}}{dt}$	LIVR_1DA_BL(I)	The rate of change of the amount of the ith chemical in the Bile.
$\frac{dA_{LV,E_i}}{dt}$	LIVR_1DA_LV_E(I)	The rate of elimination of the ith chemical from the Liver.
$\frac{dA_{M,LV_{i,j}}}{dt}$	LIVR_1DA_LV_M(I,J)	The rate of formation of the jth Liver metabolite of the ith chemical.
R_{BL,DUL_i}	LIVR_1R_BL_DUL(I)	Bile to Duodenum lumen partition coefficient for the ith chemical.
$V_{LV}\frac{dC_{LV_i}}{dt}$	LIVR_1DA_LV(I)	The rate of change of the amount of the ith chemical in the Liver.
$I_{C,l,m}$	I_CMPD(I,M)	The index of the chemical that is the mth metabolite of the lth chemical.
NM_i	N_M(I)	The number of metabolites for the ith chemical.
$Q_{B,LV}$	QB_LV	The volumetric flow rate of blood through the Liver.
R_{LV,VB_i}	LIVR_1R_LV_VB(I)	The partition coefficient for flow of the ith chemical from the Liver to the Venous Blood.

7.3.12 Chylomicron Flow in the Other Compartments

An additional term representing Chylomicron flow is added to the equations previously specified for the compartments, Brain, Carcass, Derma, Fat, Kidney, Liver, Pulmonary Capillaries, Rapidly Perfused Tissue, Spleen, Slowly Perfused Tissue, and the static lung. Using the Fat compartment as an example, Chylomicrons enter the Fat via the arterial blood (Lipids from the Lymph Pool). The Chylomicrons are mostly removed from the blood by the Liver and the Fat. Table 12 contains the description of the variables used in the equation for the Fat.

Table 12. Variables for the Fat

Variable in Documents	Variable in ERDEM	Description
C_{FT_i}	FAT_1C_FT(I)	The concentration of the ith chemical in the Fat.
C_{FT,F_i}	FAT_1C_FT_F(I)	The concentration of Free ith chemical in the Fat.
$\frac{dA_{FT,E_i}}{dt}$	FAT_1DA_FT_E(I)	The rate of elimination of the ith chemical from the Fat.
$A_{M,FT_{i,j}}$	FTME_1DA_FT_M(I,J)	The rate of formation of the jth Fat metabolite of the ith chemical.
$V_{FT}\frac{dC_{FT_i}}{dt}$	FAT_1DA_FT(I)	The rate of change of the amount of the ith chemical in the Fat.
$Q_{B,FT}$	QB_FT	The volumetric flow rate of blood through the Fat.
R_{FT,VB_i}	FAT_1R_FT_VB(I)	The partition coefficient for flow of the ith chemical from the Fat to the Venous Blood.

$$V_{FT}\frac{dC_{FT_i}}{dt} = Q_{B,FT}C_{AB_i} + K_{LP,FT_i}A_{LP_i} - Q_{B,FT}\frac{C_{FT,F_i}}{R_{FT,VB_i}} - \frac{dA_{FT,E_i}}{dt} - \sum_{j=1}^{N_{M_i}}\frac{dA_{M,FT_{i,j}}}{dt} + \sum_{I_{C,l,m}=i}\frac{dA_{M,FT_{l,m}}}{dt} \quad (86)$$

7.4 Dermal Exposure

Dermal exposure involves contact with surfaces that results in transfer of surface residues. The mass of residue transferred to the skin is dependent on the frequency (events/unit time), duration (time/event), and magnitude or extent of body surface area

(cm^2) contacted and the transferability of the surface residue. It therefore follows intuitively, that dermal exposure is not measurable in the absence of surface contact with resultant surface-to-skin transfer of residues.

Humans come into contact with surfaces through the actions they perform in space (micro-environments) over a random or stratified period of time. This time-motion relationship has been termed the "biomechanics" of dermal exposure. The frequency, duration and magnitude of surface contact can be discerned for occupational exposure where activities are assigned and followed according to established practices, policies and procedures. Incidental dermal exposure is more problematic than occupational exposure given the random and generally unpredictable nature of contact events. Clearly, the measurement, estimation or prediction of a dermal exposure dose metric based on the biomechanics of dermal exposure is research intensive and fraught with uncertainty. We are confronted not only with the uncertainties surrounding the biomechanics of exposure but with dermal transfer factors that are residue and surface media dependent (U.S. EPA, 1998b).

One solution to this problem is to acknowledge the complexities and uncertainties of occupational and incidental dermal exposure and deal with dermal absorption at the boundary of exposure. The dermal dose metric would involve the delivered mass of chemical in a vehicle as represented by a transfer relationship from a surface medium. We are therefore interested in the absorption of the delivered dose into the test system as a means to test metabolism, distribution, elimination and untoward effects of any assigned dermal dose metric, from the perceivable low dose minimum to the most unlikely dose maximum. Dermal exposure is modeled in ERDEM according to presumed outdoor or indoor exposure as chemical residue in a vehicle on the surface of the skin. The default vehicle is aqueous (water) as used to derive the permeation coefficient (Kp) through *in vitro* testing of dermal flux (U.S. EPA, 1992). Dermal absorption from an aqueous vehicle may be compared with absorption from dry residues transferred to the skin from contact with foliage, turf, and solid indoor surfaces, e.g. carpet, vinyl flooring, and painted sheetrock (U.S. EPA, 1998b).

7.4.1 Skin Surface Exposure to Water or Other Vehicle

The skin surface is exposed to chemical in a vehicle (specified as water here) at time T_{SKW_j} for a period of time, T_{SKW,D_j}, which can be repeated at the intT_{SKW,TT_j}. Skin surface water exposures in progress at simulation start time are started and their termination is scheduled.

The concentration of the ith chemical at the skin surface is found from summing the concentrations from each of up to five exposure scenarios:

$$C_{SKS_i} = \sum_{j=1}^{N_{SKW,EXP}} C_{SKW,J_{i,j}} \quad (87)$$

The rate of change of chemical in the dermis due to the concentration C_{SKS_i} on the skin surface is given by:

$$\frac{dA_{SKW,DR_i}}{dt} = C_{SKS_i} K_{SKS,DR,PRM_i} A_{SK}. \quad (88)$$

Variable Definitions for Skin Surface Water Exposure

A_{SK} = Area of the skin covered by the solution containing the chemical,

$A_{SKW,DR}$ = The amount of the ith chemical that has moved from the skin surface to the Dermis in a water exposure,

$\frac{dA_{SKW,DR_i}}{dt}$ = The rate of change in the amount of the ith chemical moving from the skin surface to the Dermis in a water exposure,

C_{SKS} = The concentration of the ith chemical on the skin surface due to all overlapping exposures,

$C_{SKW,J_{i,j}}$ = The concentration of the ith chemical for the jth exposure on the skin surface,

K_{SKS,DR,PRM_i} = The permeation coefficient for the ith chemical from Skin Surface to Dermis.

7.4.2 Skin Surface Exposure to Transfer from a Dry Surface

A chemical exists on a surface represented as a mass per unit area. It is transferred to the skin of a subject represented by a transfer coefficient. A short exposure period would represent a bolus.

The rate of change of chemical on the dermis due to a dry exposure is:

$$\frac{dA_{sks,ex_i}}{dt} = A_{surf_i} K_{sks,rt_i} \quad \textbf{(89)}$$

Integrating this equation gives the total applied dose.

The rate of loss of chemical from the skin surface due to evaporation is given by:

$$\frac{dA_{sks,ev_i}}{dt} = (1.0 - \delta_{wof}) A_{sks_i} (\delta_{ev1} K_{sks,ev1_i} + \delta_{ev2} K_{sks,ev2_i}) \quad \textbf{(90)}$$

where δ_{wof} = 1 if a wash-off is in progress, and zero otherwise,

δ_{ev1} = 1 if the first evaporation rate constant is active and zero otherwise,

δ_{ev2} = 1 if the second evaporation rate constant is active and zero otherwise.

The rate that the ith chemical moves from the skin surface into the dermis is given by:

$$\frac{dA_{sks,dr_i}}{dt} = K_{sks,dr,prm_i} A_{sk} C_{sks_i} \quad \textbf{(91)}$$

where

$$C_{sks_i} = \frac{A_{sks_i}}{V_{sk}} \quad \textbf{(92)}$$

If no wash-off is in progress, then the rate of change of the amount of the i[th] chemical on the skin is given by the rate of application minus the rate of chemical moving into the dermis minus the rate of loss due to evaporation:

$$\frac{dA_{sks_i}}{dt} = \frac{dA_{sks,ex_i}}{dt} - \frac{dA_{sks,dr_i}}{dt} - \frac{dA_{sks,ev_i}}{dt}. \quad \textbf{(93)}$$

If a wash-off is in progress, then:

$$\frac{dA_{sks_i}}{dt} = - \frac{dA_{sks,wof_i}}{dt} \quad \textbf{(94)}$$

where the wash-off is scheduled at time t_{wof} for one time step, Δt, to remove all chemical on the dermis:

$$\frac{dA_{sks,wof_i}}{dt}(t_{wof}) = \frac{A_{sks_i}}{\Delta t}(t_{wof}). \quad \textbf{(95)}$$

Variable Definitions for Dry Skin Surface Exposure

The variables used to model the exposure to a chemical on a dry surface are:

A_{sks_i} = The amount of the ith chemical on the skin,

A_{sks,ev_i} = The amount of the ith chemical that is lost from the skin,

A_{sks,ex_i} = The amount of the dermal exposure to the ith chemical,

A_{sks,wof_i} = The amount of the ith chemical on the skin at the time of the start of wash-off,

A_{surf_i} = The amount of the ith chemical per unit area on the surface object,

$A_{surf_{i,j}}$ = The amount of the ith chemical per unit area on the surface object for the jth scenario - in mass/cm^2;

D_{sk} = The depth of the skin (in some cases it is taken as one centimeter)

K_{sks,rt_i} = The residue transfer coefficient for the ith chemical moving from the surface object to the skin of the subject - in cm^2/time;

$K_{SKS,EV1_i}$ = The rate of loss of chemical from the skin just after application due to processes such as evaporation for the ith chemical - in 1/time (used only if it is a bolus dermal exposure);

$K_{SKS,EV2_i}$ = The rate of loss of the ith chemical from the skin due to processes such as evaporation, from the end of the initial evaporation until wash-off, the end of the simulation, or the next exposure, - in 1/time;

V_{sk} = Volume of the treated skin,

$\Delta t_{ev,i}$ = The time interval between the use of the first and second evaporation rate constant.

Section 8

Chemical Disposition *in silico*

Absorption involves entry of a drug or chemical into the body. We have observed that a chemical may enter directly into the GI tract from intraperitoneal injection (subsection 6.1.1) or more naturally from ingestion of food or from purposeful or accidental "non-dietary" ingestion of filth and extraneous matter (pica or geophagia). Mathematical expressions used to describe absorption into the GI tract were presented in subsection 7.3 for the enteral route of exposure.

The parenteral route involving inhalation exposure was explored in subsection 7.1 for the static lung and subsection 7.2 for the breathing lung. The parenteral route bypasses the GI tract as an organ system of entry. Subsection 7.4 examined the dermal route of parenteral exposure.

Intravascular parenteral administration directly into the blood stream, intravenously or intra-arterially, was considered as an exposure route although this route of administration is important for laboratory or clinical testing (subsection 6.1.3). This approach was also developed for intramuscular injection (subsection 6.1.2) as an avenue of comparison with other parenteral routes of exposure, especially dermal.

Once the drug or chemical enters the blood stream, its disposition in blood and other fluids, e.g. cerebrospinal fluid (CSF), organs and tissues determines its access to the site or sites of action. Drug and chemical disposition involves distribution from blood and fluids to tissues and organs, metabolism in liver and other organs of metabolism, and elimination in exhaled breath, fluids, e.g. milk, and excreta.

8.1 Distribution of Chemical from Blood to Tissues, Organs and in Fluids

8.1.1 Binding in the Arterial Blood

The binding in the arterial blood is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is

$$A_{AB,B_i} = \frac{K_{AB,MxB_i} C_{AB,F_i}}{(K_{AB,DB_i} + ABS(C_{AB,F_i}))} V_{AB} \quad (96)$$

8.1.2 Calculation of Free Chemical in the Arterial Blood

The free chemical in the arterial blood is calculated by subtracting the amount bound from the total amount as follows:

$$A_{AB,F_i} = A_{AB_i} - A_{AB,B_i} \quad (97)$$

8.1.3 The Venous Blood

The venous blood contains chemical output from the compartments and input to the static lung or the breathing lung. The chemical output to blood from the new GI walls is passed to the portal blood.

8.1.3.1 Binding in the Venous Blood

The binding in the venous blood is of the Michaelis-Menten form but an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{VB,B_i} = \frac{K_{VB,MxB_i} C_{VB,F_i}}{(K_{VB,DB_i} + ABS(C_{VB,F_i}))} V_{VB} \quad (98)$$

8.1.3.2 Calculation of Free Chemical in the Venous Blood

The free chemical in the venous blood is calculated by subtracting the amount bound from the total amount as follows:

$$A_{VB,F_i} = A_{VB_i} - A_{VB,B_i} \quad (99)$$

8.1.4 Distribution in Tissues

8.1.4.1 Distribution in the Residual Carcass

The rate of change of the ith chemical in the carcass is given by the rate that chemical enters from the arterial blood, and in the chylomicrons from the lymph pool (when the four walled GI model is used), and exits via the venous blood. Elimination is modeled and the rate of elimination of the ith chemical is subtracted. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the

chemical in the carcass. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$V_{CR}\frac{dC_{CR_i}}{dt} = Q_{B,CR}C_{CR,F_i} + K_{LP,CR_i}A_{LP_i} - Q_{B,CR}\frac{C_{CR,F_i}}{R_{CR,VB_i}} - \frac{dA_{CR,E_i}}{dt} - \sum_{j=1}^{N_{M_i}}\frac{dA_{CR,M_{i,j}}}{dt} + \sum_{I_{C,l,m}=i}\left(\frac{dA_{CR,M_{l,m}}}{dt}\frac{MW_{(i)}}{MW_{(l)}}\right), \quad (100)$$

where MW is molecular weight (not needed if mass units are in moles), and the variable $I_{C,l,m}$ is the circulating compound that is the mth metabolite of the lth circulating compound. The equations for metabolism are presented in subsection 8.2. Binding and elimination equations are presented below.

Binding in the Carcass

The binding in the carcass is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is

$$A_{CR,B_i} = \frac{K_{CR,MxB_i}C_{CR,F_i}}{(K_{CR,DB_i} + ABS(C_{CR,F_i}))}V_{CR} \quad (101)$$

Calculation of Free Chemical in the Carcass

The free chemical in the carcass is calculated by subtracting the amount bound from the total amount as follows:

$$A_{CR,F_i} = A_{CR_i} - A_{CR,B_i} \quad (102)$$

Elimination in the Carcass

There are two types of elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the static lung and a saturable Michaelis-Menten form. The linear form is

$$\frac{dA_{CR,B_i}}{dt} = K_{CR,E_i}A_{CR,F_i} \quad (103)$$

and the saturable form for elimination is:

$$\frac{dA_{CR,E_i}}{dt} = V_{m,CR,E_i} \frac{C_{CR,F_i}}{(K_{mM,CR,E_i} + ABS(C_{CR,F_i}))} \quad (104)$$

8.1.4.2 Distribution in Fat Tissue

The rate of change of the ith chemical in the fat tissue is given by the rate that chemical enters from the arterial blood and the chylomicrons from the lymph pool and exits via the venous blood. Elimination is modeled and the rate of elimination of the ith chemical is subtracted. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the chemical in the fat tissue. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$V_{FT} \frac{dC_{FT_i}}{dt} = Q_{B,FT} C_{FT,F_i} + K_{LP,FT_i} A_{LP_i} - Q_{B,FT} \frac{C_{FT,F_i}}{R_{FT,VB_i}} - \frac{dA_{FT,E_i}}{dt} - \sum_{j=1}^{N_{M_j}} \frac{dA_{FT,M_{i,j}}}{dt} + \sum_{l_{C,l,m}=i} \left(\frac{dA_{FT,M_{l,m}}}{dt} \frac{MW_{(i)}}{MW_{(l)}} \right) \quad (105)$$

The equations for metabolism are presented in the beginning of this section. Binding and elimination equations are presented below.

Binding in Fat Tissue

The binding in the fat is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{FT,B_i} = \frac{K_{FT,MxB} C_{FT,F}}{(K_{FT,DB} + ABS(C_{FT,F}))} V_{FT} \quad (106)$$

Calculation of Free Chemical in Fat Tissue

The free chemical in the fat tissue is calculated by subtracting the amount bound from the total amount as follows:

$$A_{FT,F_i} = A_{FT_i} - A_{FT,B_i} \quad (107)$$

Elimination in Fat Tissue

There are two types of elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the

free ith chemical in the static lung and a saturable Michaelis-Menten form. The linear form is

$$\frac{dA_{FT,B_i}}{dt} = K_{FT,E_i} A_{FT,F_i} \tag{108}$$

and the saturable form for elimination is

$$\frac{dA_{FT,E_i}}{dt} = V_{m,FT,E_i} \frac{C_{FT,F_i}}{(K_{mM,FT,E_i} + ABS(C_{FT,F_i}))} \tag{109}$$

8.1.4.3 Distribution in Slowly Perfused Tissue

The rate of change of the ith chemical in the slowly perfused tissue is given by the rate that the chemical is input from intramuscular injections, from the lymph pool as chylomicrons and as input from the arterial blood that exits via the venous blood. Elimination is modeled and the rate of elimination of the ith chemical is subtracted. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the chemical in the slowly perfused tissue. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$V_{SL} \frac{dC_{SL_i}}{dt} = Q_{B,SL} C_{SL,F_i} + K_{LP,SL_i} A_{LP_i} + \frac{dA_{INM_i}}{dt} - Q_{B,SL} \frac{C_{SL,F_i}}{R_{SL,VB_i}} - \frac{dA_{SL,E_i}}{dt} - \sum_{j=1}^{N_{M_j}} \frac{dA_{SL,M_{i,j}}}{dt} + \sum_{I_{C,l,m}=i} \left(\frac{dA_{SL,M_{l,m}}}{dt} \frac{MW_{(i)}}{MW_{(l)}} \right) \tag{110}$$

The equations for metabolism are presented in subsection 8.2. Binding and elimination equations are presented below.

Binding in the Slowly Perfused Tissue

The binding in the slowly perfused tissue is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{SL,B_i} = \frac{K_{SL,MxB_i} C_{SL,F_i}}{(K_{SL,DB_i} + ABS(C_{SL,F_i}))} V_{SL} \tag{111}$$

Calculation of Free Chemical in the Slowly Perfused Tissue

The free chemical in the slowly perfused tissue is calculated by subtracting the amount bound from the total amount as follows:

$$A_{SL,F_i} = A_{SL_i} - A_{SL,B_i} \tag{112}$$

Elimination in the Slowly Perfused Tissue

There are two types of elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the static lung and a saturable Michaelis-Menten form. The linear form is:

$$\frac{dA_{SL,B_i}}{dt} = K_{SL,E_i} A_{SL,F_i} \tag{113}$$

and the saturable form for elimination is:

$$\frac{dA_{SL,E_i}}{dt} = V_{m,SL,E_i} \frac{C_{SL,F_i}}{(K_{mM,SL,E_i} + ABS(C_{SL,F_i}))} \tag{114}$$

8.1.4.4 Distribution in Rapidly Perfused Tissue

The rate of change of the ith chemical in the rapidly perfused tissue is given by the rate that chemical enters from the lymph pool as chylomicrons and from the arterial blood and exits via the venous blood. Elimination is modeled and the rate of elimination of the ith chemical is subtracted. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the chemical in the rapidly perfused tissue. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$V_{RP} \frac{dC_{RP_i}}{dt} = Q_{B,RP} C_{RP,F_i} + K_{LP,RP_i} A_{LP_i} - Q_{B,RP} \frac{C_{RP,F_i}}{R_{RP,VB_i}} - \frac{dA_{RP,E_i}}{dt} - \sum_{j=1}^{N_{M_j}} \frac{dA_{RP,M_{i,j}}}{dt} + \sum_{I_{C,l,m}=i} \left(\frac{dA_{RP,M_{l,m}}}{dt} \frac{MW_{(i)}}{MW_{(l)}} \right) \tag{115}$$

The equations for metabolism are presented in subsection 8.2. Binding and elimination equations are presented below.

Binding in the Rapidly Perfused Tissue

The binding in the rapidly perfused tissue is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{RP,B_i} = \frac{K_{RP,MxB_i} C_{RP,F_i}}{(K_{RP,DB_i} + ABS(C_{RP,F_i}))} V_{RP} \quad (116)$$

Calculation of Free Chemical in the Rapidly Perfused Tissue

The free chemical in the Rapidly Perfused Tissue is calculated by subtracting the amount bound from the total amount as follows:

$$A_{RP,F_i} = A_{RP_i} - A_{RP,B_i} \quad (117)$$

Elimination in the Rapidly Perfused Tissue

There are two types of elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the static lung and a saturable Michaelis-Menten form. The linear form is:

$$\frac{dA_{RP,B_i}}{dt} = K_{RP,E_i} A_{RP,F_i} \quad (118)$$

and the saturable form for elimination is:

$$\frac{dA_{RP,E_i}}{dt} = V_{m,RP,E_i} \frac{C_{RP,F_i}}{(K_{mM,RP,E_i} + ABS(C_{RP,F_i}))} \quad (119)$$

8.1.5 Distribution of Chemical in Organs

8.1.5.1 Distribution of Chemical from Blood to the Brain

The rate of change of the ith chemical in the brain is given by the rate that chemical enters from the arterial blood and in the chylomicrons from the lymph pool (when the four walled gastro-intestinal model is used), and exits via the venous blood. The blood/brain barrier is modeled by properly choosing the partition coefficients. Elimination of chemical from the brain is modeled and the rate of elimination of the ith chemical is subtracted. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the chemical in the brain. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$V_{BN}\frac{dC_{BN_i}}{dt} = Q_{B,BN}C_{AB,F_i} + K_{LP,BN_i}A_{LP_i} - Q_{B,BN}\frac{C_{BN,F_i}}{R_{BN,VB_i}} - \frac{dA_{BN,E_i}}{dt} - \sum_{j=1}^{N_{M_j}}\frac{dA_{BN,M_{l,j}}}{dt} + \sum_{I_{C,l,m}=i}\left(\frac{dA_{BN,M_{l,m}}}{dt}\frac{MW_{(i)}}{MW_{(l)}}\right) \quad (120)$$

The equations for metabolism are presented at the beginning of this section. Binding and elimination equations are presented below.

Binding in the Brain

The binding in the Brain is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{BN,B_i} = \frac{K_{BN,MxB_i}C_{BN,F_i}}{(K_{BN,DB_i} + ABS(C_{BN,F_i}))}V_{BN} \quad (121)$$

Calculation of Free Chemical in the Brain

The free chemical in the Brain is calculated by subtracting the amount bound from the total amount as follows:

$$A_{BN,F_i} = A_{BN_i} - A_{BN,B_i} \quad (122)$$

Elimination from the Brain

There are two types of elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the Static Lung and a saturable Michaelis-Menten form. The linear form is:

$$\frac{dA_{BN,E_i}}{dt} = K_{BN,E_i}A_{BN,F_i} \quad (123)$$

and the saturable form for elimination is

$$\frac{dA_{BN,E_i}}{dt} = V_{m,BN,E_i} \frac{C_{BN,F_i}}{(K_{mM,BN,E_i} + ABS(C_{BN,F_i}))} \quad (124)$$

8.1.5.2 Distribution of Chemical to the Liver

Stomach/Intestine Model of Distribution to the Liver

The liver compartment has the ith chemical input from the stomach and intestine following intraperitoneal injections. Input from the arterial blood is also included. The ith chemical is moved from the liver to venous blood where it may be lost due to elimination. Additional chemical is bound in the liver using an equilibrium process. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the chemical in the Liver. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$V_{LV} \frac{dC_{LV_i}}{dt} = \frac{dA_{ST,PB_i}}{dt} + \frac{dA_{IN,PB_i}}{dt} + \frac{dA_{INP_i}}{dt} + Q_{B,LV} C_{AB,F_i} - Q_{B,LV} \frac{C_{LV,F_i}}{R_{LV,VB_i}} - \frac{dA_{LV,E_i}}{dt} - \sum_{j=1}^{N_{M_j}} \frac{dA_{LV,M_{i,j}}}{dt} + \sum_{l_{C,l,m}=i} \left(\frac{dA_{LV,M_{l,m}}}{dt} \frac{MW_{(i)}}{MW_{(l)}} \right), \quad (125)$$

where the equations for the input to portal blood from the stomach and the intestine are respectively:

$$\frac{dA_{ST,PB_i}}{dt} = K_{ABS,ST,PB_i} A_{ST_i}, \quad (126)$$

and

$$\frac{dA_{IN,PB_i}}{dt} = K_{ABS,IN,PB_i} A_{IN_i}, \quad (127)$$

where the variable $I_{C,l,m}$ is the circulating compound that is the mth metabolite of the lth circulating compound. The equations for metabolism are presented at the beginning of this section. Binding and elimination equations are presented below.

Gastro-Intestinal Model of Distribution to the Liver

The liver compartment for the complete GI tract (subsection 7.3) has the ith chemical input from the portal blood (from intraperitoneal injections) and lymph pool as chylomicrons in addition to the input from the Arterial Blood. The ith chemical is moved from the liver to the venous blood to the bile which is passed to the Duodenum Lumen, and may be lost due to elimination. Additional chemical is bound in the Liver using an equilibrium process. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the chemical in the Liver. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$V_{LV}\frac{dC_{LV_i}}{dt} = Q_{B,LV}(C_{AB,F_i} - \frac{C_{LV,F_i}}{R_{LV,VB_i}}) + Q_{PB,LV}(C_{PB_i} - \frac{C_{LV,F_i}}{R_{LV,VB_i}}) - \frac{dA_{LV,E}}{dt} + K_{LP,LV_i}A_{LP_i} - Q_{BL}\frac{C_{LV,F_i}}{R_{BL,DUL_i}} - \sum_{j=1}^{N_{M_i}}\frac{dA_{LV,M_{i,j}}}{dt} + \sum_{I_{C,lm}=i}\left(\frac{dA_{LV,M_{l,m}}}{dt}\frac{MW_{(i)}}{MW_{(l)}}\right) \quad (128)$$

The intraperitoneal injection in this case is passed to the portal blood.

Binding in the Liver

The binding in the liver is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is

$$A_{LV,B_i} = \frac{K_{LV,MxB_i}C_{LV,F_i}}{(K_{LV,DB_i} + ABS(C_{LV,F_i}))}V_{LV} \quad (129)$$

Calculation of Free Chemical in the Liver

The free chemical in the liver is calculated by subtracting the amount bound from the total amount as follows:

$$A_{LV,F_i} = A_{LV_i} - A_{LV,B_i} \quad (130)$$

Elimination in the Liver

There are two types of elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the liver and a saturable Michaelis-Menten form. The linear form is:

$$\frac{dA_{LV,B_i}}{dt} = K_{LV,E_i} A_{LV,F_i} \tag{131}$$

and the saturable form for elimination is:

$$\frac{dA_{LV,E_i}}{dt} = V_{m,LV,E_i} \frac{C_{LV,F_i}}{(K_{mM,LV,E_i} + ABS(C_{LV,F_i}))} \tag{132}$$

8.1.5.3 Absorption and Distribution in the Stomach

The stomach has the ith chemical input by bolus ingestion (a plug of food or drink) and rate ingestion (food or drink input over time), with chemical output to portal blood via the liver to the intestine. The equation for the rate of change of ith chemical in the stomach is:

$$\frac{dA_{ST_i}}{dt} = \frac{dA_{BIG_i}}{dt} + \frac{dA_{RIG_i}}{dt} - K_{ABS,ST,PB_i} A_{ST_i} - K_{ST,IN_i} A_{ST_i}, \tag{133}$$

where the bolus ingestion and the rate ingestion exposures are discussed in subsection 6.2.1.

8.1.5.4 The Intestine

The rate of change of the ith chemical in the intestine is given by the rate of input from the stomach and the rate of output to the portal blood via the liver to feces. The equation is:

$$\frac{dA_{IN_i}}{dt} = K_{ST,IN_i} A_{ST_i} - K_{ABS,IN,PB_i} A_{IN_i} - K_{IN,FEC_i} A_{IN_i} \tag{134}$$

8.1.5.5 The Kidney

The rate of change of the ith chemical in the kidney is given by the rate that chemical enters from the arterial blood and in the chylomicrons from the lymph pool (when the four walled GI model is used), and exits via the venous blood and the urine. Chemical may be metabolized and the rate of metabolism further reduces the rate of increase of the chemical in the kidney. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$\begin{aligned} V_{KD} \frac{dC_{KD_i}}{dt} = {} & Q_{B,KD} C_{AB,F_i} + K_{LP,KD_i} A_{LP_i} - Q_{B,KD} \frac{C_{KD,F_i}}{R_{KD,VB_i}} - \frac{dA_{KD,URN_i}}{dt} - \\ & \sum_{j=1}^{N_{M_j}} \frac{dA_{KD,M_{i,j}}}{dt} + \sum_{I_{C,l,m}=i} \left(\frac{dA_{KD,M_{l,m}}}{dt} \frac{MW_{(i)}}{MW_{(l)}} \right) \end{aligned} \tag{135}$$

The equations for metabolism are presented at the beginning of this section. Binding and elimination equations are presented below.

Binding in the Kidney

The binding in the kidney is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{KD,B_i} = \frac{K_{KD,MxB_i} C_{KD,F_i}}{(K_{KD,DB_i} + ABS(C_{KD,F_i}))} V_{KD} \quad \textbf{(136)}$$

Calculation of Free Chemical in the Kidney

The free chemical in the kidney is calculated by subtracting the amount bound from the total amount as follows:

$$A_{KD,F_i} = A_{KD_i} - A_{KD,B_i} \quad \textbf{(137)}$$

Elimination in the Kidney

There are two types of urine elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the Static Lung and a saturable Michaelis-Menten form. The linear form is

$$\frac{dA_{KD,URN_i}}{dt} = K_{KD,URN_i} A_{KD,F_i} \quad \textbf{(138)}$$

and the saturable form for elimination is:

$$\frac{dA_{KD,URN_i}}{dt} = V_{m,KD,URN_i} \frac{C_{KD,F_i}}{(K_{mM,KD,URN_i} + ABS(C_{KD,F_i}))} \quad \textbf{(139)}$$

8.1.5.6 The Spleen

The rate of change of the ith chemical in the spleen is given by the rate that chemical enters from the arterial blood, and in the chylomicrons from the lymph pool (when the four walled GI model is used), and exits via the portal blood (or into the liver if the stomach/intestine GI is used). Elimination is modeled and the rate of elimination of the ith chemical is subtracted. Chemical may be metabolized and the rate of metabolism

further reduces the rate of increase of the chemical in the spleen. Other metabolites may metabolize to the ith chemical and their rate of formation is added. The equation is:

$$V_{SP}\frac{dC_{SP_i}}{dt} = Q_{B,SP}C_{SP,F_i} + K_{LP,SP_i}A_{LP_i} - Q_{B,SP}\frac{C_{SP,F_i}}{R_{SP,PB_i}} - \frac{dA_{SP,E_i}}{dt} - \sum_{j=1}^{N_{M_j}}\frac{dA_{SP,M_{i,j}}}{dt} + \sum_{I_{C,l,m}=i}\left(\frac{dA_{SP,M_{l,m}}}{dt}\frac{MW_{(i)}}{MW_{(l)}}\right) \quad (140)$$

The equations for metabolism are presented at the beginning of this section. Binding and elimination equations are presented below.

Binding in the Spleen

The binding in the spleen is of the Michaelis-Menten form but is an equilibrium relationship so that the amount of the ith chemical that is bound is calculated rather than the rate. The equation is:

$$A_{SP,B_i} = \frac{K_{SP,MxB_i}C_{SP,F_i}}{(K_{SP,DB_i} + ABS(C_{SP,F_i}))}V_{SP} \quad (141)$$

Calculation of Free Chemical in the Spleen

The free chemical in the spleen is calculated by subtracting the amount bound from the total amount as follows:

$$A_{SP,F_i} = A_{SP_i} - A_{SP,B_i} \quad (142)$$

Elimination in the Spleen

There are two types of elimination currently implemented in ERDEM. A linear form in which the rate of elimination is proportional to the rate of change of the amount of the free ith chemical in the static lung and a saturable Michaelis-Menten form. The linear form is:

$$\frac{dA_{SP,B_i}}{dt} = K_{SP,E_i}A_{SP,F_i} \quad (143)$$

and the saturable form for elimination is:

$$\frac{dA_{SP,E_i}}{dt} = V_{m,SP,E_i} \frac{C_{SP,F_i}}{(K_{mM,SP,E_i} + ABS(C_{SP,F_i}))} \quad (144)$$

8.1.5.7 The Dermal Tissue

The dermal tissue receives the ith chemical by permeation through the skin and from the arterial blood and is released to the venous blood according to the equation:

$$V_{DR} \frac{dC_{DR_i}}{dt} = \frac{dA_{SKS,DR_i}}{dt} + K_{LP,DR_i} A_{LP_i} + Q_{B,DR} C_{AB,F_i} - Q_{B,DR} \frac{C_{DR_i}}{R_{DR,VB_i}} \quad (145)$$

where

$$\frac{dA_{SKS,DR_i}}{dt} = C_{SKS_i} K_{PRM,SKS,DR_i} AREA_{SK} \quad (146)$$

8.2 Metabolism in Selected Tissues and Organs

The term metabolism refers to any reaction that produces a new compound. ERDEM has been designed to handle multiple circulating compounds. It is assumed that *all metabolites are circulating and the metabolism structure is the same in all compartments*. The metabolism parameters, however, can be different in each compartment. The equations implemented in ERDEM are presented for the following areas:

- **Enzyme Destruction and Re-synthesis**:

  Maximum rate of change of metabolite formation, taking enzyme destruction and re-synthesis into consideration, is calculated.

- **Maximum Rate of Metabolite Formation**:

  The maximum rate of formation of the metabolite is found for the liver by scaling for species and body volume. The maximum rate for other compartments is scaled from the Liver value.

- **Saturable and Linear Metabolites**:

  Equations and parameters for calculating the rate of metabolite formation.

- **Inhibition**:

  A metabolite or circulating compound may work in such a manner as to inhibit the formation of another metabolite. There are four types of inhibition modeled here,

competitive inhibition, mixed inhibition, strictly non-competitive Inhibition, and uncompetitive Inhibition.

Equations are presented for the liver metabolism with circulating metabolites. The other compartments use similar equations. This is a general form which can be applied to the test case for trichloroethylene (TCE). Chart 1 shows one rendering of TCE which has five (six if DCA is included) circulating compounds including the parent chemical. The chloral and DCA may be treated as if they are circulating compounds in the metabolism structure, but metabolism parameters would be set so that they do not circulate (the DCA is excreted completely in feces and urine so there must be some circulation). The chemical CH is a metabolite of chloral and of TCOH. There is no inhibition depicted in this chart. All seven compounds are handled as circulating compounds in all compartments. The equation for each metabolism process would be the same in each compartment.

The metabolism parameters, maximum velocity (V-Max) and the Michaelis-Menten constant (Km) could be different in each compartment. Each circulating compound may or may not be metabolized in any compartment. Chart 2 shows the separate metabolism for each compound from Chart 1 with the numbering that would be applied. Each circulating compound is shown with its metabolites. The separate numbering of the metabolites of a circulating compound is required since separate metabolism parameters are required for each metabolite.

We are only concerned with the V-Max for metabolism in the Liver. The V-Max for metabolism in other compartments is calculated from that used in the Liver. If the units of volume are changed, the units of the input V-Max cannot be changed. Also the units of the volume of the body used for the scaling conversion cannot be changed. In other words, there can be no volume units conversion before the calculation of the scaled version of the V-Max.

An input reference body volume is assumed (currently one unit) and the V-Max input is assumed to be in units of amount per unit time. The calculation of V-Max then always works. A volume units change is applied both to the reference body volume as well as the current body volume. This then would be consistent for the scaling of the V-Max for elimination as will the maximum binding value in the calculation of the amount bound. This ratio of body volumes will be used throughout the scaling processes in ERDEM.

8.2.1 Implementation Outline

If a circulating compound is metabolized, then one or more metabolites are defined. These may be linear, saturable, or be effected by one of four types on inhibition. Each of these metabolites are themselves considered to be circulating.

The user will input the circulating compound number for each metabolite. The number of metabolites for each circulating compound is used as the input. These metabolites are also assumed to be circulating. The user will input metabolism parameters using i,j with "i" being the index to the circulating compound and "j" being the metabolite counter for the metabolites of circulating compound i. The user will need to input set, print, display and plot statements using the index i.

The individual metabolite amounts are calculated in the compartmental calculations for the individual chemical. The metabolism section for each compartment calculates two sums. The first is the sum of all rates of metabolite formation of the ith circulating compound. The second is the sum of the rate of formation of all metabolites that are the same as the ith circulating compound. These rate sums are integrated in the circulating compound section for each compartment.

8.2.2 Variable Names for Metabolism Parameters

Table 13 presents variable names, with a short description, that are used globally in all compartments. The variables used in the metabolism calculations are shown in Table 14 (the liver compartment for example). Those variables that now have one or two indices but have unchanged names are not listed.

Table 13. Metabolism Variables Used in All Compartments

Variable Name	Variable Description	Notes
CH_NM_SH(I)	Chemical Short Name for ith circulating compound. In SET statements use CH_NM_SH(1,I)	Eight characters, used in error statements.
CH_NM_LG(I)	Chemical Long Name for ith circulating compound.	Thirty characters for use in descriptive text.
N_M(I)	Number of metabolites of the ith circulating compound.	A two digit integer. Maximum value is six. NM_i
I_CMPD(I,J)	Number of the circulating compound that is the jth metabolite of the ith circulating compound.	For j=1 to N_M(i) In eqns: $I_{c,i,j}$
TYPE_M(I,J)	Type of the jth metabolite (equation(s) to use) of the ith circulating compound. In SET statements use TYPE_M(1,I,J).	Up to three characters to specify equation(s) to use.

Table 14. Variables Used in Metabolism Calculations (Liver Example)

Variable Name (Used in Program)	**Variable Description**	**Variable Name** (In documents)
A_LV_F(I)	Amount of the ith chemical that is free.	A_{LV,F_i}
C_LV_F(I)	Concentration of the ith circulating compound that is free.	$C_{LV,Fi}$
A_LV_M_SUM(I)	Sum of the amounts of Liver metabolite of the ith chemical. (mg)	A_{M,LV,SUM_i}
A_LV_MC_SUM(I)	Sum of amounts of Liver metabolite that are the same as the ith chemical. (mg)	A_{MC,LV,SUM_i}
DA_LV_M(I,J)	Rate of formation for the kth Liver metabolite for the ith chemical. (mg/H)	$\frac{dA_{M,LV_{i,j}}}{dt}$
DA_LV_M_SUM(I)	Sum of rates of formation for all Liver metabolites of the ith chemical. (mg/H).	$\frac{dA_{M,LV,SUM_i}}{dt}$
DA_LV_MC_SUM(I)	Sum of rates of formation of all metabolites that are the same chemical as the ith circulating compound. (mg/H)	$\frac{dA_{MC,LV,SUM_i}}{dt}$
DCM_M_LV(I,J)	Maximum rate of change of kth Liver metabolite concentration for the ith chemical. (mg/L/H).	$V_{Mx_0 LV_{i,j}}$
DRM_LV_MEDR(I,J)	Rate of change of the maximum jth Liver metabolite metabolic rate including enzyme destruction and resynthesis for the ith chemical.	$\frac{dV_{Mx,LV,edr_{i,j}}}{dt}$
K_LV_ML(I,J)	The rate constant for the Linear form of the metabolism calculation.	$K_{ML,LV_{i,j}}$
K_MD1_LV(I,J)	First dissociation constant for the inhibitor to formation of the jth Liver metabolite of the ith chemical.	$K_{MD1,LV_{i,j}}$
K_MD2_LV(I,J)	Second dissociation constant for the inhibitor to formation of the jth Liver metabolite of the ith chemical.	$K_{MD2,LV_{i,j}}$
K_MM_LV(I,J)	Michaelis-Menten constant for jth Liver metabolite of ith chemical. (mg/L)	$K_{mm,LV_{i,j}}$
K1_MER(I,J)	First order rate of jth Liver metabolite enzyme resynthesis for ith chemical, (for CHCL3, zero for human and rat). (1/H)	$K_{1M,er_{i,j}}$
K2_MED(I,J)	Second order rate of jth Liver metabolite enzyme destruction for the ith chemical, (for CHCL3, zero for human and rat). (L/MG)	$K_{2M,ed_{i,j}}$
VM_M_LV(I,J)	Maximum rate of jth Liver metabolite metabolism for the ith chemical. (MG/H)	$V_{Mx,LV_{i,j}}$
VM_MEDR_LV(I,J)	Maximum rate of jth Liver metabolite metabolism after taking enzyme change into account for the ith chemical. (MG/H)	$V_{Mx,LV,edr_{i,j}}$

8.2.3 Calculation of Maximum Rate of Change of Metabolism

The equation for the maximum rate of change of metabolism in the Liver for the jth metabolite of the ith chemical is given by

$$V_{Mx,LV_{i,j}} = V_{Mx_0,LV_{i,j}}\left(\frac{V_B}{V_{ref}}\right)^{r_m} \quad \textbf{(147)}$$

where

V_B = volume of the body,
V_{ref} = reference volume for $V_{Mx_0 LV_{i,j}}$
r_m = power of the volume of the body for interspecies scaling.

8.2.4 Calculations When Including Enzyme Destruction and Re-synthesis

The equation for the rate of change of maximum metabolic rate in the liver including enzyme destruction and re-synthesis for the jth metabolite of the ith circulating compound is given by:

$$\frac{dV_{Mx,LV,edr_{i,j}}}{dt} = K_{1M,er_{i,j}}(V_{Mx,LV_{i,j}} - V_{Mx,LV,edr_{i,j}}) - K_{2M,ed_{i,j}} V_{Mx,LV,edr_{i,j}} \frac{dA_{M,LV_{i,j}}}{dt} / V_{LV} \quad (148)$$

where the variable definitions are given in Table 14, and V_{LV} = the volume of the Liver. The value of the maximum metabolic rate taking enzyme destruction and re-synthesis into consideration is obtained by integration as:

$$V_{Mx,LV,edr_{i,j}} = \int \frac{dV_{Mx,LV,edr_{i,j}}}{dt} dt + V_{Mx,LV_{i,j}}. \quad (149)$$

8.2.5 The Rate of Formation of Saturable and Linear Metabolite in the Liver

The rate of formation of the jth metabolite, when saturable, in the liver from the ith circulating compound is given by:

$$\frac{dA_{M,LV_{i,j}}}{dt} = V_{Mx,LV,edr_{i,j}} \frac{C_{LV,F_i}}{\left(K_{mm,LV_{i,j}} + |C_{LV,F_i}|\right)} \quad (150)$$

where the indices *i*, and *j* are defined above and parameters are defined in Table 14. For those metabolites which the user wants to be strictly linear, then the linear form of the equation would apply. The rate of formation of a linear metabolite in the liver is:

$$\frac{dA_{M,LV_{i,j}}}{dt} = K_{ML,LV_{i,j}} A_{LV,F_i}. \quad (151)$$

The sum of the rates of formation of the metabolites for the ith circulating compound can be calculated according to where the rate of formation of metabolites determines the loss in the rate of increase of amount in the liver for the ith circulating compound:

$$\frac{dA_{M,LV,SUM_i}}{dt} = \sum_{j=1}^{N_M} \frac{dA_{M,LV_{i,j}}}{dt}, \quad \textbf{(152)}$$

8.2.6 Circulating Compounds which are Metabolites

The rates of formation of metabolites, in this case in the liver, which are the same as one of the circulating compounds are summed and then added to the rate of increase of the amount of the circulating compound. This is accomplished by assuming that every metabolite could be any of the circulating compounds. An index $I_{c,i,j}$ is saved for each metabolite. If the *j*th metabolite of the ith circulating compound is the same compound as the *k*th circulating compound, then the index *k* for the circulating compound is saved in $I_{c,i,j}$ otherwise the index $I_{c,i,j}$ is set to zero. If the index is non-zero, then the rate of formation of that metabolite is added to a sum for that circulating compound. The rate of formation of a circulating metabolite may be linear or saturated (with inhibition if applicable) where equations (150) and (151) apply. Then

$$\frac{dA_{MC,LV,SUM_k}}{dt} = \sum_{I_{c,i,j}=k} \left(\frac{dA_{M,LV_{i,j}}}{dt} \frac{MW_{(k)}}{MW_{(i)}} \right), \quad \textbf{(153)}$$

where $\frac{dA_{M,LV_{i,j}}}{dt}$ = the contribution to the rate of change of the *k*th chemical in the Liver from the rate of formation of the jth metabolite of the ith chemical.

8.2.7 Inhibition in the Metabolism Process

Compounds elsewhere in the metabolism chains for any of the circulating compounds may inhibit the formation of a given metabolite. There are four kinds of inhibition addressed here. They are defined by the formulas for an apparent V_{max}, and an apparent Michaelis-Menten constant K_{mm} (See Table 15).

$$\frac{dA_{M,LV_{i,j}}}{dt} = V_{\max,App_{i,j}} \frac{C_{LV,F_i}}{\left(K_{mm,App_{i,j}} + |C_{LV,F_i}|\right)}, \quad \textbf{(154)}$$

where $V_{max,App}$ and $K_{mm,App}$ are taken from Table 15 for the inhibition case that applies.

Table 15. Parameter Formulas for Four Types of Inhibition of Metabolism

Type of Inhibition	$V_{max,App}$	$K_{mm,App}$
Competitive Inhibition	$V_{Mx,LV,edr_{i,j}}$	$K_{mm,LV_{i,j}}(1 + C_{LV,F_{Ii,j}} / K_{MD1,LV_{i,j}})$
Mixed Inhibition	$\frac{V_{Mx,LV,edr_{i,j}}}{(1 + C_{LV,F_{Ii,j}} / K_{MD2,LV_{i,j}})}$	$K_{mm,LV_{i,j}} \frac{(1 + C_{LV,F_{Ii,j}} / K_{MD1,LV_{i,j}})}{(1 + C_{LV,F_{Ii,j}} / K_{MD2,LV_{i,j}})}$

Table 15. Parameter Formulas for Four Types of Inhibition of Metabolism

Type of Inhibition	$V_{max,App}$	$K_{mm,App}$
Pure non-competitive Inhibition	$\frac{V_{Mx,LV,edr_{i,j}}}{(1 + C_{LV,F_{Ii,j}} / K_{MD2,LV_{i,j}})}$	$K_{mm,LV_{i,j}}$
Uncompetitive Inhibition	$\frac{V_{Mx,LV,edr_{i,j}}}{(1 + C_{LV,F_{Ii,j}} / K_{MD2,LV_{i,j}})}$	$\frac{K_{mm,LV_{I,i,j}}}{(1 + C_{LV,F_{Ii,j}} / K_{MD2,LV_{i,j}})}$

where $I_{i,j}$ = zero or the index to the chemical that is the inhibitor to the jth metabolite of the ith circulating compound

8.2.8 Metabolism in the Other Organs and Tissues

8.2.8.1 Metabolism in the Brain

The brain metabolism equations are the same as those for the liver except that the equation for the V-Max is given as a function of the Liver value from the equation:

$$V_{Mx,BN_{i,j}} = V_{Mx,LV_{i,j}} R_{M,BN,LV_{i,j}} \frac{V_{BN}}{V_{LV}} \quad \textbf{(155)}$$

where $R_{M,BN,LV_{i,j}}$ is a scaling factor for V-Max in the Brain for the jth metabolite of the ith chemical.

8.2.8.2 Metabolism in the Kidney

The kidney metabolism equations are the same as those for the liver except that the equation for the V-Max is given as a function of the liver value from the equation:

$$V_{Mx,KD_{i,j}} = V_{Mx,LV_{i,j}} R_{M,KD,LV_{i,j}} \frac{V_{KD}}{V_{LV}} \quad \textbf{(156)}$$

where $R_{M,KD,LV_{i,j}}$ is a scaling factor for V-Max in the Kidney for the jth metabolite of the ith chemical.

8.2.8.3 Metabolism in the Carcass

The carcass metabolism equations are the same as those for the liver except that the equation for the V-Max is given as a function of the Liver value from the equation:

$$V_{Mx,CR_{i,j}} = V_{Mx,LV_{i,j}} R_{M,CR,LV_{i,j}} \frac{V_{CR}}{V_{LV}} \quad \textbf{(157)}$$

where $R_{M,CR,LV_{i,j}}$ is a scaling factor for V-Max in the Carcass for the jth metabolite of the ith chemical.

8.2.8.4 Metabolism in the Fat

The fat metabolism equations are the same as those for the liver except that the equation for the V-Max is given as a function of the liver value from the equation:

$$V_{Mx,FT_{i,j}} = V_{Mx,LV_{i,j}} R_{M,FT,LV_{i,j}} \frac{V_{FT}}{V_{LV}} \quad \textbf{(158)}$$

where $R_{M,FT,LV_{i,j}}$ is a scaling factor for V-Max in the Fat for the jth metabolite of the ith chemical.

8.2.8.5 Metabolism in the Slowly Perfused Tissue

The slowly perfused tissue metabolism equations are the same as those for the Liver except that the equation for the V-Max is given as a function of the Liver value from the equation:

$$V_{Mx,SL_{i,j}} = V_{Mx,LV_{i,j}} R_{M,SL,LV_{i,j}} \frac{V_{SL}}{V_{LV}} \quad \textbf{(159)}$$

where $R_{M,SL,LV_{i,j}}$ is a scaling factor for V-Max in the slowly perfused tissue for the jth metabolite of the ith chemical.

8.2.8.6 Metabolism in the Rapidly Perfused Tissue

The rapidly perfused tissue metabolism equations are the same as those for the liver except that the equation for the V-Max is given as a function of the Liver value from the equation:

$$V_{Mx,RP_{i,j}} = V_{Mx,LV_{i,j}} R_{M,RP,LV_{i,j}} \frac{V_{RP}}{V_{LV}} \quad \textbf{(160)}$$

where $R_{M,RP,LV_{i,j}}$ is a scaling factor for V-Max in the rapidly perfused tissue for the jth metabolite of the ith chemical.

8.2.8.7 Metabolism in the Spleen

The spleen metabolism equations are the same as those for the liver except that the equation for the V-Max is given as a function of the liver value from the equation:

$$V_{Mx,SP_{i,j}} = V_{Mx,LV_{i,j}} R_{M,SP,LV_{i,j}} \frac{V_{SP}}{V_{LV}} \quad \textbf{(161)}$$

where $R_{M,SP,LV_{i,j}}$ is a scaling factor for V-Max in the spleen for the jth metabolite of the ith chemical.

Section 9

Exposure Related Dose Estimating Model (ERDEM) Enzyme Kinetics Implementation

9.1 The ERDEM Equations for Enzyme Kinetics

A set of enzymes is defined for each compartment. This section of the report only presents equations for the liver but these equations are the same for all other compartments: brain, arterial blood, venous blood, kidney, slowly perfused tissue, lung tissue or static lung, portal blood, and, pulmonary capillaries. There is currently no enzyme kinetics in the spleen, stratum corneum, testicles, ovaries, carcass, fat, or, rapidly perfused tissue. Variable definitions are provided at the end of this section.

The user is expected to input the set of chemicals which must include the substrate and metabolites. In addition, the user inputs a set of enzymes for a given simulation. The user sets flags for the enzymes used in each compartment and the chemicals that serve as substrates for the designated enzymes. A given compartment may have only one enzyme and another may have more. The rate, amount, and concentration variables are referenced by the ith chemical and lth enzyme, where the inputs from the ERDEM front end are by chemical and enzyme name where N_Z is the number of enzymes for the simulation. Flags are used in ERDEM that indicate which enzymes are active for the simulation, and which chemicals are competing with the substrate being acted on by an enzyme:

L_LV_Z is a logical flag set to true if there is any enzyme reaction in the Liver.

L_LV_Z_L(l) (is a logical flag set to true if there is an enzyme reaction in the Liver for the lth enzyme.

L_LV_Z_I_L(i,l) (is a logical flag set to true if the lth enzyme is inhibited by the ith chemical. When using the front end, the enzymes and chemicals are input by name, not by index.

9.2 Elimination of Chemical Due to Competition with Enzyme Metabolism

The loss of ith chemical due to competition with the substrate during the metabolism by the lth enzyme is given by

$$\frac{dA_{LV,Z,E_{j,l}}}{dt} = \frac{dA_{LV,Z,F,I_{i,j}}}{dt} \quad \textbf{(162)}$$

This equation is an additional elimination term that is included in the body mass balance for the liver.

9.3 Enzymatic Reactions in the Liver

The enzyme reaction in the Liver is a function of each enzyme and the current chemical. Equation 162 expresses the rate of loss of the current chemical due to interaction with each enzyme in the liver. This involves formation of a substrate-enzyme complex which reduces the expected steady state level of free enzyme. A regeneration function replaces some of the enzyme that was lost due to formation of the substrate-enzyme complex. A enzyme re-synthesis function also replaces some enzyme that was degraded. This is expressed in the equation below where the first term is the regeneration, the second is the re-synthesis term and the third represents substrate-enzyme complex formation. The degradation term was removed because it operates on enzyme that has been inhibited and then aged. The mass balance equation for the rate of change of activity (mass) of kth free enzyme in the liver due to one or more chemicals is given by

$$\frac{dA_{LV,F,Z_k}}{dt} = \sum_{i \in N_{LV,Z,I_{i,k}}} \left(\frac{dA_{LV,F,Z,R_{i,k}}}{dt} + \frac{dA_{LV,F,Z,S_{i,k}}}{dt} - \frac{dA_{LV,F,Z,I_{i,k}}}{dt} \right) \quad \textbf{(163)}$$

where the kth enzyme may bind with more than one chemical. The set of chemicals that may bind the kth enzyme is in $N_{LV,Z,I_{i,k}}$.

9.3.1 Enzymatic Inhibition

The rate of change of the kth enzyme due to the ith inhibiting chemical is determined by the concentration of kth free enzyme and the concentration of the ith chemical causing the inhibition.

$$\frac{dA_{LV,Z,I_{i,k}}}{dt} = K_{LV,Z,I_{i,k}} C_{LV,F,Z_k} C_{LV,F_i} V_{LV} \quad \textbf{(164)}$$

where the concentration of free kth enzyme in the liver is found by integrating equation 163 and dividing by the volume of the liver to get the concentration.

9.3.2 Enzyme Regeneration

Enzyme regeneration occurs when enzyme titer is reduced due to binding activity. The regeneration process acts only when enzyme-substrate or inhibitor complexes are formed (reduced by the amount that is aged, regenerated and re-synthesized) and is dependent on the affinity of the substrate chemical or competing inhibiting chemical for the enzyme. Thus regeneration occurs for the current titer of kth enzyme caused by binding of the ith chemical. Each chemical may influence a different rate of regeneration.

$$\frac{dA_{LV,Z,R_k}}{dt} = K_{LV,Z,R_k}(A_{LV,Z,I_k} - A_{LV,Z,R_k} - A_{LV,Z,S_k} - A_{LV,Z,A_k}) \quad \textbf{(165)}$$

where the amount of inhibited kth enzyme is obtained by integrating equation 164. Or in a saturable form where V_{mx} and K_{mm} are not defined at this time.

$$\frac{dA_{LV,Z,R_k}}{dt} = \frac{V_{MX,Z,R_k}(C_{LV,Z,I_k} - C_{LV,Z,R_k} - C_{LV,Z,S_k} - C_{LV,Z,A_k})}{K_{mm,Z,R_k} + \left|C_{LV,Z,I_k} - C_{LV,Z,R_k} - C_{LV,Z,S_k} - C_{LV,Z,A_k}\right|} \quad \textbf{(166)}$$

9.3.3 Enzyme Re-synthesis

$$\frac{dA_{LV,Z,S_{ik}}}{dt} = K_{LV,Z,S_{ik}}(A_{LV,Z,D_{ik}} - A_{LV,Z,S_{ik}}) \quad \textbf{(167)}$$

Enzyme re-synthesis acts to replace degraded enzyme (lost). Aging involves tightly bound enzyme-substrate or more likely, enzyme-inhibitor complexes. The degradation is modeled to act on the aged enzyme and the bound enzyme. The enzyme re-synthesis is a function of the enzyme only and is given by (linear form)

where the concentration of the degraded kth enzyme is found by summing the amounts found from integrating equations 170 and 171. The saturable form might be given by (where V_{mx} and K_{mm} are not defined at this time)

$$\frac{dA_{LV,Z,S_{ik}}}{dt} = \frac{V_{Mx,LV,Z,S_{ik}}(C_{LV,Z,D_{ik}} - C_{LV,Z,S_{ik}})}{K_{mm,LV,Z,S_{ik}} + \left|C_{LV,Z,D_{ik}} - C_{LV,Z,S_{ik}}\right|} \quad \textbf{(168)}$$

9.3.4 Enzyme Aging and Degradation

Enzyme degradation is modeled to act on bound enzymes and aged enzyme. The degraded enzyme no longer exists (replaced by re-synthesis). The amount of bound and aged enzyme is then reduced by the degradation. The rate of formation of aged enzyme is a function of the amount of bound enzyme (reduced by the amount aged, regenerated, and re-synthesized), and is given by (in a linear form)

$$\frac{dA_{LV,Z,A_{i,k}}}{dt} = K_{LV,Z,A_{i,k}} \left(A_{LV,Z,I_{i,k}} - A_{LV,Z,R_{i,k}} - A_{LV,Z,S_{i,k}} - A_{LV,Z,A_{i,k}}\right) \quad (169)$$

The equation for the rate of formation of degraded bound enzyme consists of the amount bound, reduced by the amount aged, regenerated, and re-synthesized.

$$\frac{dA_{LV,Z,DI_{i,k}}}{dt} = K_{LV,Z,DI_{i,k}} \left(A_{LV,Z,I_{i,k}} - A_{LV,Z,R_{i,k}} - A_{LV,Z,S_{i,k}} - A_{LV,Z,A_{i,k}}\right) \quad (170)$$

The equation for the rate of formation of aged bound enzyme is the amount of aged enzyme reduced by the amount of bound enzyme already aged:

$$\frac{dA_{LV,Z,DA_{i,k}}}{dt} = K_{LV,Z,DA_{i,k}} \left(A_{LV,Z,A_{i,k}} - A_{LV,Z,DA_{i,k}}\right) \quad (171)$$

The total amount degraded enzyme is then

$$A_{LV,Z,D_{i,k}} = A_{LV,Z,DA_{i,k}} + A_{LV,Z,DI_{i,k}} \quad (172)$$

9.4 Nomenclature for the Liver Enzyme Equations

9.4.1 Amounts in the Liver

$A_{LV,Z,A_{i,k}}$ = Amount of kth enzyme resulting from aging of the enzyme bound to the ith chemical,

$A_{LV,Z,D_{i,k}}$ Amount of the kth enzyme that is degraded, due to the action of the ith chemical,

$A_{LV,Z,DA_{i,k}}$ Amount of the aged kth enzyme that is degraded, due to the action of the ith chemical,

$A_{LV,Z,E_{i,k}}$ Amount of the kth enzyme that is eliminated due to binding of the ith chemical,

$A_{LV,Z,I_{i,k}}$ = Amount of the kth enzyme that is bound by the ith chemical,

$A_{LV,Z,R_{i,k}}$ = Amount of the bound kth enzyme that is regenerated, due to the action of the ith chemical,

$A_{LV,Z,S_{i,k}}$ = Amount of the degraded kth enzyme that is re-synthesized, due to the action of the ith chemical.

9.4.2 Concentrations in the Liver

$C_{LV,Z,A_{i,k}}$ = Concentration of the kth enzyme resulting from aging of the enzyme bound by the ith chemical,

$C_{LV,Z,D_{i,k}}$ Concentration of the kth enzyme that is degraded, due to the action of the ith chemical,

$C_{LV,Z,I_{i,k}}$ = Concentration of the kth enzyme that is bound by the ith chemical,

$C_{LV,Z,R_{i,k}}$ = Concentration of the bound kth enzyme that is regenerated, due to the action of the ith chemical,

$C_{LV,Z,S_{i,k}}$ = Concentration of the degraded kth enzyme that is re-synthesized, due to the action of the ith chemical.

9.4.3 Rates of Change of the Amount of Enzyme in the Liver

$\frac{dA_{LV,Z,A_{i,k}}}{dt}$ = Rate of change of the amount of kth enzyme resulting from aging of the enzyme bound to the ith chemical,

$\frac{dA_{LV,Z,D_{i,k}}}{dt}$ = Rate of change of the amount of the kth enzyme that is degraded, due to the action of the ith chemical,

$\frac{dA_{LV,Z,I_{i,k}}}{dt}$ = Rate of change of the amount of the kth enzyme that is bound to the ith chemical,

$\frac{dA_{LV,Z,R_{i,k}}}{dt}$ = Rate of change of the amount of the bound kth enzyme that is regenerated, due to the action of the ith chemical,

$\frac{dA_{LV,Z,S_{i,k}}}{dt}$ = Rate of change of the amount of the degraded kth enzyme that is re-synthesized, due to the action of the ith chemical.

9.4.4 Rate Constants for the Reactions

$K_{LV,Z,A_{i,k}}$ = Rate constant for the aging of the kth enzyme that was bound by the ith chemical,

$K_{LV,Z,DA_{i,k}}$ = Rate constant for the degradation of the aged kth enzyme that occurs due to the action of the ith chemical,

$K_{LV,Z,DI_{i,k}}$ = Rate constant for the degradation of the bound kth enzyme that occurs due to the action of the ith chemical,

$K_{LV,Z,I_{i,k}}$ = Rate constant for the bound of the kth enzyme by the ith chemical,

$K_{LV,Z,R_{i,k}}$ = Rate constant for the regeneration of the bound kth enzyme that is due to the action of the ith chemical,

$K_{LV,Z,S_{i,k}}$ = Rate constant for the re-synthesis of the degraded kth enzyme, due to the action of the ith chemical.

References

Abbas, R., Fisher, W.F. (1997). A Physiologically Based Pharmacokinetic Model for Trichloroethylene and Its Metabolites, Chloral Hydrate, Trichloroacetate, Dichloroacetate, Trichloroethanol, and Trichloroethanol Glucuronide in B6c3f1 Mice. *Toxicology and Applied Pharmacology* **147**, 15-30 (Page 18).

Fisher, J.W., Mahle, D., Abbas, R. (1998). A Human Physiologically Based Pharmacokinetic Model for Trichloroethylene and Its Metabolites, Trichloroacetic Acid and Free Trichloroethanol. *Toxicology and Applied Pharmacology* **152**, 339-359.

Ness, Shirley A., 1994. Surface and Dermal Monitoring for Toxic Exposure, Van Nostrand Reinhold, New York, NY.

U.S. EPA, 1992. Dermal Exposure Assessment: Principles and Applications, January 1992. EPA/600/8-01/011B, Interim Report.

U.S. EPA, 1998b. Assessment of Time-Motion Videoanalysis for the Acquisition of Biomechanics Data in the Calculation of Exposure to Children, February 1998. EPA/600/x-98/002A-D.

United States
Environmental Protection
Agency

Please make all necessary changes on the below label, detach or copy, and return to the address in the upper left-hand corner.

If you do not wish to receive these reports CHECK HERE ☐; detach, or copy this

PRESORTED STANDARD

POSTAGE AND FEES PAID

EPA PERMIT NO. G-35

Offic

e of Research
and Development (8101R)
Washington, DC 20460

Official Business
Penalty for Private Use
$300

EPA/600/R-06/061
June 2006
www.epa.gov