OncoLogic™ Quick Start Tutorial

A Step-by-Step Guide to

Using OncoLogic™ to Predict Potential Carcinogenicity

OncoLogic™ – How it Works

- Designed to mimic the thinking and reasoning of human experts
- Uses knowledge-based rules for chemical classes to predict cancer concern
- Evaluates how substituents on the chemical may affect carcinogenicity
  - Concern level changes accordingly
- Assigns a baseline concern level ranging from low to high

Concern Levels

OncoLogic™ Concern	Definition
Low	**Unlikely to be carcinogenic**
Marginal	**Likely to have equivocal carcinogenic activity**
Low – Moderate	**Likely to be weakly carcinogenic**
Moderate	**Likely to be a moderately active carcinogen**
Moderate – High	**Highly likely to be a moderately active carcinogen**
High	**Highly likely to be a potent carcinogen**

OncoLogic™ – How it Works

- Two separate methods are used to predict potential carcinogenicity
  - SAR analysis (i.e., structural analysis)
  - Functional analysis

SAR Analysis

- OncoLogic™ uses mechanism-based SAR analysis to predict potential carcinogenicity
- Analysis is based upon knowledge of the structural and biological bases of carcinogenicity of various classes of chemical carcinogens
- Incorporates knowledge-based rules and chemical-specific user input
- Rules were developed jointly by cancer experts and system development experts based on cancer studies and scientific publications

Functional Analysis

- Integrates the results of available mechanistic / non-cancer studies on the chemical to predict potential carcinogenicity
  - Study results are entered by the user
  - If no such studies are available, only SAR Analysis can be performed
- Must be performed independently of SAR Analysis
- Can be used to provide support to the results of structural analysis, or can be used as an independent method of analysis of carcinogenicity

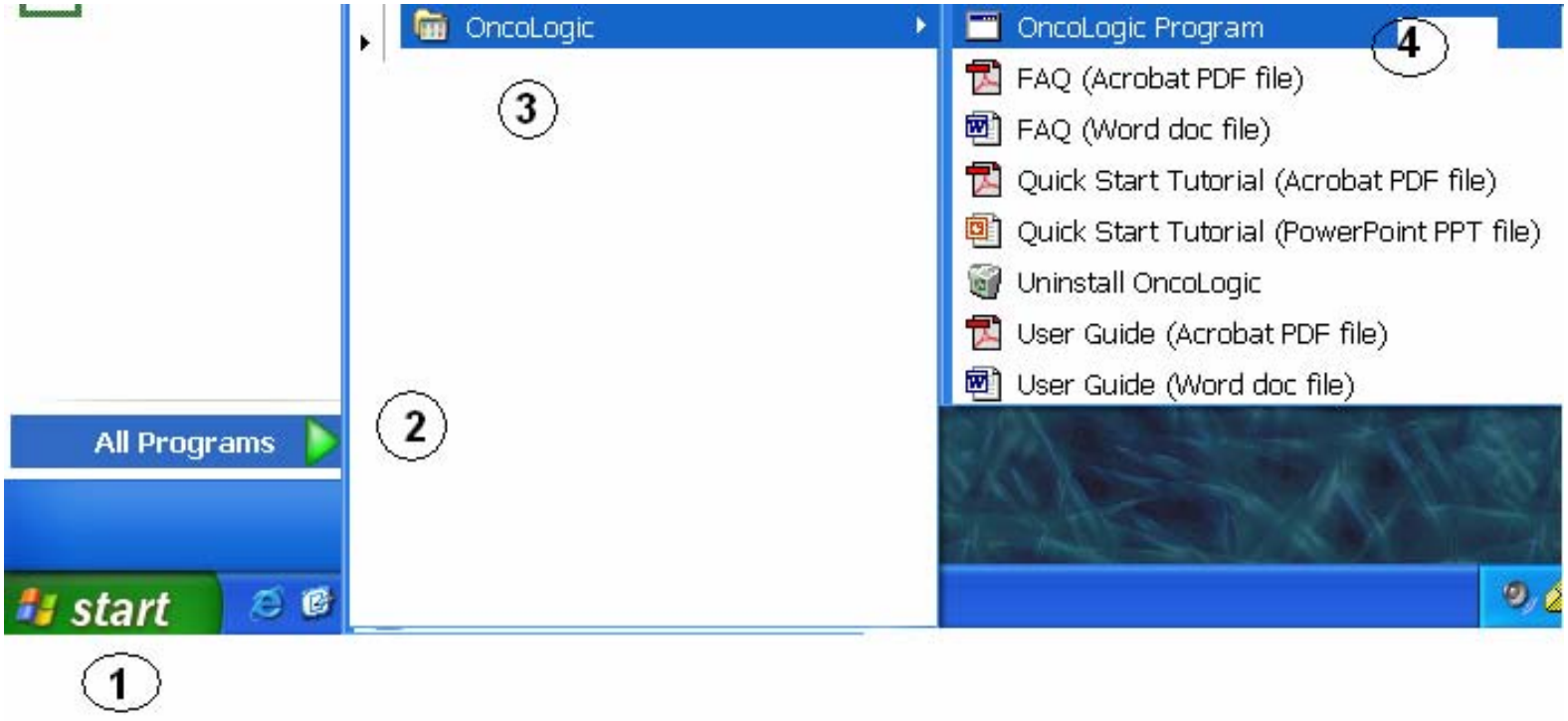
Starting OncoLogic™ (Method 1)

The OncoLogic Set-Up (Installation) Program places a "**Desktop Icon**" on the Windows Desktop similar to the Icon shown here:

If desired, this Icon is easily removed from the Windows Desktop by "dragging" it to the Recycle Bin or by placing the mouse pointer on the Icon, right-mouse button clicking, and then deleting.

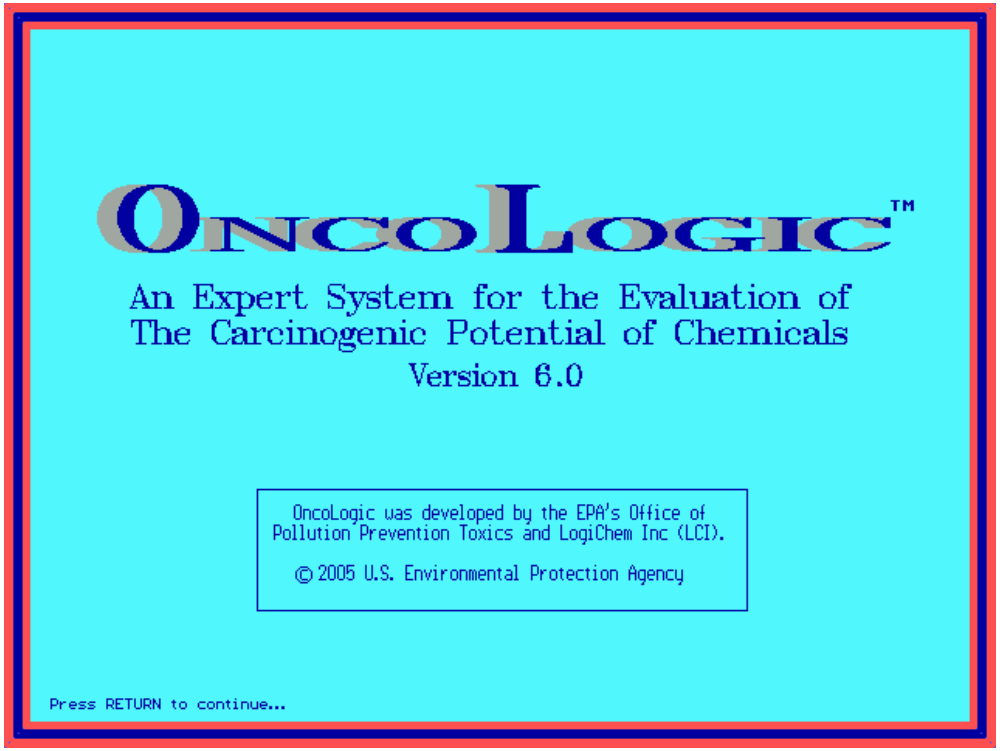
Starting OncoLogic™ (Method 2)

(1) Press the “Start” Button
(2) Select “All Programs”
(3) Select “OncoLogic”
(4) Select “OncoLogic Program”



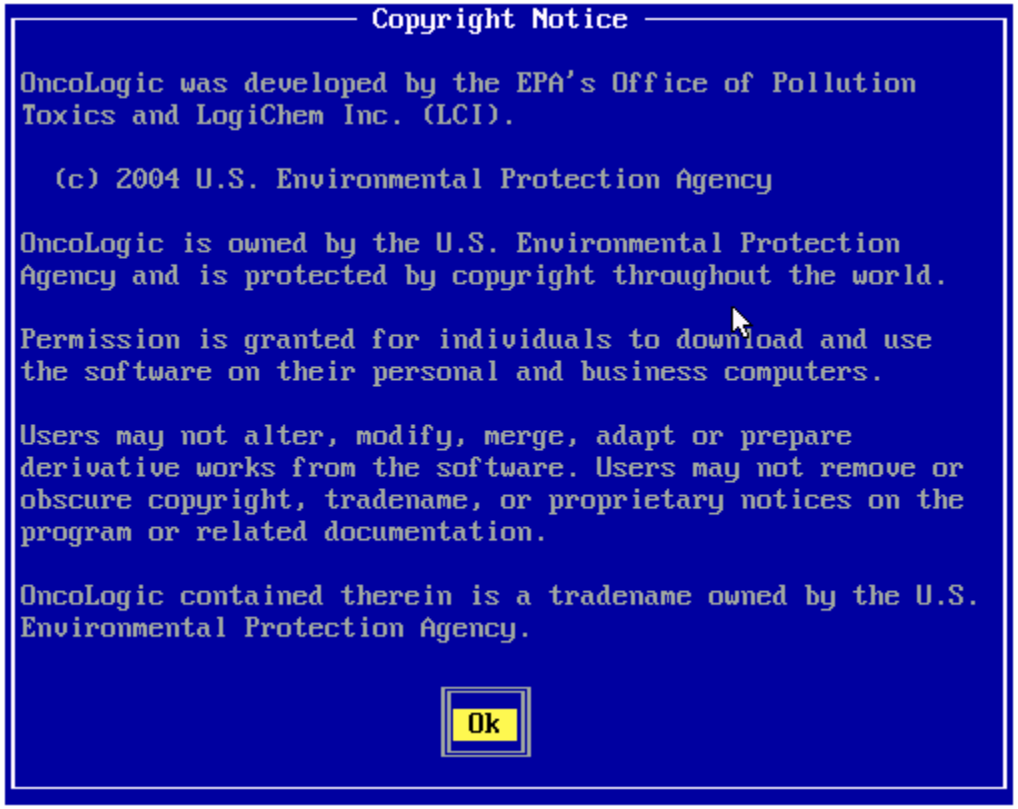
Running OncoLogic™

- Press “Enter” on your keyboard at the Welcome screen



Running OncoLogic™ (cont.)

- Click “Ok” at the Disclaimer screen to acknowledge that you accept the terms and conditions of using OncoLogic™

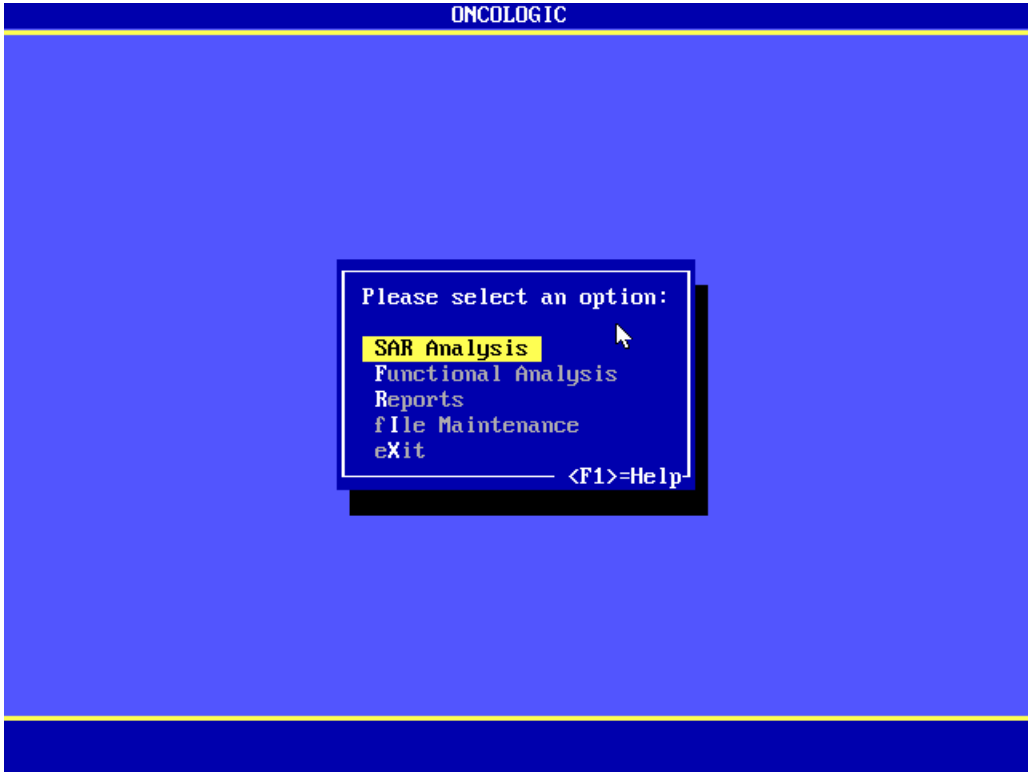


Running OncoLogic™ (cont.)

- Click “Ok” at the screen that describes the development of OncoLogic™ rules

Running OncoLogic™ (cont.)

- Select from one of the five options displayed, which are briefly described on the next slide



Running OncoLogic™ (cont.)

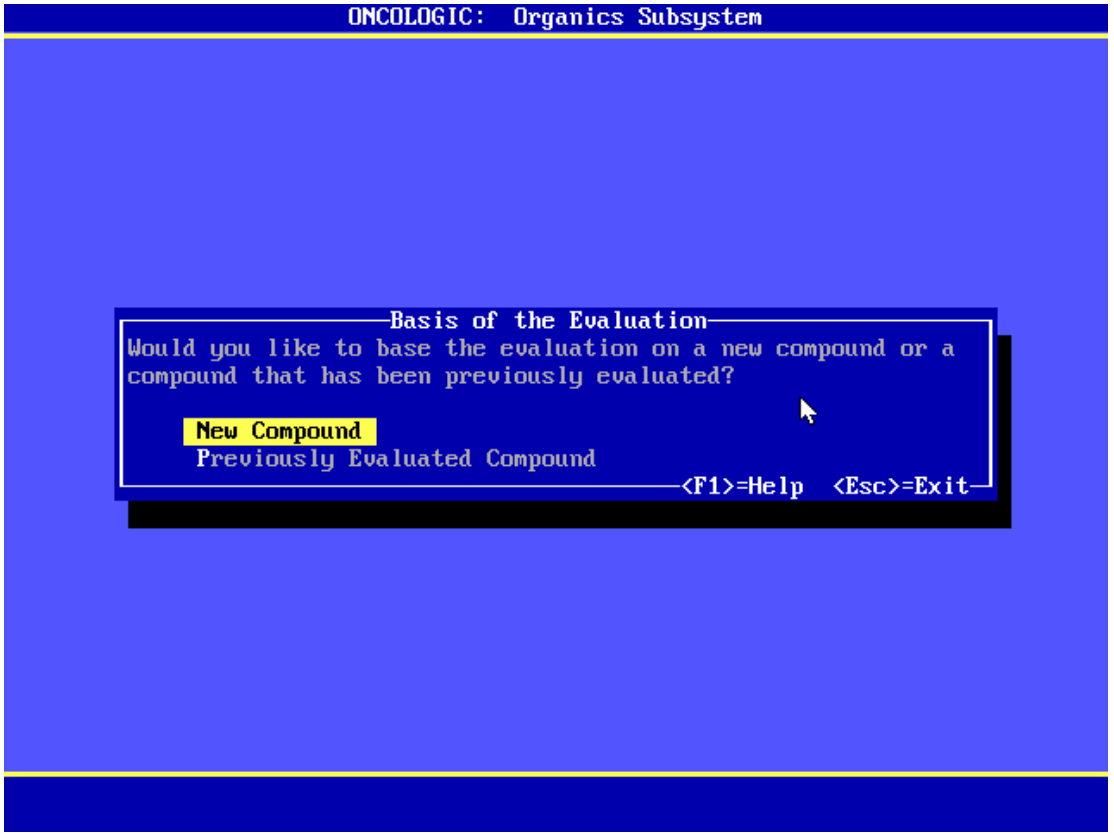
- SAR Analysis
  - Uses knowledge rules to predict carcinogenicity
- Functional Analysis
  - Uses mechanistic / non-cancer studies to predict carcinogenicity
- Reports
  - View or print OncoLogic™ reports and user input data
- File Maintenance
  - Delete or save reports
- Exit

SAR Analysis

- Four modules
  - Organics
  - Metals
  - Polymers
  - Fibers
- Different methods are used to evaluate each type of substance

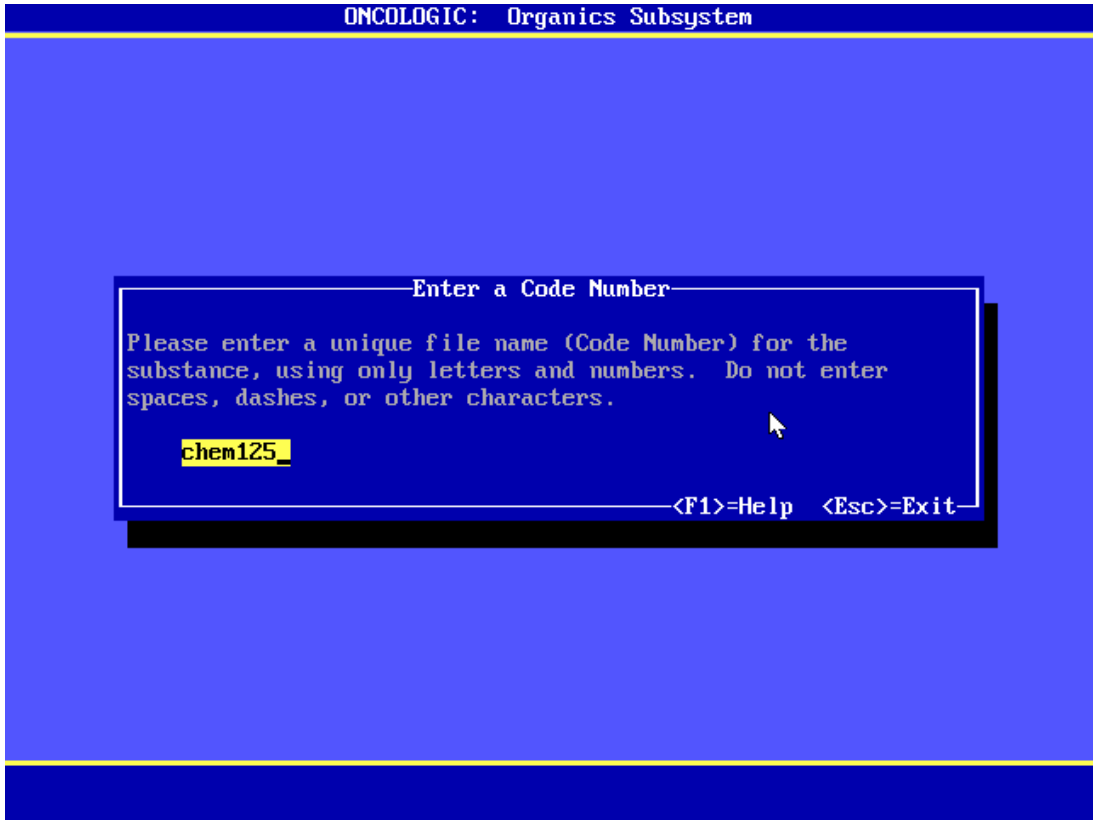
Running OncoLogic™: Organics Module

- Select either “New Compound” or “Previously Evaluated Compound”



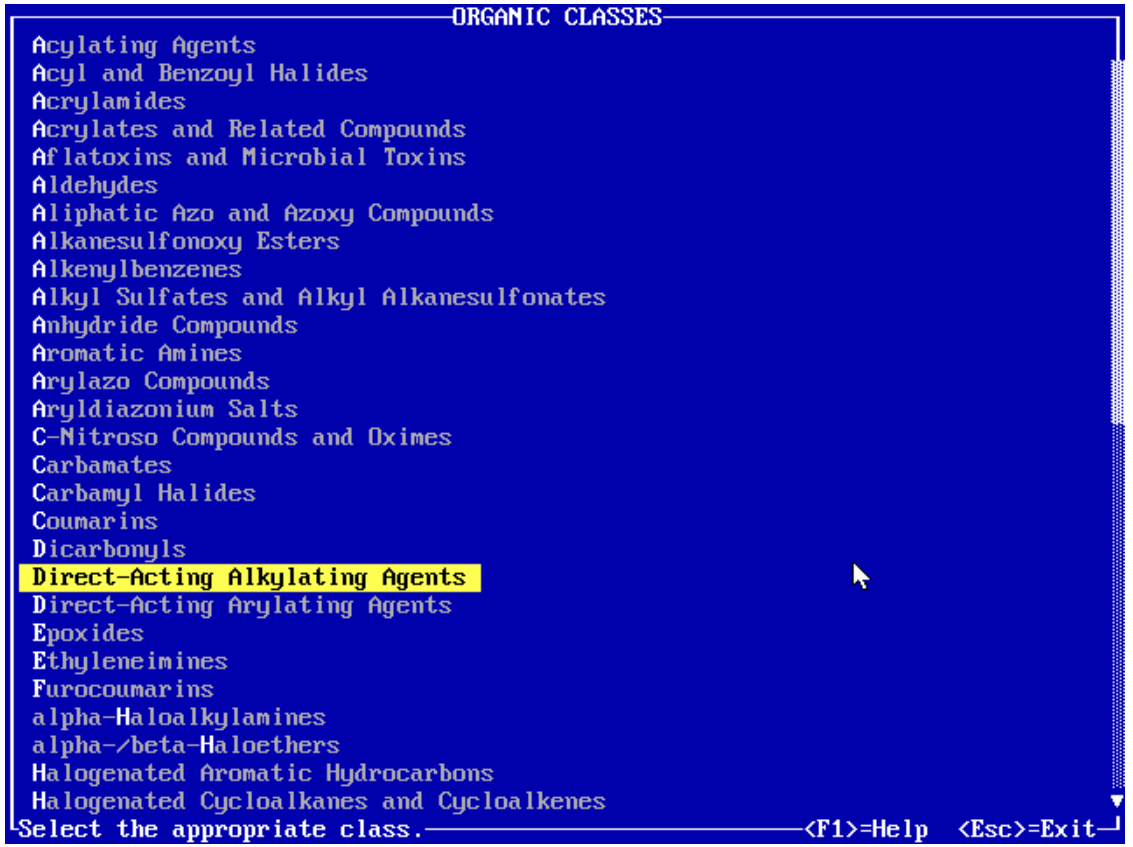
Running OncoLogic™: Organics Module (cont.)

- Enter a Code Number
  - Unique
  - Letters / numbers only
  - Record ID since it will be needed to view and print reports and user inputs



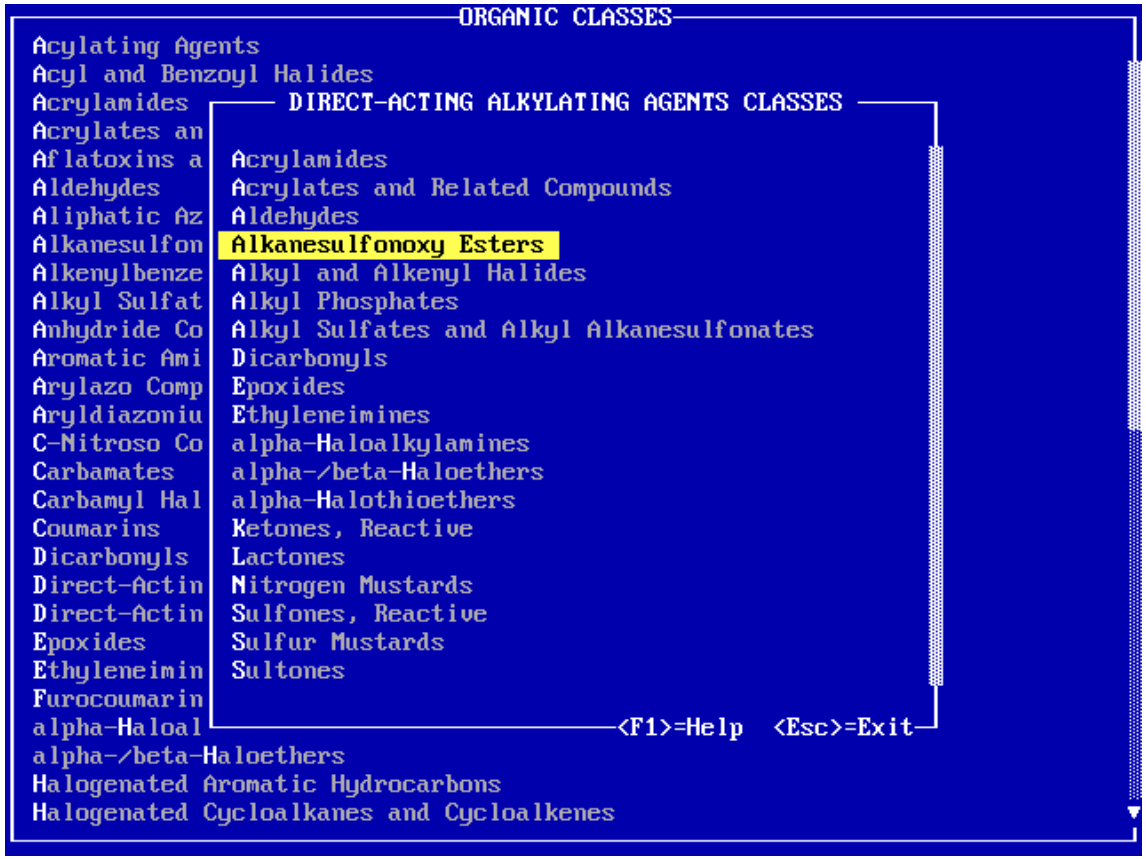
Running OncoLogic™: Organics Module (cont.)

- Select an appropriate chemical class from the Organic Classes screen
  - View sample structures by highlighting a class and pressing “F1”



Running OncoLogic™: Organics Module (cont.)

- Select a subclass, if you are prompted to do so

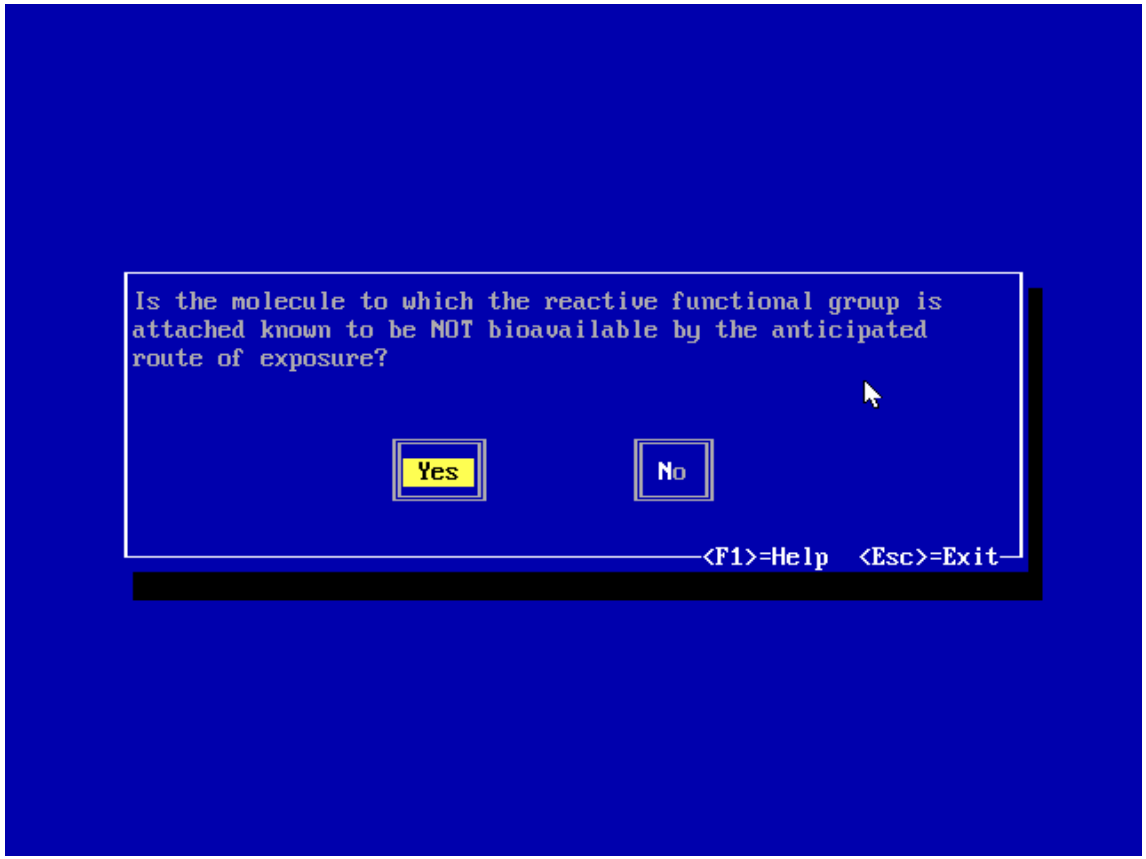


Running OncoLogic™: Organics Module (cont.)

- Enter a Substance Identification number

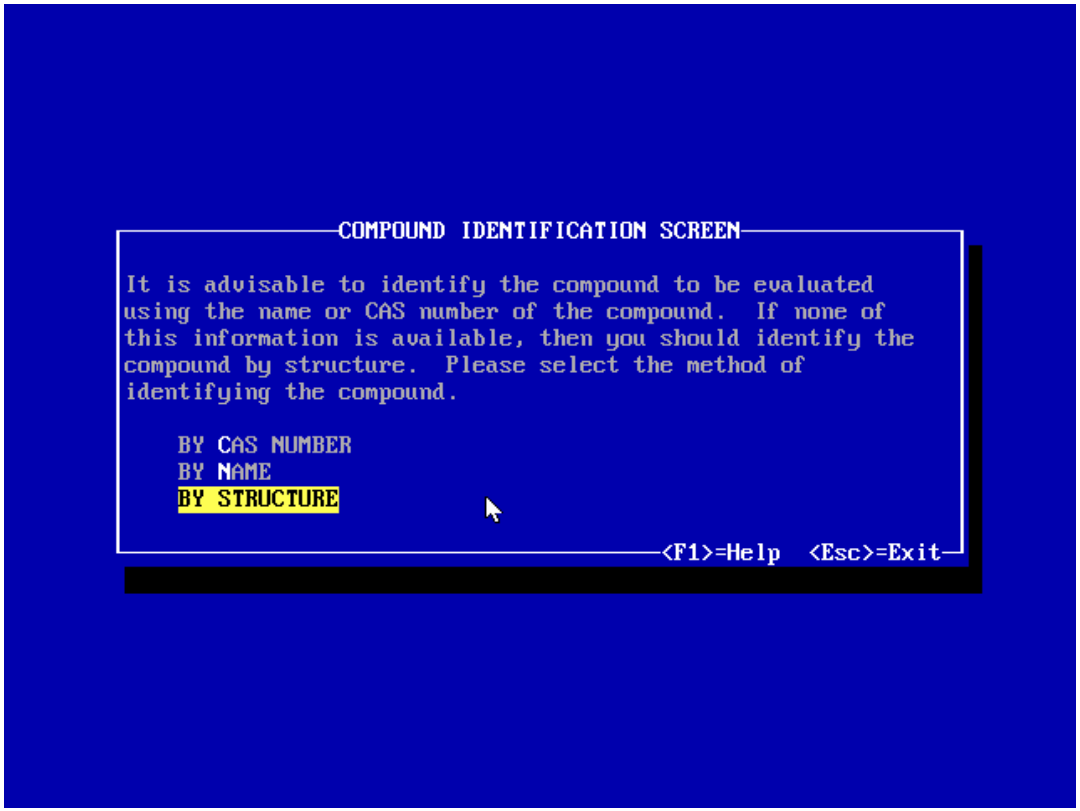
Running OncoLogic™: Organics Module (cont.)

- Answer all of the questions that are displayed



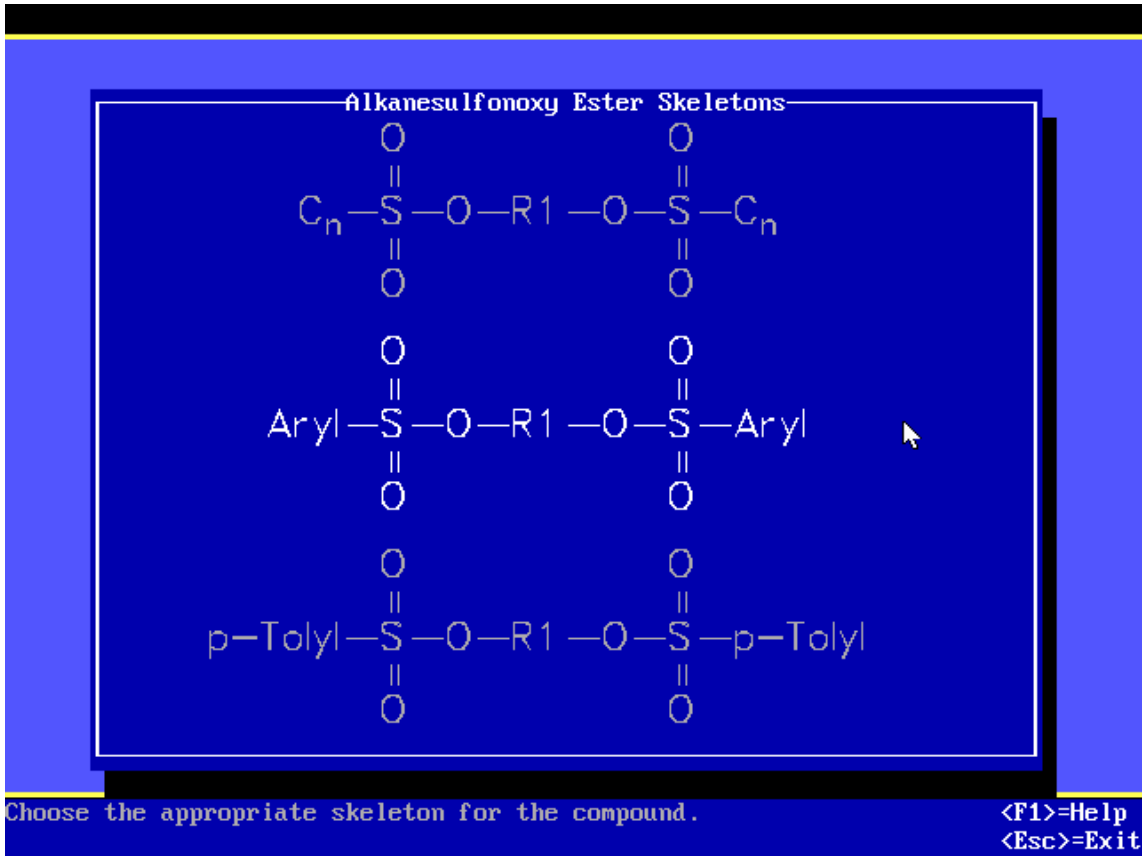
Running OncoLogic™: Organics Module (cont.)

- Select how you will enter the chemical into OncoLogic™
  - Note: A relatively small proportion of chemical names and CAS numbers are stored in OncoLogic™, so it is often necessary to enter the chemical structure



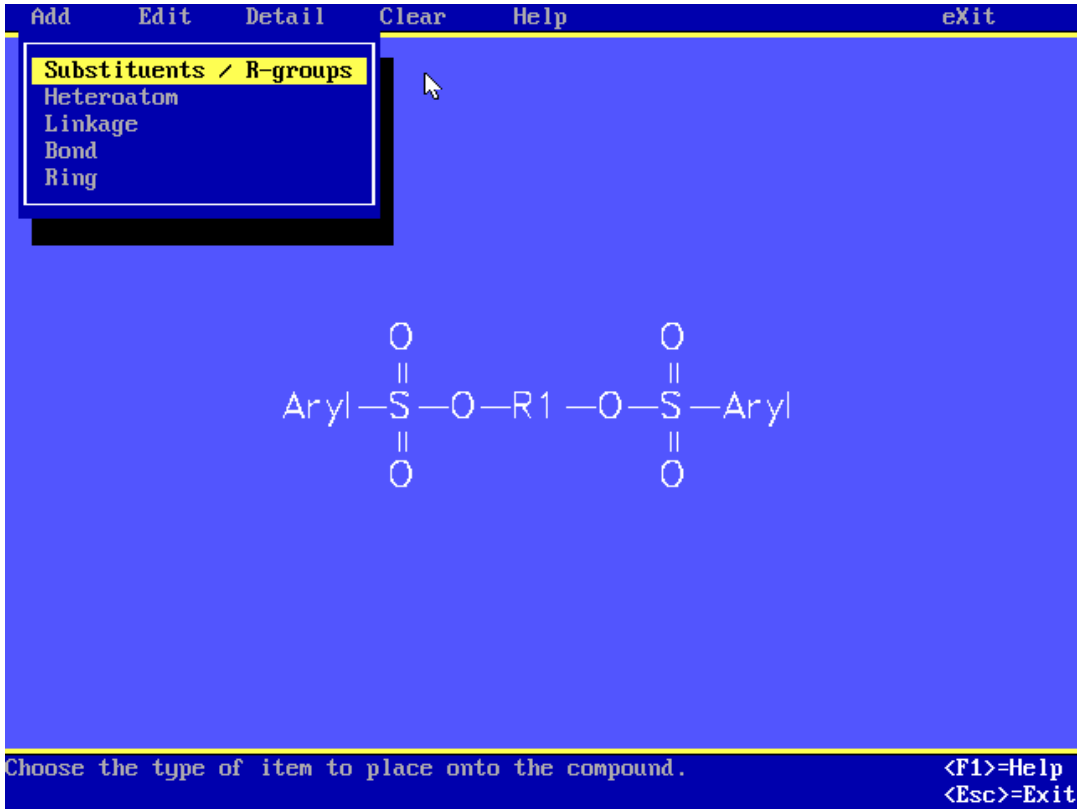
Running OncoLogic™: Organics Module (cont.)

- Select an appropriate backbone structure, if more than one is displayed



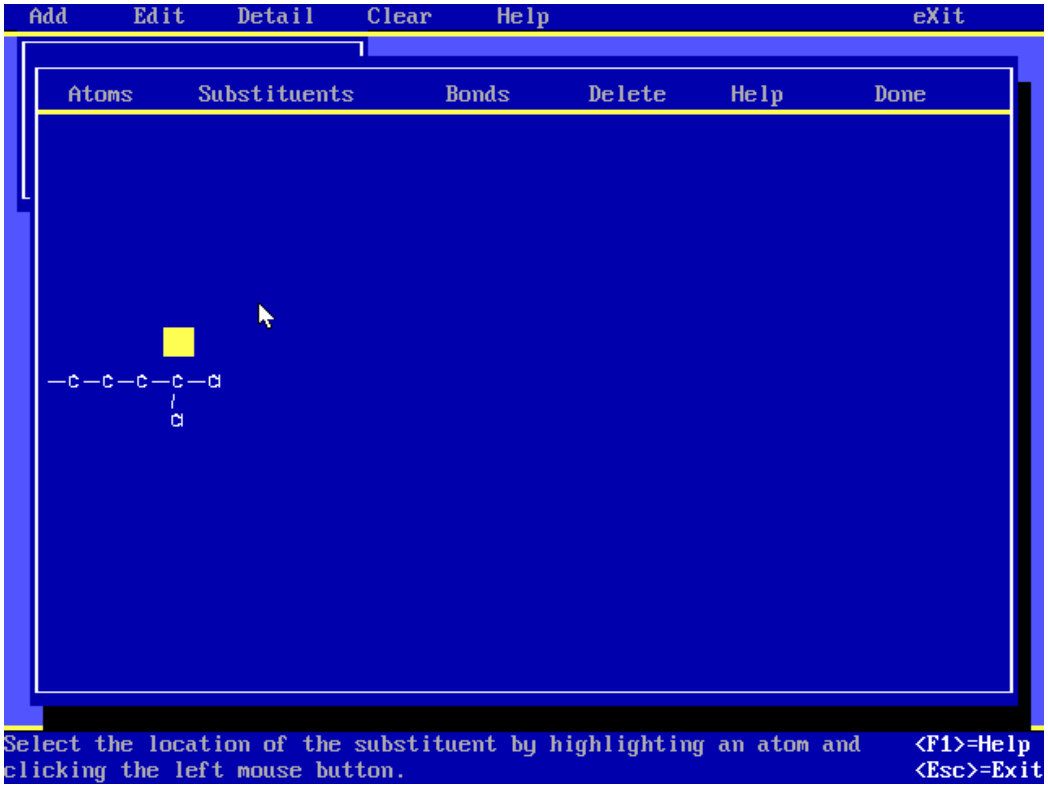
Running OncoLogic™: Organics Module (cont.)

- The selected backbone structure will be displayed on the drawing screen
- Add atoms from the pull-down menus to complete the chemical structure
- Press “Escape to move between menus or back to a menu from the drawing



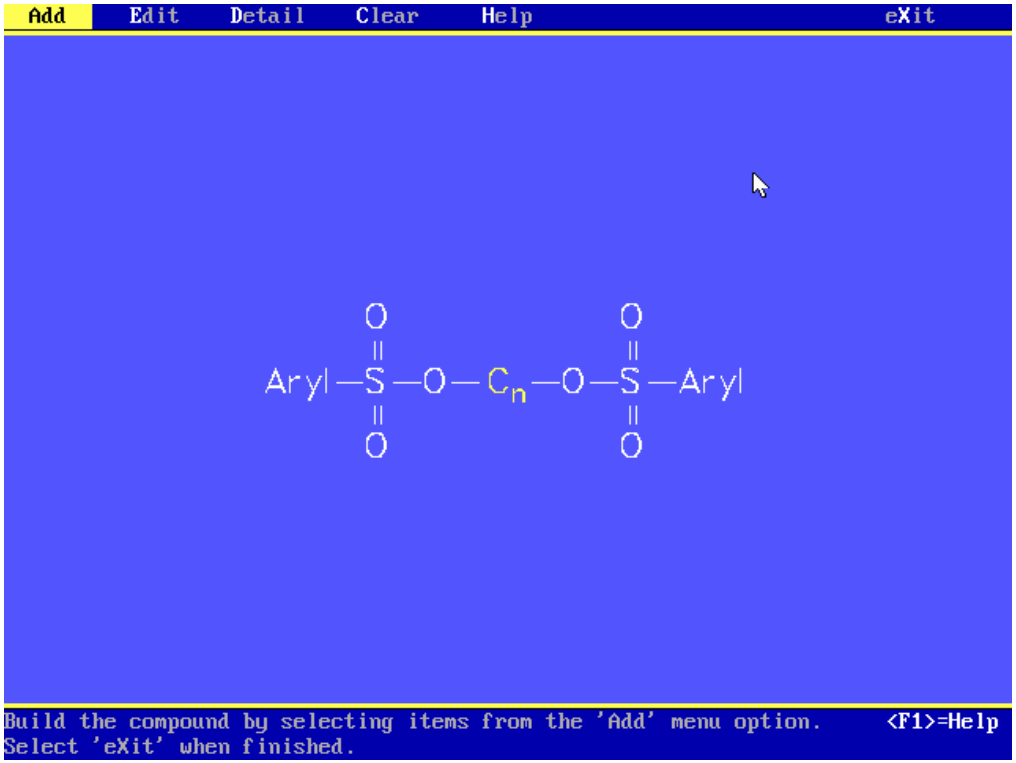
Running OncoLogic™: Organics Module (cont.)

- Draw the chemical structure of each substituent / R-group
- When drawing each substituent, the yellow box that appears indicates the position where the selected atom will be added
- Select “Done” when the structure of each substituent is complete
- You will then be prompted to indicate where you would like to add the substituent on the backbone structure



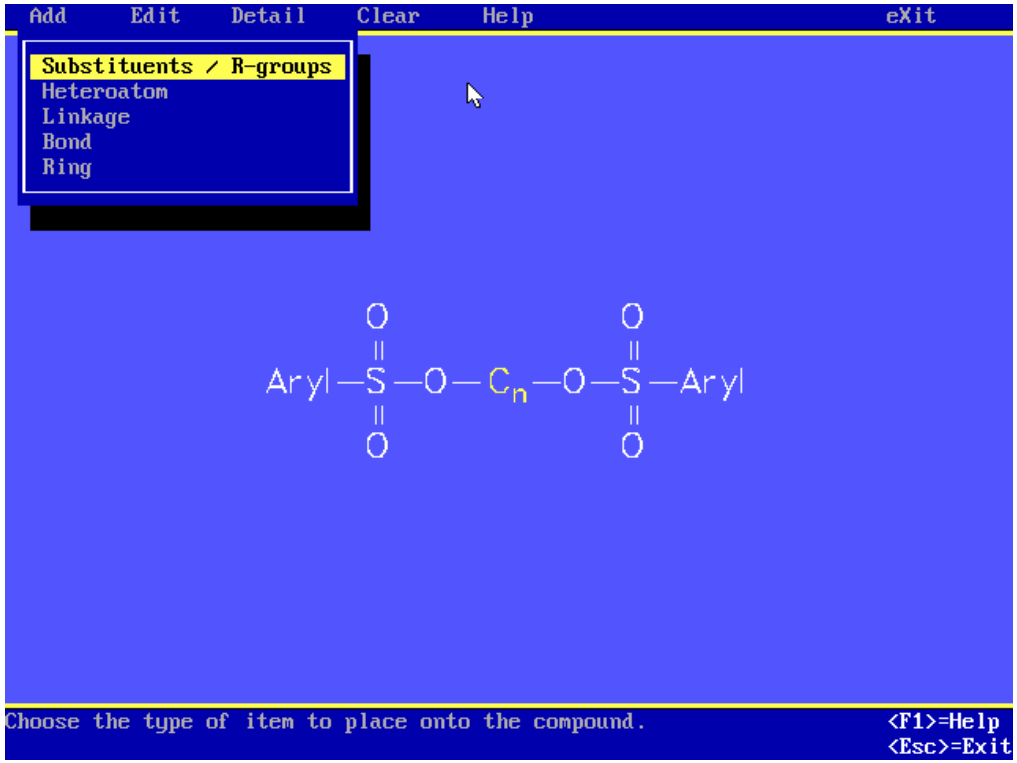
Running OncoLogic™: Organics Module (cont.)

- For the structure displayed at the right, "C_n" represents an added substituent
- Each different C_n added to the structure will be defined in the printed copy of the OncoLogic™ output
- Variable heteroatoms (e.g., S or O) are displayed as "X" in the backbone structure (not applicable to this example)



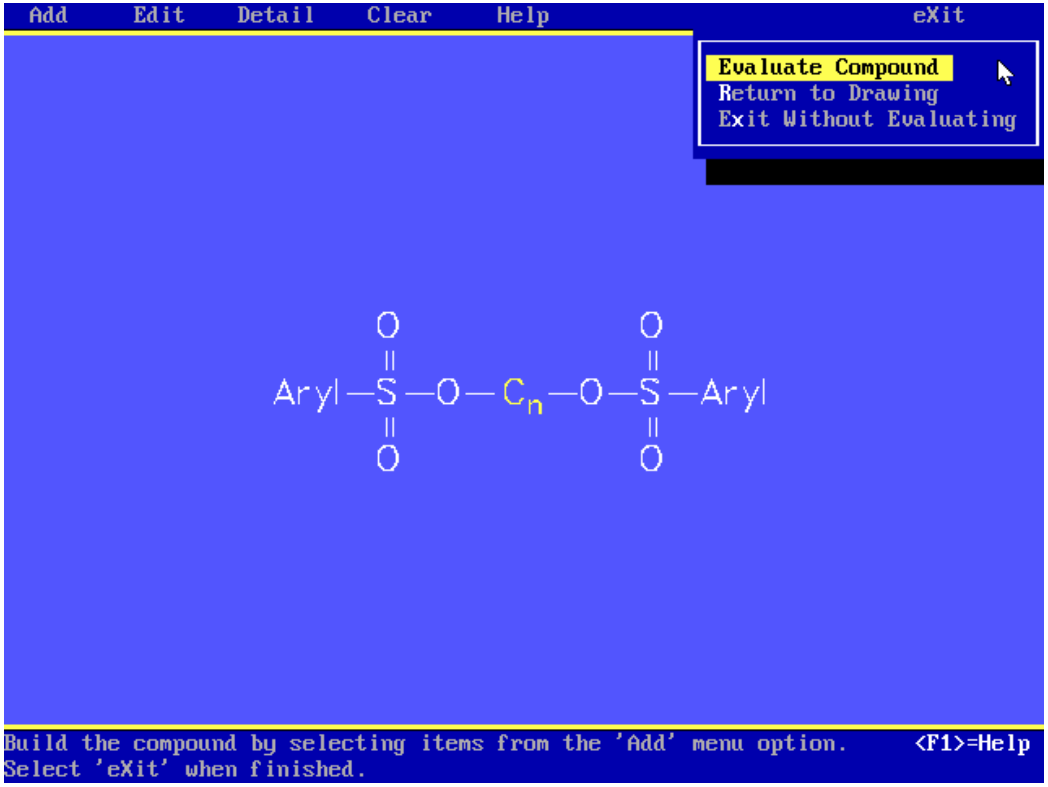
Running OncoLogic™: Organics Module (cont.)

- Not all of the menu items in the drawing screen can be selected
  - Dependent upon the chemical class selected
  - e.g., For the Alkanesulfonoxy esters subclass, Heteroatom, Linkage, Bond, and Ring cannot be selected from the “Add” menu
  - Refer to the OncoLogic™ User’s Manual (2004) for chemical class-specific information



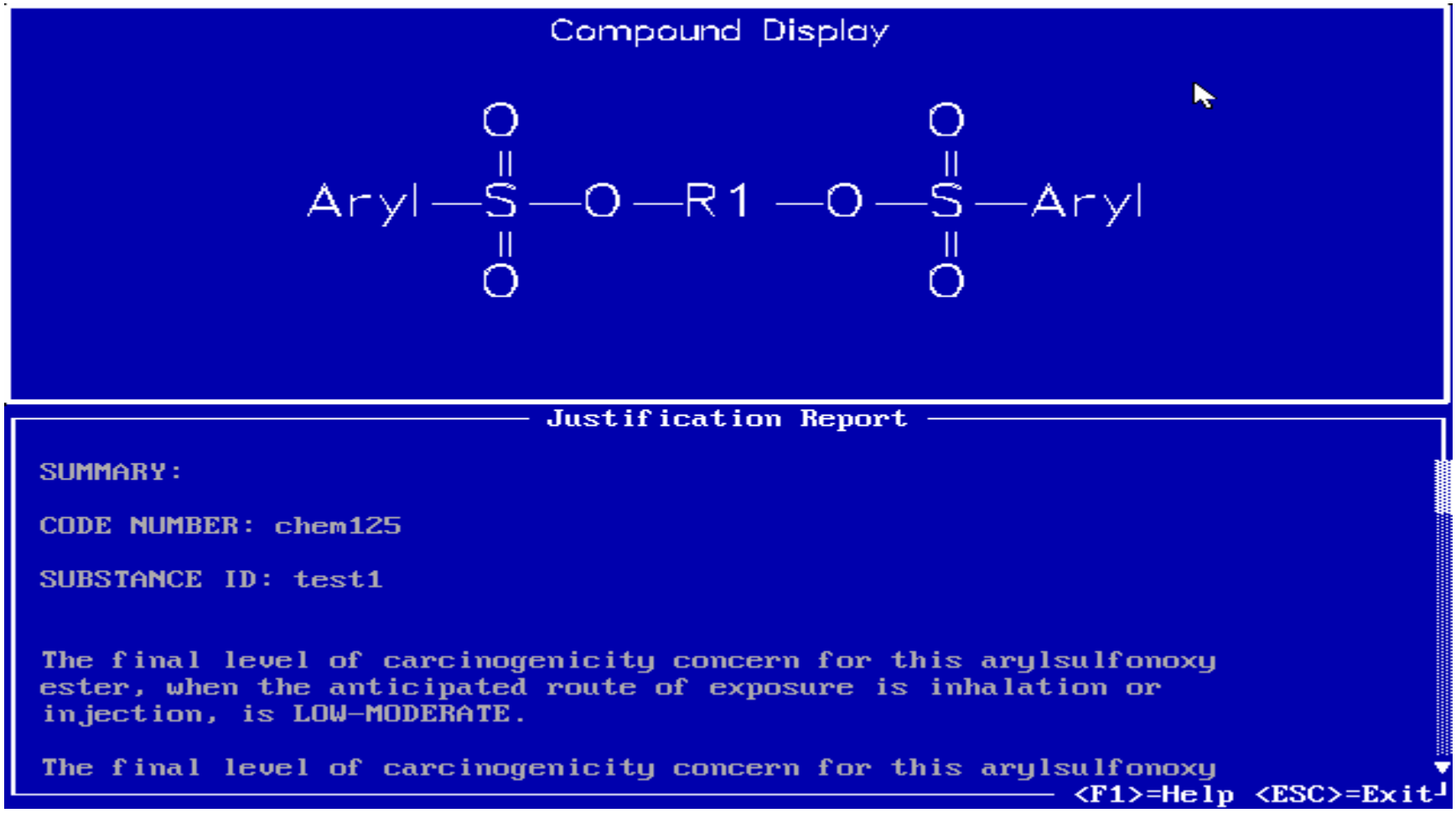
Running OncoLogic™: Organics Module (cont.)

- Click “Exit” on the menu bar
- Select “Evaluate Compound” when you have finished drawing the chemical structure



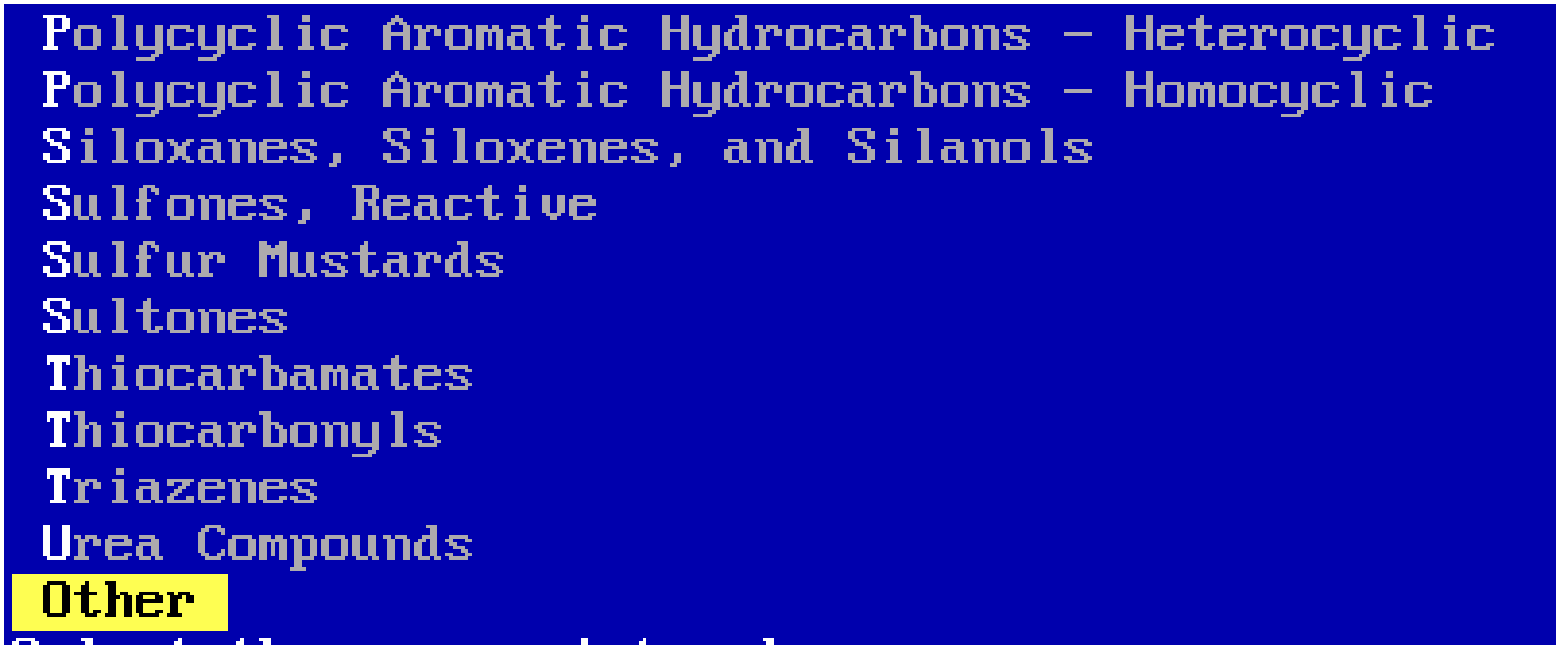
Running OncoLogic™: Organics Module (cont.)

Perform Evaluation



Running OncoLogic™: Organics Module (cont.)

- In addition to SAR analysis, OncoLogic™ includes evaluations of approximately 90 specific chemicals that do not fit into any OncoLogic™ class
  - Identified under “Other” in the Organics module at the Organic Classes screen



Running OncoLogic™: Organics Module (cont.)

- Return to the main menu
  - Select “Reports”, and then answer the questions displayed to
    - View or print the OncoLogic™ carcinogenicity report or user input data
    - Print the structure evaluated
  - Select “File Maintenance” to delete files or save them to another disk or format

Running OncoLogic™: Metals, Polymers, and Fibers Modules

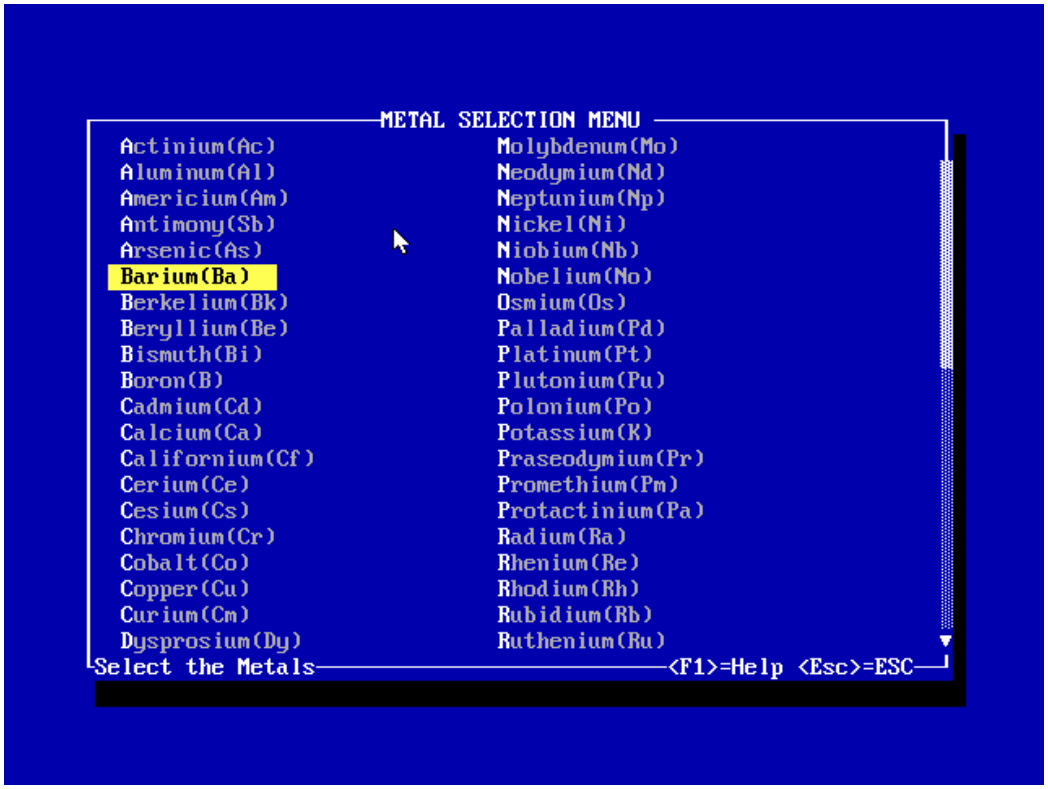
- Similar to the Organics module
- Each module prompts the user to enter specific information
- Information is entered through a sequence of screens and menus until all requisite data have been reported

Running OncoLogic™: Metals Module

- Substances containing As, Sb, Be, Cr, Cd, or Ni are evaluated using mechanism-based SAR analysis
- Substances containing metal(s) other than these are evaluated based on carcinogenicity data stored in the OncoLogic™ database
  - The expert, mechanism-based SAR analysis system of OncoLogic™ is not used to provide an overall concern for the potential carcinogenicity of such substances
  - OncoLogic™ provides concern levels for one or more substances containing the same metal(s) as the chemical in question
  - The user will need to use their own judgment, based on the information provided in the OncoLogic™ output, in order to determine the potential carcinogenicity of the chemical in question
- See Section 5.2 of the OncoLogic™ User's Manual (2004) for more information on using the metals module

Running OncoLogic™: Metals Module

- Select the metal(s) contained in the substance to be evaluated



Running OncoLogic™: Metals Module (cont.)

- Questions may request information on
  - Nature/form of the metal / metalloid
    - Organometal, metal powder
  - Crystalline / amorphous
  - Type of chemical bonding (e.g., organic, ionic)
  - Dissociability / solubility
    - Valence / oxidation state
  - Breakdown products (e.g., organic moieties)
  - Exposure scenario

Running OncoLogic™: Fibers Module

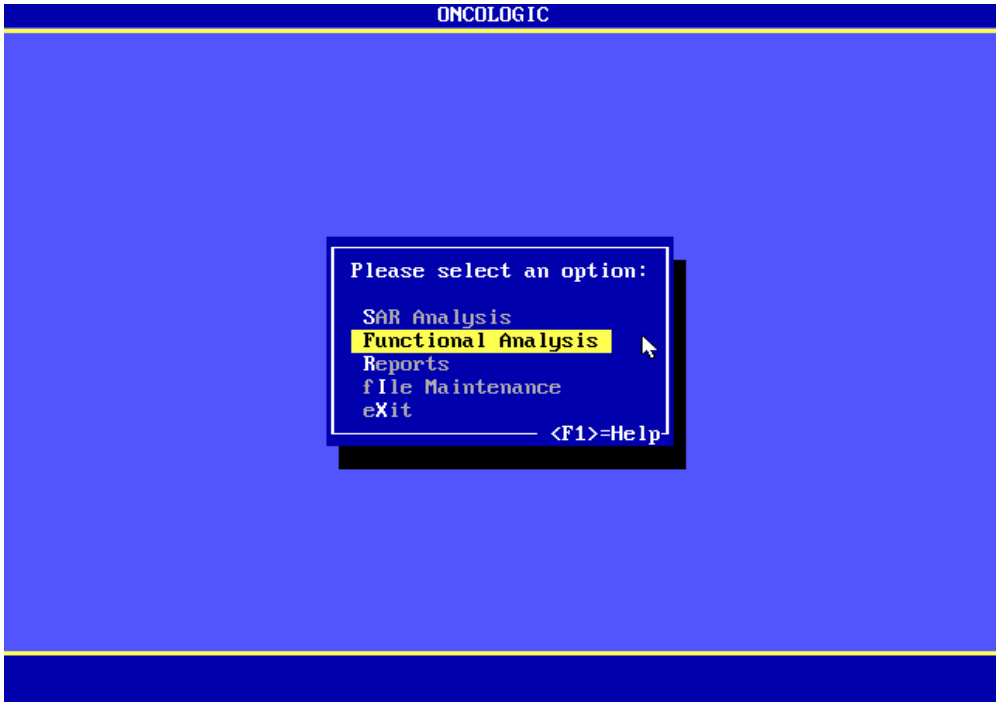
- Evaluations are based on physical dimensions and physicochemical properties
- Questions may request information on
  - Physical dimensions
    - Diameter, length, aspect ratio
  - Physicochemical properties
    - High density charge, flexibility, durability, biodegradability, smooth and defect-free surface, longitudinal splitting potential
    - Presence of high MW polymer, low MW organic moiety, metals/metalloids

Running OncoLogic™: Polymers Module

- Polymer must consist of covalently linked repeating units and have a number average molecular weight >1000
- Questions may request information on
  - Percentage of polymer with MW <500 and <1000
  - Percent of residual monomer
  - Identification of reactive functional groups (RFGs)
  - Solubility
  - Special features (e.g., polysulfation, water-swellability)
  - Exposure routes
  - Breakdown products (e.g., hydrolysis)

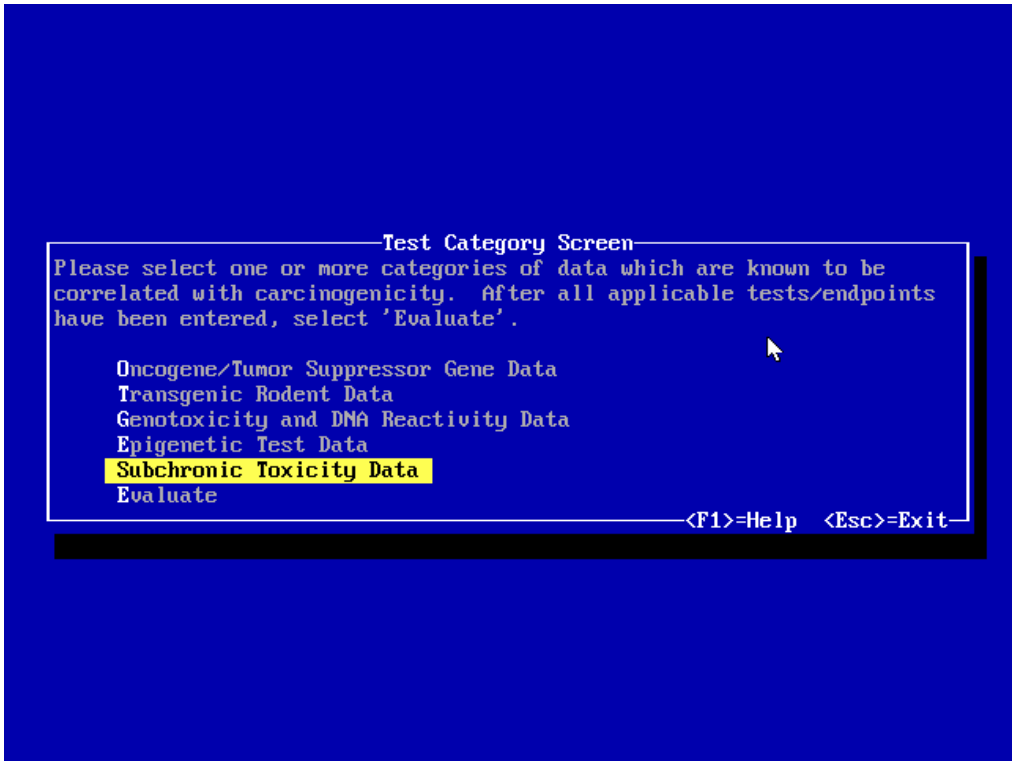
Functional Analysis

- Predicts
  - Whether the chemical is likely to be a tumor initiator, promoter, and/or progressor
  - Potential carcinogenicity
- To start, select the Functional Analysis item on the main screen
  - A Code Number and Substance Identification number is requested, similar to the SAR Analysis



Functional Analysis (cont.)

- Enter the results of available mechanistic / non-cancer studies on the chemical by selecting the appropriate test category for each of the available studies
  - Select “Evaluate” when all available data have been entered



Running OncoLogic™: Additional Information

- Press “Escape” on your keyboard to return to a previous screen
- Press the “Windows” key or the “Alt” + “Enter” keys to minimize the OncoLogic™ window
- Finally, refer to the OncoLogic™ User’s Manual (2004) and the OncoLogic™ FAQs for more information on using OncoLogic™