

OncoLogic™

User's Manual

**An Expert System for Prediction of
The Carcinogenic Potential of Chemicals**

Version 7.0

© 2009-2010, U.S. Environmental Protection Agency

OncoLogic™

User's Manual

*An Expert System for Prediction of
The Carcinogenic Potential of Chemicals*

March 09, 2010

OncoLogic™ was developed by Dr. Joseph Arcos, Dr. Mary Argus, Dr. David Lai, and Dr. Yin-tak Woo of the U.S. Environmental Protection Agency.

TABLE OF CONTENTS

1. Introduction To OncoLogic™	4
2. Getting Started	7
3. Input Requirements	10
4. Output Produced	11
4.1 Justification Report	11
4.2 Data Report	13
5. Sub-system Specific Guides	13
5.1 Introduction	13
5.2 General Tips	14
5.2.1 Fiber, Metal and Polymer Systems:	14
5.2.2 Organic System	15
5.2.3 Report Utility	15
5.3 Specific Organic Subsystem Tips	16
5.3.1 Acyl and Benzoyl Halide Type Compounds	16
5.3.2 Acrylate Reactive Functional Groups	17
5.3.3 Acrylamide Reactive Functional Groups	18
5.3.4 Aflatoxin Type Compounds	19
5.3.5 Aldehyde Type Compounds	20
5.3.6 Aliphatic Azo and Azoxy Type Compounds	21
5.3.7 Alkanesulfonyl Ester Type Compounds	22
5.3.8 Alkyl Sulfate and Alkyl Alkanesulfonate Type Compounds	23
5.3.9 Aromatic Amine Type Compounds	24
5.3.10 Anhydride Type Compounds	27
5.3.11 Arylazo Type Compounds	28
5.3.12 Aryldiazonium Salts	29
5.3.13 C-Nitroso and Oxime Type Compounds	30
5.3.14 Carbamate Type Compounds	31
5.3.15 Carbamyl Halide Type Compounds	33
5.3.16 Coumarin and Furocoumarin Type Compounds	34
5.3.17 Dicarbonyl Type Compounds	35
5.3.18 Epoxide Reactive Functional Groups	36
5.3.19 Ethyleneimine Reactive Functional Groups	38
5.3.20-Haloalkylamine Reactive Functional Groups	40
5.3.21 β Haloether Reactive Functional Groups	42

5.3.22 Halogenated Aromatic Hydrocarbon Type Compounds	43
5.3.23 Halogenated Cycloalkane Type Compounds	45
5.3.24 ortho-Halogenated Heterocyclic Type Compounds	47
5.3.25 Halogenated Nitroaromatic Type Compound	48
5.3.26 Halogenated Linear Aliphatic Type Compounds	49
5.3.27-Halothioether Reactive Functional Groups	50
5.3.28 Hydrazo Type Compounds	51
5.3.29 Reactive Ketone Reactive Functional Groups	53
5.3.30 Lactone Type Reactive Functional Groups	55
5.3.31 Nitrosamide Type Compounds	56
5.3.32 Nitrosamine Type Compounds	58
5.3.33 Nitroalkane and Nitroalkene Type Compounds	59
5.3.34 Nitrogen Mustard Reactive Functional Groups	60
5.3.35 Organophosphorus Type Compounds	62
5.3.36 Peroxide Type Compounds	64
5.3.37 Phenol Type Compounds	65
5.3.38 Phosgene Type Compounds	66
5.3.39 Polycyclic Aromatic Hydrocarbons - Heterocyclic	67
5.3.40 Polycyclic Aromatic Hydrocarbons - Homocyclic	68
5.3.41 Siloxane Type Compounds	69
5.3.42 Reactive Sulfone Reactive Functional Groups	70
5.3.43 Sulfur Mustard Reactive Functional Groups	72
5.3.44 Sultone Reactive Functional Groups	74
5.3.45 Thiocarbamate Type Compounds	75
5.3.46 Thiocarbonyl Type Compounds	77
5.3.47 Triazene Type Compounds	78
5.3.48 Urea Type Compounds	79
6. Direct-Acting Alkylating Agents - A Guided Tour	80
6.1 Stand-alone Compounds	80
6.2 Reactive Functional Groups	80
7. Steps For Evaluating an RFG	81
7.1 Step 1	81
7.2 Step 2	82
7.3 Step 3	82
7.4 Step 4	83
7.5 Step 5	83
8. Tutorials	84

8.1 Fiber Sample.....	85
8.2 Polymer Sample.....	95
8.3 Metal Sample.....	116
8.4 Organic Sample	128

1. Introduction To OncoLogic™

OncoLogic™ is a unique expert system that predicts the potential carcinogenicity of chemicals by applying rules of structure activity relationship (SAR) analysis, and high level expert judgement that incorporates what is known about metabolism, mechanisms of action, and human epidemiological studies.

OncoLogic™ is the only knowledge-based software developed in cooperation with the United States Environmental Protection Agency's (EPA) Structure Activity Team (SAT). These internationally recognized experts are responsible for evaluating the carcinogenic potential of all new chemicals developed in the United States or imported and intended to be marketed within the United States.

The goals of developing OncoLogic™ were:

- to provide guidance to industries on elements of concern for developing safer chemicals,
- to provide a source of information to all interested parties on the rationale for identifying potential cancer hazard of chemicals,
- to provide a forum for reaching a common understanding among various regulatory agencies in hazard identification of chemical carcinogens, and
- to simulate research to fill knowledge gaps.

To accomplish these goals, the EPA experts, in cooperation with LogiChem Inc., developed “rule packages” which formalized current SAR knowledge based on data from a variety of sources including:

- ‘Chemical Induction of Cancer’ Series (seven volumes) Academic Press (1968-1995) by J.C. Arcos, M.F. Argus, Y.-t. Woo, and D.Y. Lai.
- IARC Monographs
- NCI/NTP Bioassay Reports
- PHS Publication No. 149: ‘Survey of Compounds Which Have Been Tested for Carcinogenic Activity’
- Non-confidential data and information from EPA files.

Since OncoLogic™ mimics the decision-making process used by the EPA during the Pre-Manufacture Notification (PMN) Process, you get the same evaluation the EPA experts would generate if they reviewed the chemical. A bioassay costs millions of dollars and takes several years to conduct. OncoLogic™ can provide information on the inherent hazard of a new chemical. This, combined with exposure information, gives you important insight as to whether this costly study will be recommended or required.

OncoLogic™ has the ability to reveal its line of reasoning, just as human experts can. The user can enter information about the structure of a compound, obtain the assessment of the potential carcinogenicity, and then access the scientific line of reasoning used to arrive at the assessment outcome. This provides the user with a detailed explanation of a chemical's cancer causing potential.

Because OncoLogic™ allows you to evaluate new chemicals early in their development, “go/no go” decisions can be reached before large investments are made. OncoLogic™ provides a “window” to recognized expert thinking on a product before it is submitted for review. Therefore, OncoLogic™ can save companies time and money. You can anticipate months, or even years, prior to a submittal if the compound will be approved or require a multi-million dollar bioassay. Because OncoLogic™ has the ability to reveal its line of reasoning, it can assist in the development of safer alternative chemicals. You can also plan and design your testing strategically to reduce animal testing, and hence not only reduce the costs of research and development, but also minimize the adverse publicity associated with animal testing.

OncoLogic™ can be used to evaluate the safety of existing chemicals. In the U. S. alone, an estimated 1,700,000 employees are exposed to chemicals in the workplace on

an annual basis. There are 80,000 chemicals in use today. Of these, less than 2,000 have been tested for carcinogenic activity, and 64,000 have never been assessed for any health effects. OncoLogic™ can help evaluate the carcinogenic potential of these untested chemicals

OncoLogic™ can be used strategically to examine process intermediates in alternative synthesis routes, to help select the safest manufacturing process. The program can evaluate chemical by-products that can introduce carcinogens into the work environment and the community beyond.

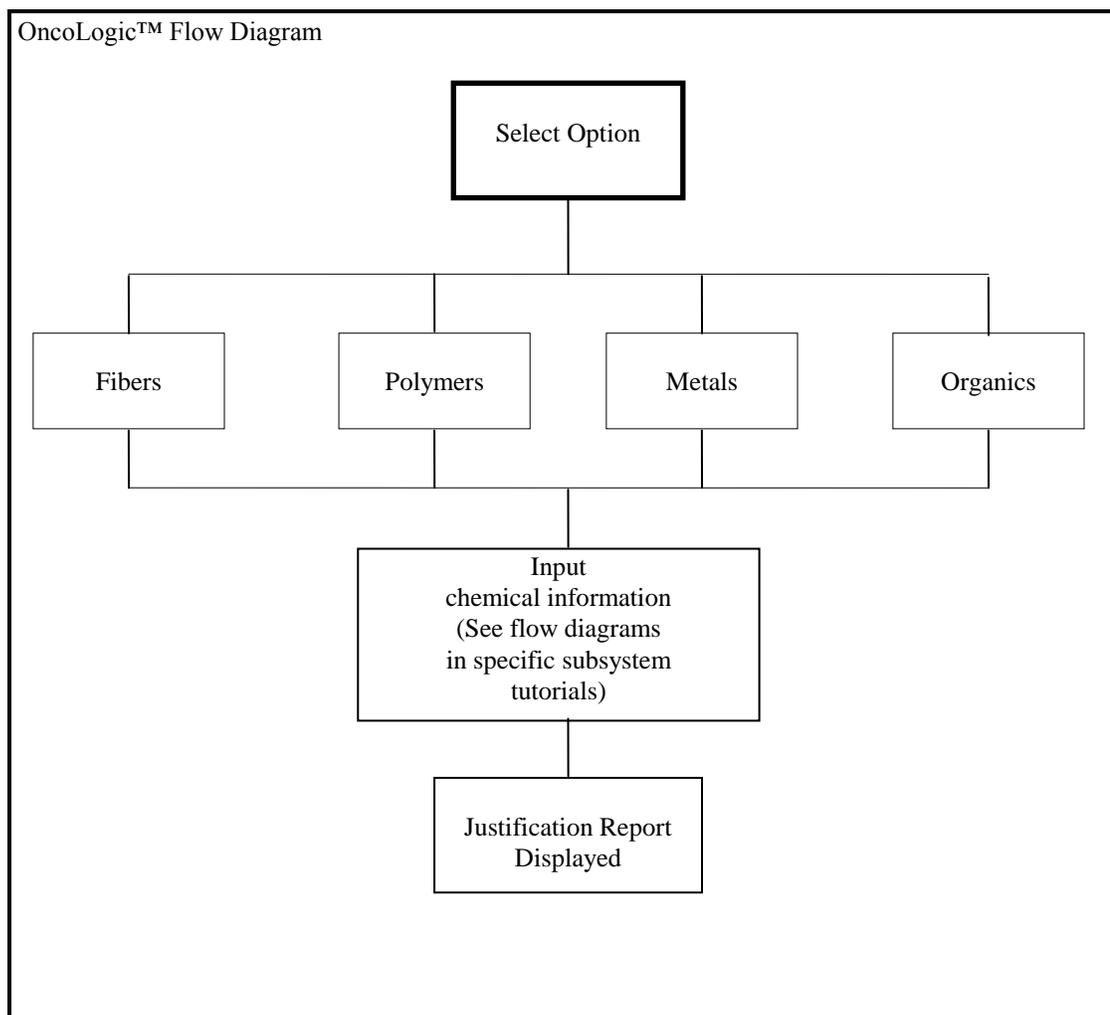
OncoLogic™ consists of four major subsystems:

- Fibers
- Polymers
- Metals, Metalloids, and Metal containing compounds
- Organic chemicals

OncoLogic™ can be used by individuals with a good understanding of organic chemical terminology. Minimum hardware requirements are: 386 computer operating under MS-DOS 5.0 or later, with 1 megabyte of RAM, 60 megabytes of fixed disk space, equipped with a mouse, a VGA board, and a color monitor.

2. Getting Started

The OncoLogic™ expert system provides an interactive, user friendly interface that assumes the user to have a basic understanding of chemistry. The Fibers, Metals, and Polymers subsystems require the user to enter information about substances by selecting items from menus or entering data through data entry screens. The Organics subsystem allows the user to draw the molecule to be evaluated through the use of an uncomplicated, straightforward drawing package designed specifically for this program. The flow diagram below outlines the general structure of the system.



Across all subsystems, OncoLogic™ provides information through the display of advice and help screens. You can find the following information in this manual:

1. How to interpret the semantic terms used by OncoLogic™ as they capture the thinking at the U.S. EPA.
2. How to use the various subsystems.
3. The hardware and software requirements.
4. How to use the menus, help screens, and data entry screens.
5. What information is provided in the reports.
6. A tutorial containing evaluations of previously selected compounds
7. How to use the report facility.

To run the OncoLogic™ program, you must first be sure that you are in the ONCO directory, (C:\ONCO). The OncoLogic™ system is then started by typing the word "ONCO" at the system prompt. An OncoLogic™ welcome screen will be displayed (See **Error! Reference source not found.**).

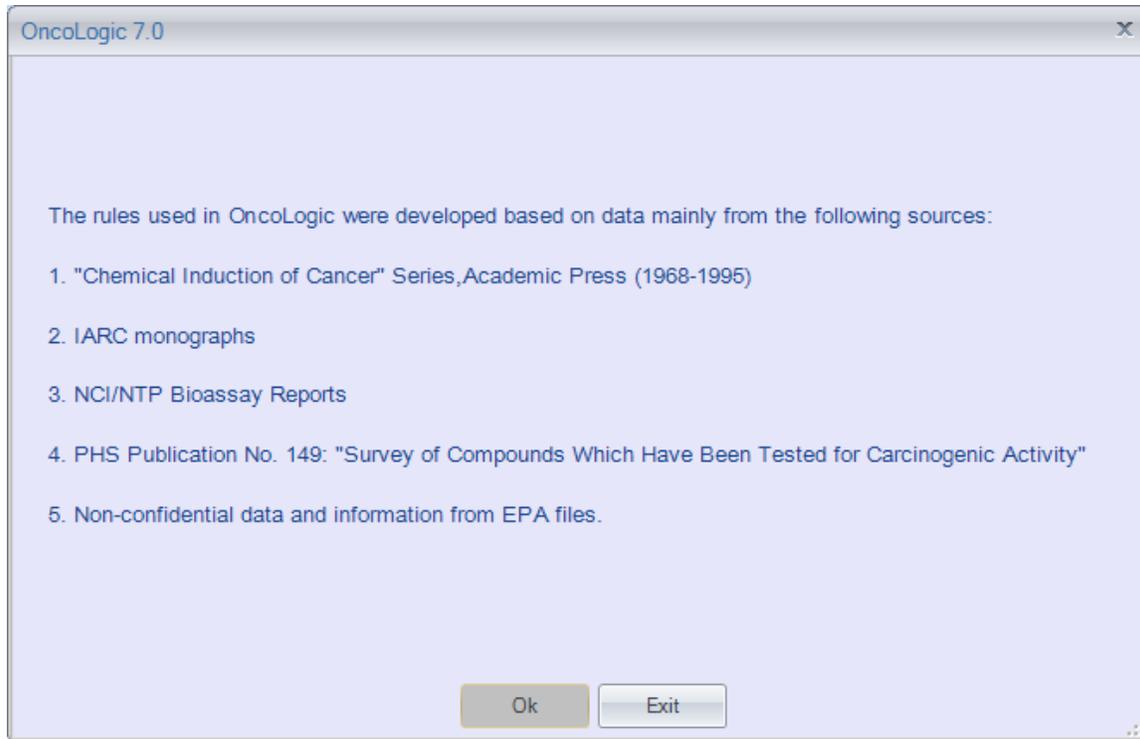
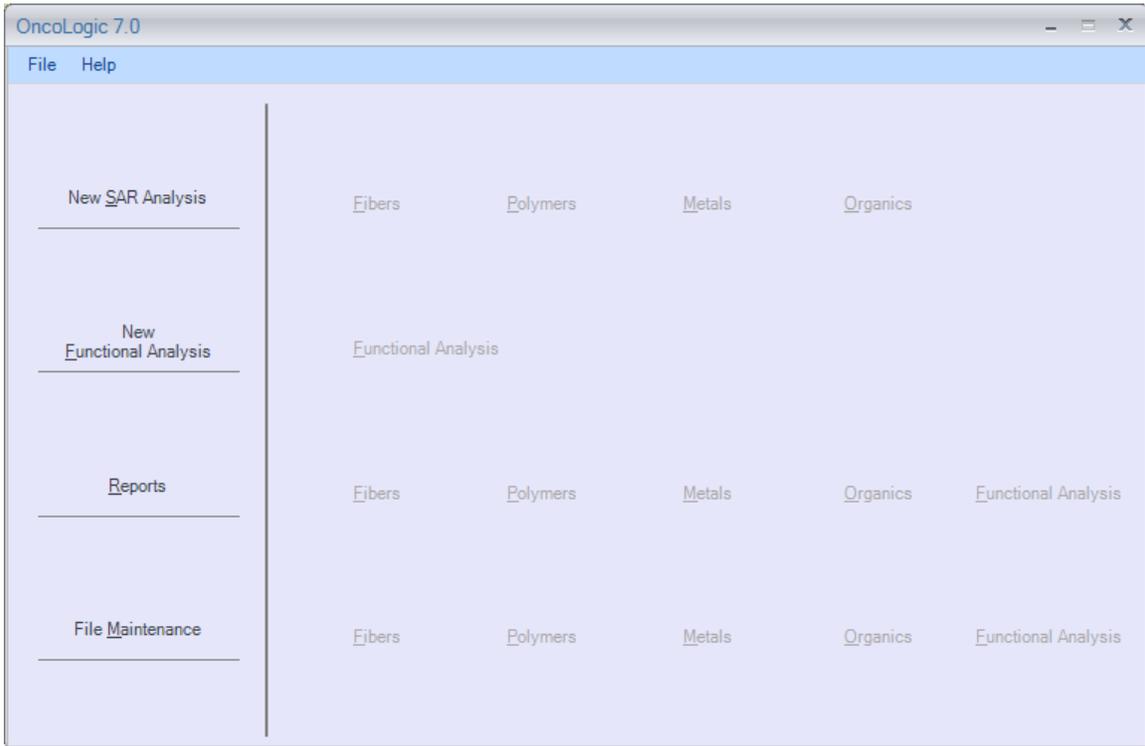


Figure 1.

Press the "OK" button by either hitting the <Return> key or clicking on the button with the mouse pointer.



This is the main menu screen from which all evaluations will begin.

3. Input Requirements

Each subsystem needs specific information about the compound before an evaluation can be performed. Figure 2 contains a chart highlighting the types of information needed to perform an evaluation for each subsystem.

Subsystem	Required Information
Fibers	Physical dimensions Physicochemical characteristics (optional)
Polymers	Molecular Weight Water solubility Identity of reactive functional groups Structure of the backbone (optional) Expected routes of exposure
Metals	Form (i.e. organometallic, metal powder) Solubility (for some metals) Expected routes of exposure
Organics	Structure Expected routes of exposure (for some compounds)

Figure 2: Table of Required Information

4. Output Produced

Once an evaluation has been performed, the OncoLogic™ System produces reports explaining the carcinogenicity concern for the evaluated compound. There are two types of reports produced. One report is called a Justification report. This report contains a summary of the predicted concern level for the compound and the line of reasoning used by the expert system to arrive at the concern level. The other report is a Data report. This report restates the information the user entered upon which the evaluation was based. Examples of both types of reports can be found in the Tutorial section of this manual.

4.1 Justification Report

The justification report consists of two parts: a summary of the evaluation and a line of reasoning (justification) of how the final conclusions were derived. Within the summary section, a final level of concern is stated along with any other messages that merit special attention. The concern levels used by the OncoLogic™ system are semantic terms used by the U.S. EPA Structure Activity Team (SAT) for ranking the hazard levels of chemicals. The specific terms in order from highest concern to lowest concern are: HIGH, HIGH-MODERATE, MODERATE, LOW-MODERATE, MARGINAL, LOW. See Error! Reference source not found. for the concern levels for representative carcinogens.

Concern Level	Description	Examples
Low	Unlikely to be carcinogenic	Pyrene, Di-n-octylnitrosamine
Marginal	Likely to have equivocal carcinogenic activity or may be weakly carcinogenic at doses at or exceeding maximum tolerated doses	Benzo[e]pyrene, Acetamide, BHT, TPA
Low-Moderate	Likely to be weakly carcinogenic, or carcinogenic toward a single target/species, or carcinogenic at relatively high doses	Benzo[a]anthracene, Vinylidene chloride, Trimethyl phosphate
Moderate	Likely to be a moderately active carcinogen toward one or more target/species	Dibenzo[a,j]anthracene, Nitrosopyrrolidine, Chloroethane
High-Moderate	Highly likely to be a moderately active carcinogen toward one or more target/species	Dibenzo[a,h]anthracene, Nitrosopiperidine, Vinyl chloride, Methylethylnitrosamine
High	Highly likely to be a potent carcinogen even at relatively low doses, or carcinogenic toward multiple targets/species	Benzo[a]pyrene, 7,12-Dimethylbenzanthracene

Figure 3: OncoLogic™ Concern Levels

The line of reasoning part of the justification report keeps track of the rules that are used to arrive at a level of concern. The line of reasoning is specific to each evaluation and represents the actual rules used for the particular compound. The line of reasoning section also will draw attention to special considerations flagged for the compound, but in further detail than the summary section.

4.2 Data Report

The data report contains the information that was entered about the compound. Essentially it becomes a reference report of the data entered upon which the OncoLogic™ system based its evaluation.

5. Sub-system Specific Guides

5.1 Introduction

Since OncoLogic™ depends upon the classification of the compound to be evaluated, this guide has been developed, in part, to help you select the appropriate component to use for the evaluation. In it you will find the class of the compound (component), the type of evaluation available (database or expert system), and the basic skeleton templates upon which the compound can be defined. There are also two additional sections: one which tells you how to draw the compound with less detail and still get a valid evaluation (exceptions) and one which gives some additional information pertaining to the particular component (comments). All skeleton templates, substituent groups, heteroatoms, etc. are made available through pull down menus, and “point and click” methods.

The majority of the data entry screens and menus include context-sensitive help. Press the F1 key when ever you need additional information about a screen or menu. Press the Escape key to close the help window.

The databases contain the level of concern, assigned by the EPA carcinogenesis experts, based on SAR analysis and actual test data. You should first attempt to evaluate the compound in the database before evaluating it based on its structure (SAR analysis). In order to use the database, you will need the CAS number or name of the compound.

In general, most menus have a menu item “Other” or “Z”. This allows you to build a compound with an R group or a substituent that is not on one of the menus provided. If you choose to build such a structure, please note that the expert system does not contain rules for these non-specific groups and this adds a degree of uncertainty for the resulting level of concern. This is plainly noted in the justification report.

The User's Guide also contains some tips that apply to the entire OncoLogic™ System. For a full tutorial on each system in OncoLogic™, refer the OncoLogic™ User's Manuals.

5.2 General Tips

When performing any evaluation, there is information which is always entered to reference the compound and reports that will be generated. The specific information which is needed is the filename and the substance identification.

1. The filename (Code Number) you are asked to enter is not the name of the compound. This is a unique name or number which is used to name the file that contains the evaluation information and is stored on the hard drive of the computer. This may any arbitrary name or number. This name or number should be significant to you or to the evaluation so you can retrieve the information at a later date. This filename is limited to 8 letters and/or numbers.
2. The name of the compound is entered in The Substance Identification Screen. The information is optional and does not affect the evaluation. It is simply used for reference purposes.

5.2.1 Fiber, Metal and Polymer Systems:

Each of these systems have the same overall approach for performing an evaluation. Information is entered through a sequence of screens and menus until all of the requisite data has been reported. Once the information has been gathered, the

evaluation is performed and the two reports (data and justification) are generated. The following features are available to each of these systems.

1. The <ESC> key is enabled to return the user to the previous screen or menu.
2. Help information is available for each screen by pressing the <F1> key.
3. Menu options can be quickly accessed by pressing the key of the highlighted letter of a specific menu option.

5.2.2 Organic System

The components contained in the Organic system obtain most of the needed information through the use of a specialized drawing program. With the use of specific skeleton templates, the you draw the compound to be evaluated. These systems also include the features contained in the Fibers, Polymers, and Metals, and have the following additional features.

1. For exposure questions, your selections are indicated by a check mark (√). If exposure is not known, no selection is made.
2. During the drawing process, pressing the <Esc> key returns you to the menu bar, the previous pull down menu, exits a menu without making a selection, or to return to the previous screen.

5.2.3 Report Utility

1. To scroll the justification screen, press the PageUp/PageDown Key, use the mouse on the side scroll bar, or use the up/down arrow keys. The arrow keys must be pressed several times before the screen begins to scroll.
2. To view the R groups on the compound display, highlight the R group by placing the mouse over the "R", the press the left mouse key.

5.3 Specific Organic Subsystem Tips

This section provides tips for each of the organic components. If you are having trouble in an organic class, refer to subsection dealing with the organic class giving problems.

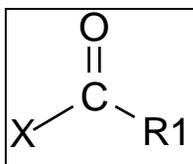
5.3.1 Acyl and Benzoyl Halide Type Compounds

Component: Acyl and Benzoyl Halides (direct-acting acylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1: alkyl (C_n)
aryl (phenyl, benzyl, phenylethyl)

X: Halogen (Cl, Br, I, F)

Substituents: None.

Exceptions: Substituents, such as sulfonic acid, hydroxyl, etc., are not considered when establishing a level of concern, nor are heteroatoms. Therefore these characteristics can not be placed on the alkyl or aryl R group. The degradation products of more complex R groups may be considered in other components and the higher concern level used. If the degradation products are not known then enter the alkyl/aryl group replacing the heteroatoms with carbon atoms.

Comments:

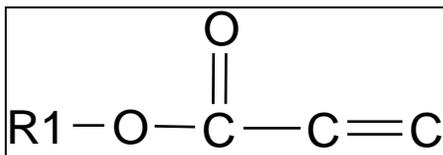
5.3.2 Acrylate Reactive Functional Groups

Component: Acrylates “esters of 2-propenic acid” (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)
 other types (H, benzyl, phenylethyl)

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The ethylene moiety (C=C) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, Other, and cyano (CN).

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the ethylene moiety. Heteroatoms can not be replace the carbon atoms in the R1 alkyl chain nor can oxo groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. Refer to Section 51 for more details on Direct-Acting Alkylating Agents.

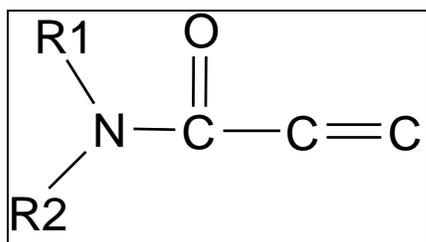
5.3.3 Acrylamide Reactive Functional Groups

Component: Acrylamides “amides of 2-propenoic acid” (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid,
 purine, etc.)
 other types (H, benzyl, phenylethyl)

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The ethylene moiety (C=C) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, Other, and cyano (CN).

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the ethylene moiety. Heteroatoms can not replace carbon atoms in the alkyl chain nor can oxo groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. Refer to Section 50 for details on Direct-Acting Alkylating Agents.

5.3.4 Aflatoxin Type Compounds

Component: Aflatoxins and Microbial Toxins

Database: Yes

Expert System: No

Skeleton Templates: None.

Exceptions: Aflatoxins are a part of the coumarin & furocoumarin component. There are several aflatoxins in the database. Aflatoxins can not be evaluated by structure.

Comments:

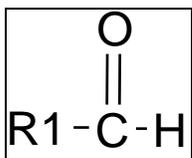
5.3.5 Aldehyde Type Compounds

Component: Aldehyde

Database: Yes

Expert System: Yes

Skeleton Templates:



R1: aliphatic (alkyl chain)
alicyclic (build as s-alkyl)
aromatic (aromatic ring system 1-2 rings)
other types (H, benzyl, phenylethyl, COOH, COO-,
C(O)Cn, etc.)

Substituents: The following substituents may be placed on R1 groups: hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), Other, and, additionally, alkyl (Cn) groups on aromatic rings.

Exceptions: Heteroatoms can not replace carbon atoms in the alkyl chain nor can oxo groups be added. The degradation products of these compounds should be considered separately. If the R group contains heteroatoms and degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: Although aldehydes are direct-acting alkylating agents, they are evaluated without concern for additional RFGs on the molecule. See Section 51 for details on Direct Acting Alkylating Agents.

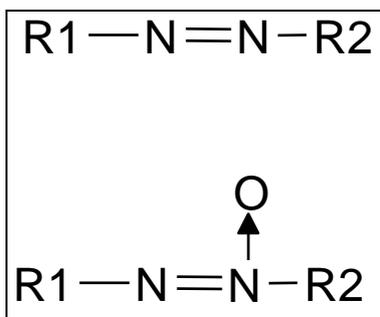
5.3.6 Aliphatic Azo and Azoxy Type Compounds

Component: Aliphatic Azo & Azoxy

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2: aliphatic (alkyl chain, cycloC6, vinyl, allyl)
aromatic types (phenyl, benzyl, phenylethyl)

Substituents: Halogens (Cl, Br, I, F), cyano (CN), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), alkoxy (OR), acyloxy(O(O)CR), and additionally, alkyl group (C_n) on alkyl groups.

Exceptions: Other than the vinyl and allyl R groups on the menu, other unsaturated aliphatic chain can not be drawn. When placing substituents on aromatic rings, select the group from the menu, then answer the number/position questions. When placing substituents on the alkyl R group, you will be asked to first construct the alkyl chain, then add the substituents. The chain must be at least 3 carbon atoms in length. If the R group is methyl or ethyl, select CH₃ or C₂H₅. Heteroatoms can not replace carbon atoms in the alkyl chain nor can oxo groups be added. The degradation products of these compounds should be considered separately or the heteroatoms may be replaced with carbon atoms for the evaluation.

Comments: This earlier version of the build screen has substituents posted on the menu bar not in pull down menus as in later versions.

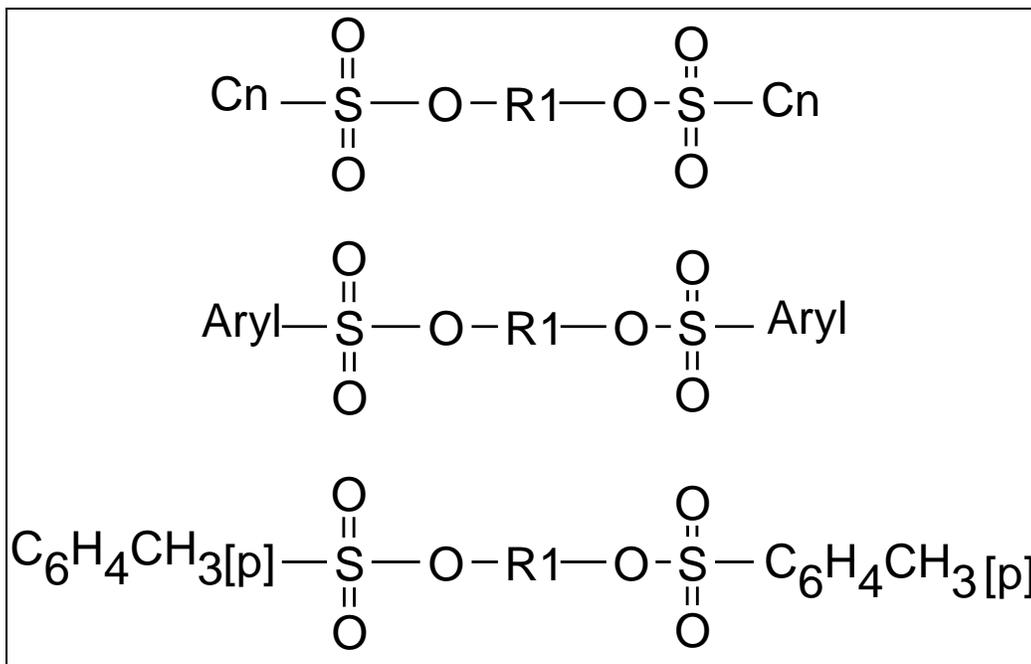
5.3.7 Alkanesulfonyloxy Ester Type Compounds

Component: Alkanesulfonyloxy Esters

Database: Yes

Expert System: Yes

Skeleton Templates:



R1: aliphatic alkyl chain

Substituents: Substituents : carboxylic acid (COOH), sulfonic acid (SO₃H), hydroxyl (OH), and halogens (Cl, Br, I, F) may be placed on the R1 group.

Exceptions: The substituents can only be placed on the R1 between the sulfonyloxy groups. Double bonds be placed within the R1 group alkyl chain, however, keto groups C=O, can not be attached to the chain. Each Cn of the ester moiety must have the same number of carbons, also the aryl groups are the same. Aryl represents any aromatic ring system. The two carbons of R1 to which the sulfonyloxy groups are attached must be defined.

Comments:

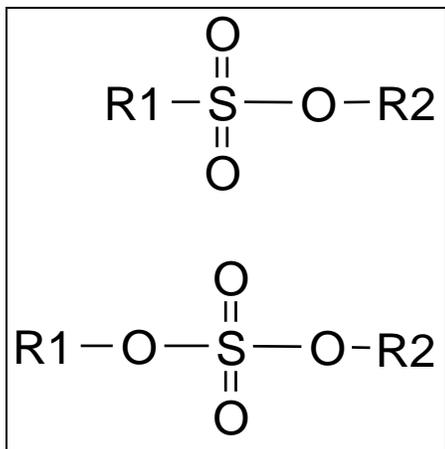
5.3.8 Alkyl Sulfate and Alkyl Alkanesulfonate Type Compounds

Component: Alkyl Sulfates and Alkyl Alkanesulfonates

Database: No

Expert System: Yes

Skeleton Templates:



R1: Alkyl Alkanesulfonate: aryl, phenyl, benzyl, phenylethyl, aliphatic alkyl chain and p-toluene. Alkyl Sulfate: aryl, phenyl, benzyl, phenylethyl, and aliphatic alkyl chain.

R2: Aryl, phenyl, benzyl, phenylethyl, aliphatic alkyl chain.

Substituents: None.

Exceptions: Substituents such as, COOH, SO₃H, OH, and halogens, or heteroatoms are not considered in the evaluation and therefore can not be placed on the structure.

Comments:

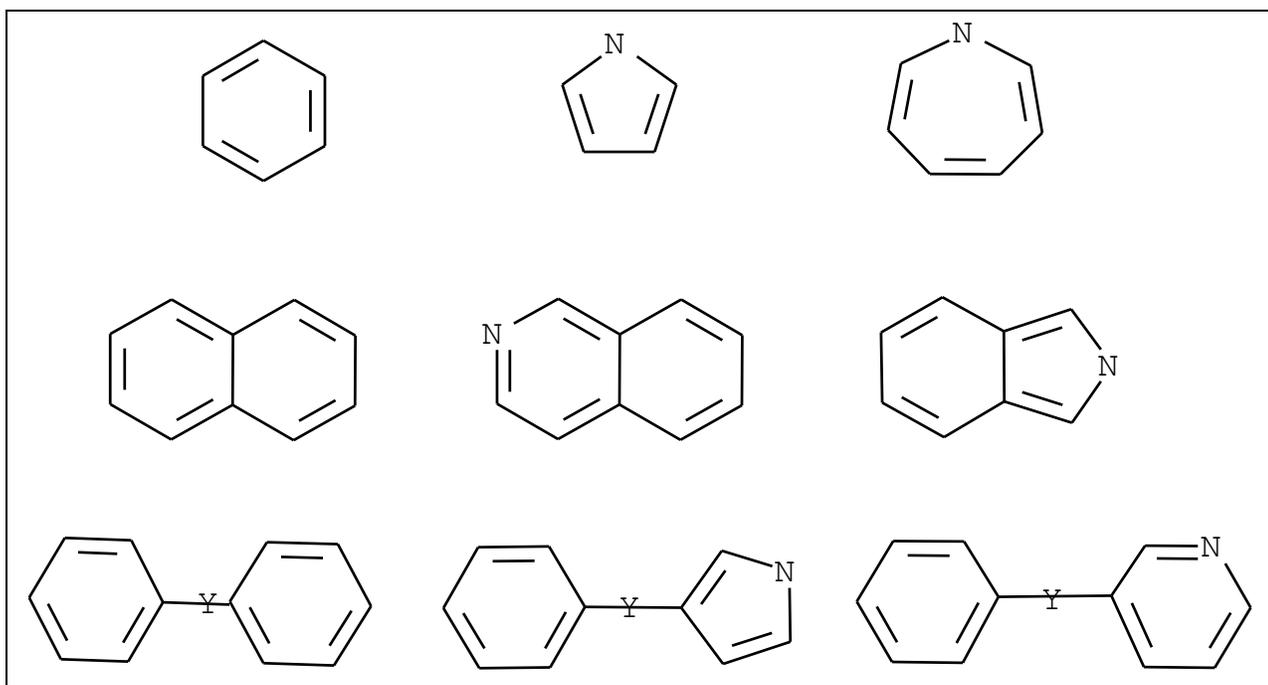
5.3.9 Aromatic Amine Type Compounds

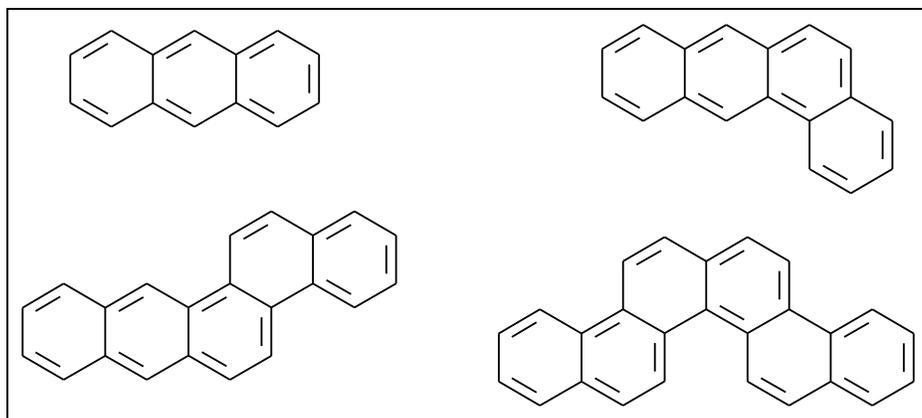
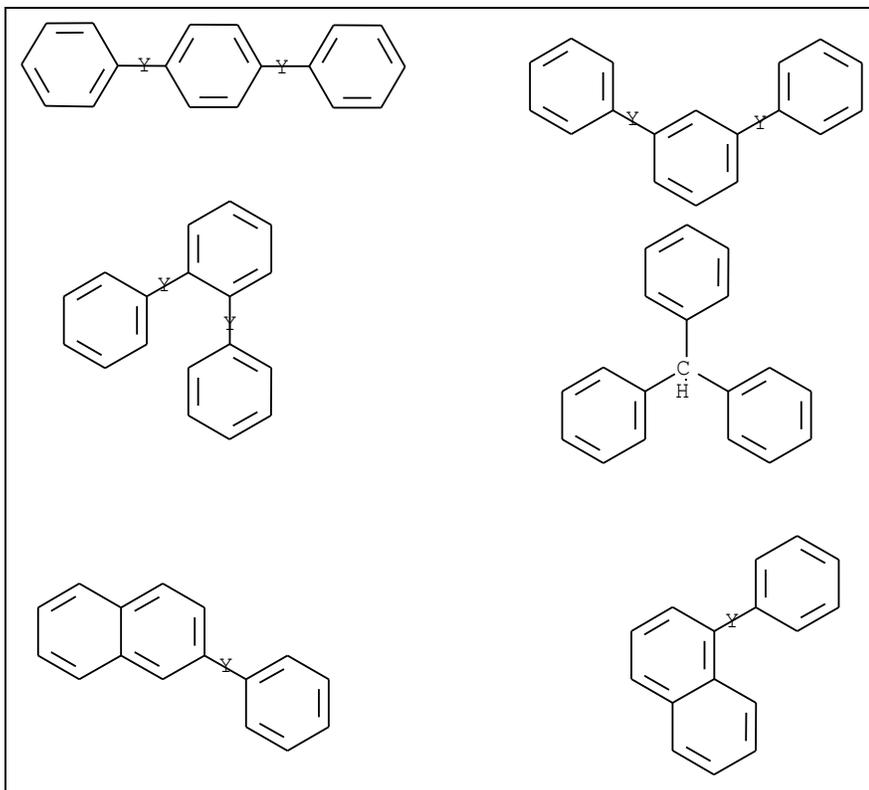
Component: Aromatic Amines

Database: Limited to Heteroaromatic Compounds

Expert System: Yes

Skeleton Templates:





Substituents: Hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), cyano (CN), aldehyde (CHO), carbamoyl (C(O)NR₂), carboxymethyl (COOCH₃), Other, Alkyl, Hydroxyalkyl, Alkoxy.

Exceptions:

Questionnaire Screen: Since there are so many different ring configurations for aromatic amine compounds, you are asked to enter the number of rings and answer a few general questions to define the basic skeleton template, a menu of skeletons, or the database to be used

Heteroaromatic Skeletons: The nitrogen atom can be replaced by O, S, NH, and in some cases As, Si, P, etc. There may be more than one nitrogen atom placed within the ring. The number and position of the heteroatoms vary but are limited to maintain the aromaticity of the structure.

Linked Skeletons: The linkage, designated by "Y" may be defined with one of 18 different linkages. Only the configurations shown can be evaluated.

Fused, Linear and Nonlinear, Homocyclic, Aromatic Structures with 3-6 Rings: Several configurations of skeleton templates are available.

Linked and Fused, Heterocyclic, Aromatic Structures with 3-6 Rings: These compounds can be evaluated only through the database.

Substituents: Ring substituents can be selected from menus and include alkyl chains, hydroxyl, carboxylic acid, sulfonic acid, cyano, etc. If the ring substituent is an alkyl group with a substituent, CH₂F for example, the F is treated as a hydrogen and can not be explicitly drawn. Also, a menu of nitrogen-containing groups such as NO, NH₂, NR₁R₂ where R₁ and R₂ are alkyl or aryl, is provided; at least one must be placed on the ring system.

Comments:

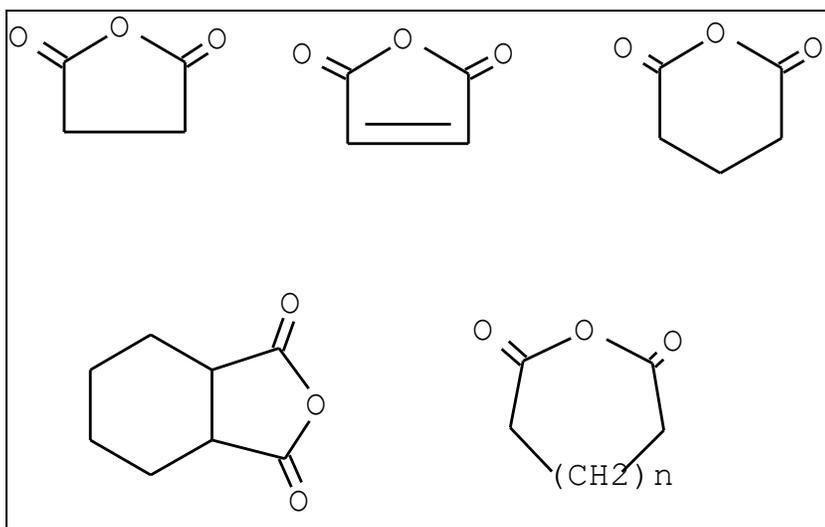
5.3.10 Anhydride Type Compounds

Component: Anhydrides (direct-acting acylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



Ring Substituents: Ring substituents, alkyl groups (Cn), halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), and sulfonic acid (SO₃H) may be added to the ring carbons.

Exceptions: Substituents may not be added to the alkyl ring substituents. Heteroatoms may not replace ring carbon atoms.

Comments:

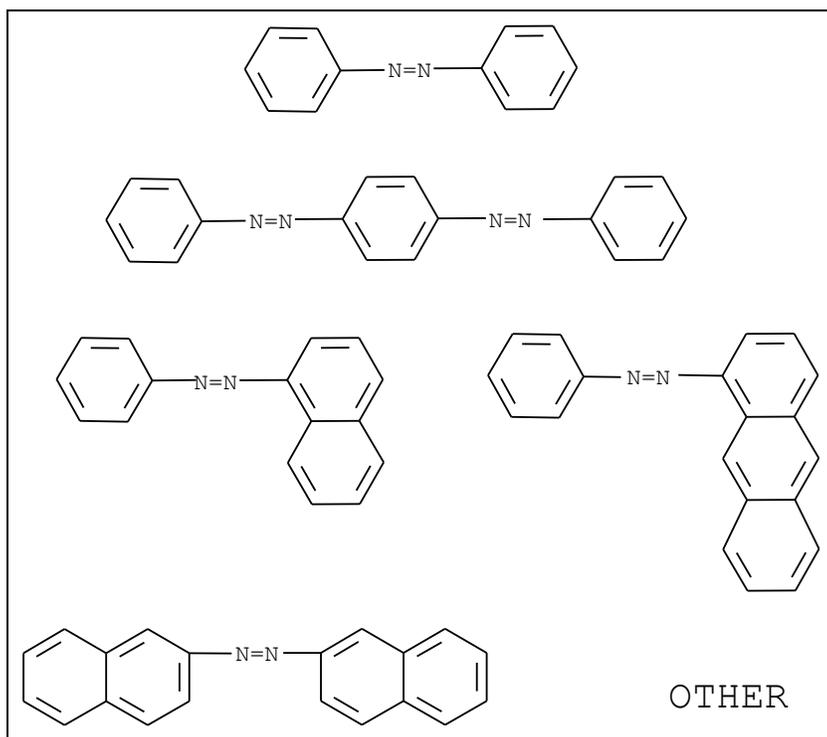
5.3.11 Arylazo Type Compounds

Component: Arylazo Compounds

Database: Yes

Expert System: Uses Aromatics Amines

Skeleton Templates:



Exceptions: The “By Structure” evaluation is carried out in the aromatic amine component. When one of the above skeleton templates is selected, a description of the resulting compounds is given with instructions to evaluate the products in the aromatic amine component.

Comments: The following may be used to find a compound in the arylazo database: CI Number, CI Name, Non CI Name, and CAS Number.

5.3.12 Aryldiazonium Salts

Component: Aryldiazonium Salts (direct-acting arylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



Heteroatoms: Nitrogen (N) may replace a ring carbon.

Ring Substituents: Ring substituents, alkyl groups (Cn), halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), and sulfonic acid (SO₃H) may be added to the ring carbons. At least one N⁺≡N ring substituent must be placed on the skeleton.

Exceptions: Substituents may not be added to the alkyl ring substituents. A nitrogen atom may replace a ring atom but may not have a ring substituent attached.

Comments:

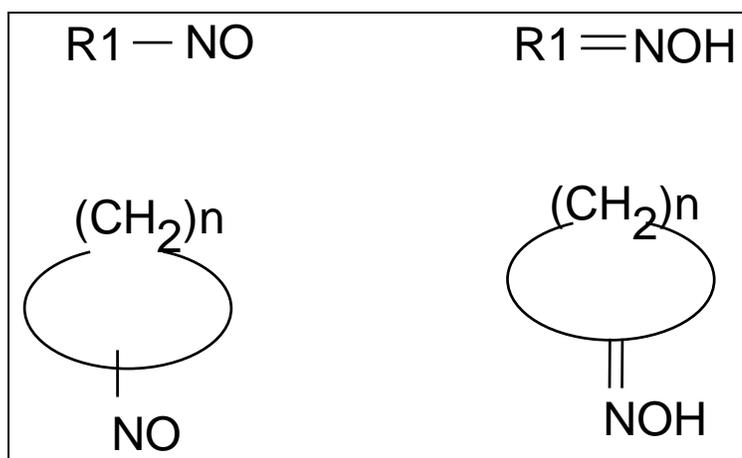
5.3.13 C-Nitroso and Oxime Type Compounds

Component: C-Nitroso and Oxime

Database: Yes

Expert System: Uses Aromatic Amines or Nitroalkane

Skeleton Templates:



Aliphatic R1: Alkyl chains

Cycloaliphatic: Enter a number for “n” representing the number of atoms in the ring. “N” must be greater than 2.

Substituents: Substituents that may be added to an aliphatic chain include halogens (Cl, Br, I, F), cyano (CN), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), esterified carboxylic acid (COOR), acyloxy (O(O)CR), and alkoxy groups (OR), nitroso (NO₂), nitro (NO), and oxime (NOH).

Exceptions: The nitroso (NO) or oxime (NOH) **must** be placed on the aliphatic chain. One is incorporated into the cycloaliphatic structures.

Comments: Aromatic compounds with nitroso or oxime are evaluated as aromatic amines. Entering the C-Nitroso and oxime component and selecting “Aryl” as the compound type will transfer the evaluation to the aromatic amine component.

Since the nitroso and oxime groups of the aliphatic/alicyclic C-nitroso and oxime compounds is metabolically converted to a nitro group, these compounds behave as nitroalkanes and are evaluated as such. The justification report contains the relative information on this metabolism and transfer.

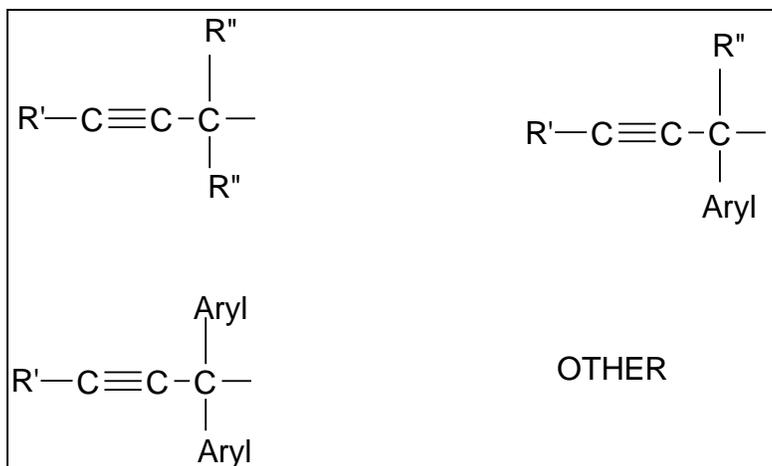
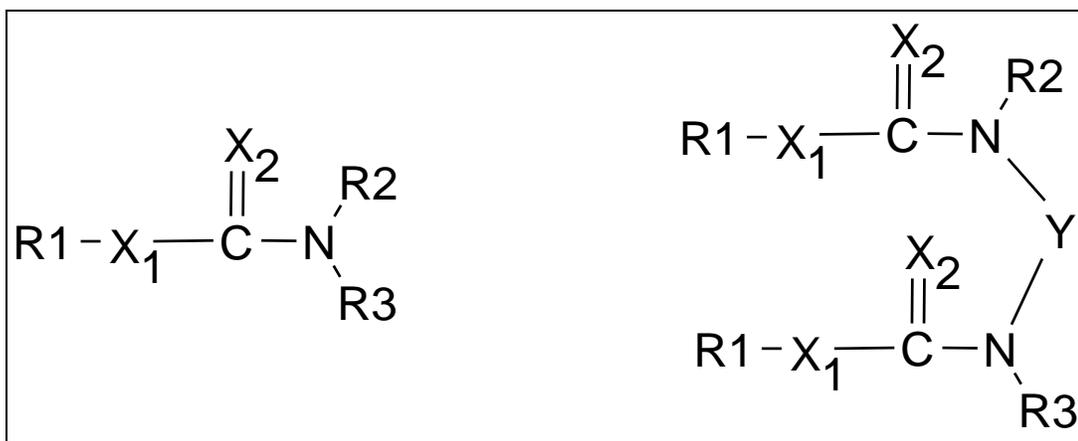
5.3.14 Carbamate Type Compounds

Component: Carbamates

Database: Yes

Expert System: Yes

Skeleton Templates:



R1: The acetylenic R group (R1) may be replaced by one of the R groups on the left. If Other is chosen, then the R1 can be defined using one of the menus provided for R2 and R3.

R'/R''/R2/R3: These R groups may be defined using menus containing various alkyl groups, aryl groups, halogens, hydroxyl, etc. Substituents may be added to these R groups.

X1/X2: Oxygen or Sulfur atoms.

Substituents: Substituents that may be added include: halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), sulfonate (SO₃), and acyloxy (O(O)CC_n).

Y: One of four linkages are provided in a menu to define the linkage for dicarbamates.

Exceptions: For the dicarbamate skeleton, note that the R1 groups will be identical to each other as will the X1 heteroatoms and the X2 heteroatoms.

In some cases, the menu item you have selected to define one of the R groups may not be allowed. You will be given a message to that effect. For example, the hydroxyl (OH) is not valid on R' or R'' positions. It may be placed only at R2 or R3.

Comments:

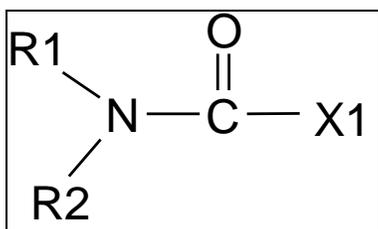
5.3.15 Carbamyl Halide Type Compounds

Component: Carbamyl Halides (direct-acting acylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2: aliphatic (alkyl chain)
aromatic types (phenyl, benzyl,
phenylethyl,)
hydrogen

X1: Cl, Br, I, F

Substituents: None.

Exceptions: Substituents such as hydroxyl, halogens, etc. are not considered and may not be placed on the R1 and R2 groups. Heteroatoms can not replace carbon atoms in the alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, heteroatoms may be replaced with carbon atoms.

Comments:

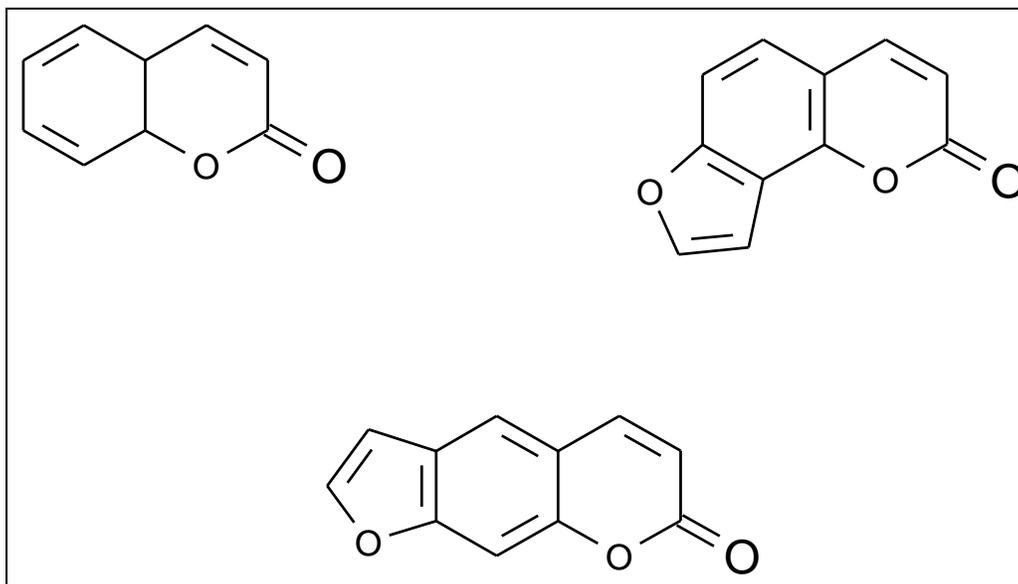
5.3.16 Coumarin and Furocoumarin Type Compounds

Component: Coumarins and Furocoumarins

Database: Yes

Expert System: Yes

Skeleton Templates:



Ring Substituents: Groups that may be placed on the ring are alkyl groups (Cn, OCn), hydroxyalkyl (CnOH), carbamoyl (C(O)NR₂), cyano (CN), acyl halide (Cn(O)X), aldehyde (C(O)H), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), and halogens (Cl, Br, F, I). Substituents on these groups are not allowed.

Exceptions: It is not necessary to define the halogen of the acyl halide. The size of substituents is defined by entering the number of carbons in the chain. If heteroatoms, other than the predefined oxygen are present, are in the carbon chain, consider these as carbon atoms. If selecting the carbamoyl, you will build the two R alkyl chains, without substituents and heteroatoms.

Comments: Coumarins and Furocoumarins (psoralen and angelicin) are evaluated in the same component.

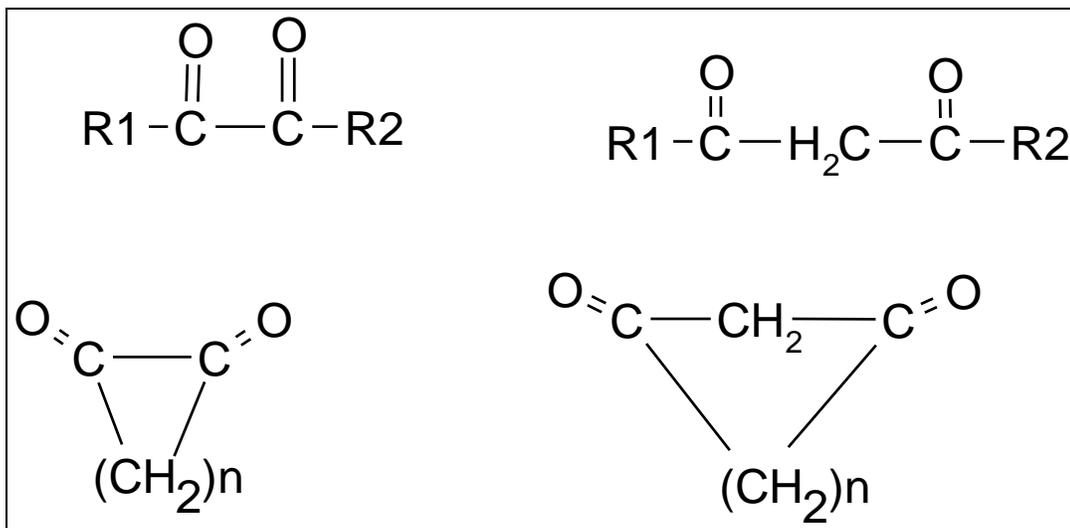
5.3.17 Dicarbonyl Type Compounds

Component: Dicarbonyls

Database: No

Expert System: Yes

Skeleton Templates:



Aliphatic R1/R2: phenyl, benzyl, phenylethyl, aliphatic and alicyclic alkyl groups.

Cycloaliphatic: Enter a number for “n” representing the number of atoms in the ring. “N” must be greater than 3. Ring substituents include halogens, alkyl chains, sulfonic and carboxylic acids, and hydroxyl.

Substituents: Halogens (Cl, Br, I, F), carboxylic acid (COOH), sulfonic acid (SO₃H), hydroxyl (OH), Other.

Exceptions: Substituents that may be added to an aliphatic R1/R2 groups and the methylene carbon of the dicarbonyl structures but not on the alkyl chains that are attached to cycloaliphatic dicarbonyl structures.

Comments:

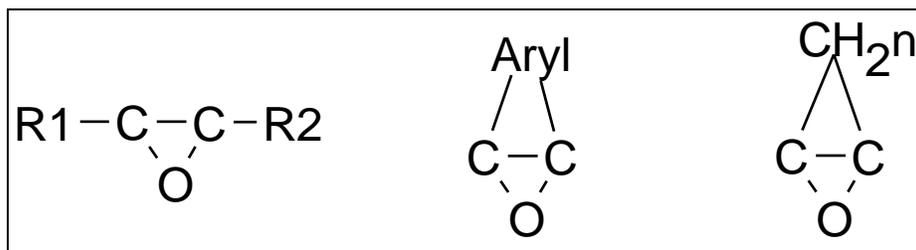
5.3.18 Epoxide Reactive Functional Groups

Component: Epoxides (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)
 other types (H, benzyl, phenylethyl)

Aryl: You are given a choice for the aryl group: 1-3 6-membered rings either linked or fused.

CH₂ⁿ: Enter the number of atoms in the ring for “n”.

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The epoxide carbons may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, alkyl (C_n), alkoxy (OC_n) and acyloxy (O(O)C_n).

Exceptions: Unsaturated alkyl chains other than vinyl and allyl are considered as saturated.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. Refer to Section 51 for details on the Direct Acting Alkylating Agents.

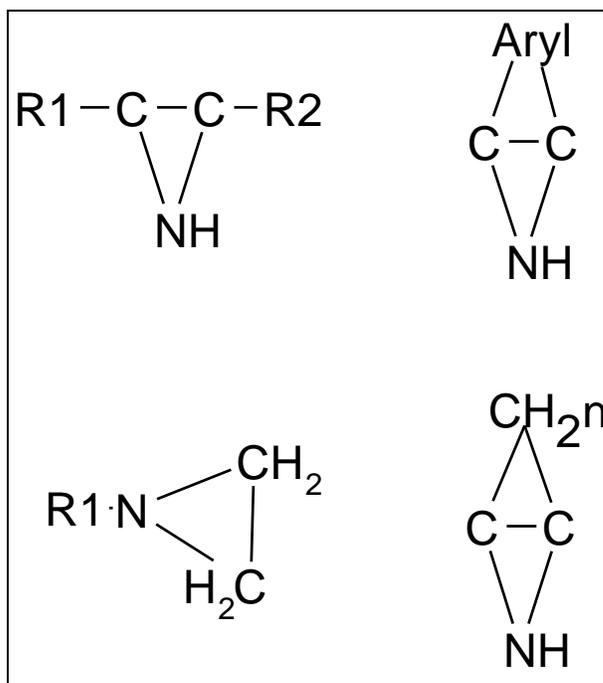
5.3.19 Ethyleneimine Reactive Functional Groups

Component: Ethyleneimines (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)
 other types (H, benzyl, phenylethyl)

Aryl: You are given a choice for the aryl group: 1-3 6-membered rings either linked or fused.

CH₂n: Enter the number of atoms in the ring for “n”.

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The ethyleneimine carbons may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, alkyl (C_n), alkoxy (OC_n) and acyloxy (O(O)C_n). The

ethyleneimine nitrogen may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, Cn, OCn, O(O)Cn, sulfonyl (SO₂Cn), acyl (C(O)Cn), and aryl.

Exceptions: Unsaturated alkyl chains other than vinyl and allyl are considered as saturated.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. Refer to Section 51 for additional details on Direct Acting Alkylating Agents.

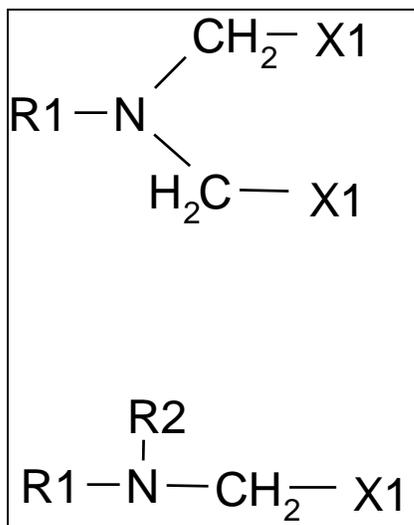
5.3.20 α -Haloalkylamine Reactive Functional Groups

Component: alpha-Haloalkylamine (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)

other types (H, benzyl, phenylethyl)

X1: Halogens: Cl, Br, I, F

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The methylene moiety (C-X) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, and Other.

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the methylene moiety. Heteroatoms can not replace the carbon atoms in the R1 alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be

the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. Refer to Section 51 for additional details on Direct Acting Alkylating Agents.

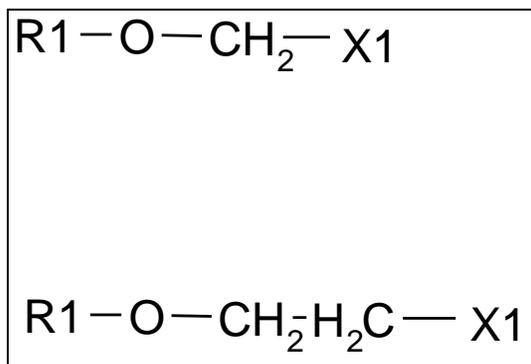
5.3.21 α β Haloether Reactive Functional Groups

Component: alpha-beta-Haloether (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)
 other types (H, benzyl, phenylethyl)

X1: Halogens(Cl, Br, I, F)

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The methylene/ethylene moiety (C-X/C-C-X) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, and Other.

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the methylene/ethylene moiety. Heteroatoms can not be replace the carbon atoms in the R1 alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered.

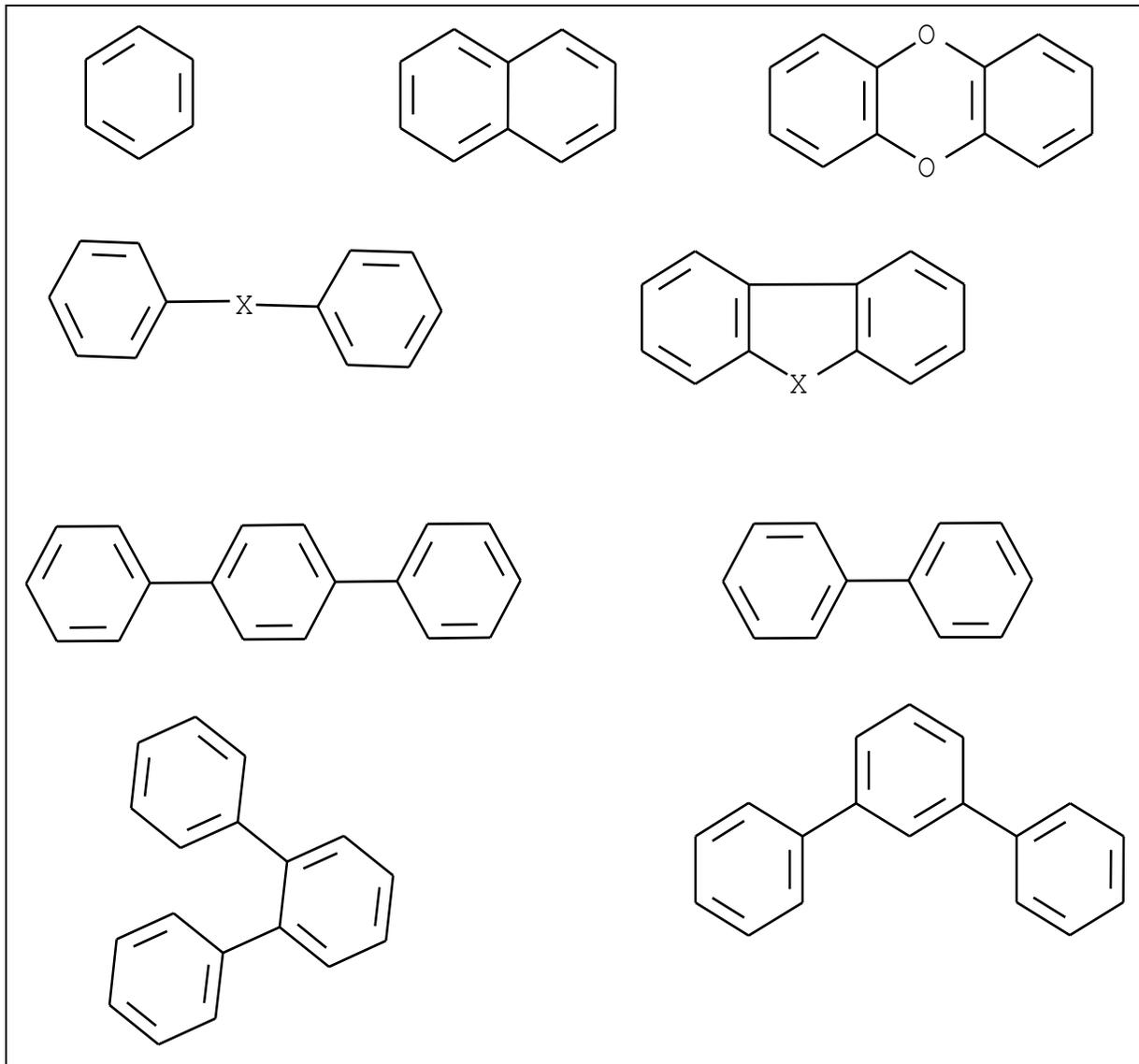
5.3.22 Halogenated Aromatic Hydrocarbon Type Compounds

Component: Halogenated Aromatic Hydrocarbons

Database: Yes

Expert System: Yes

Skeleton Templates:



Ring Substituents: Ring substituents can be selected from menus and include: halogens (Cl, BR, I, F), alkyl chains (Cn), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid

(SO₃H), cyano (CN), aldehyde (C(O)H), and alkoxy (OCn), and Other. By definition of halogenated aromatic, at least one halogen must be placed on the structure.

Exceptions:

List Of Compound Screen: After selecting 'By Structure' for your evaluation choice, a list of compound types is displayed: Halogenated Biphenyl, Halogenated Naphthalene, etc. By selecting one of these, the appropriate skeleton will be displayed on the screen.

Diphenyl Linked Skeleton: The linkage, designated by "X" may be defined with one of 12 different linkages.

Substituents: If the ring substituent is an alkyl group with a substituent, CH₂F for example, the F is treated as a hydrogen and can not be explicitly drawn.

Comments:

5.3.23 Halogenated Cycloalkane Type Compounds

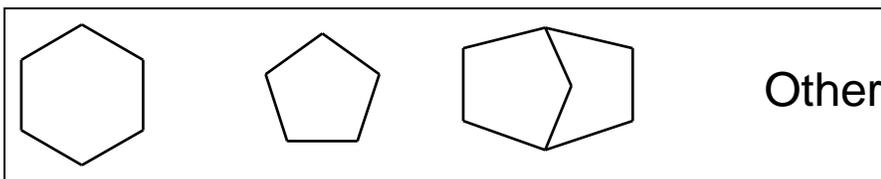
Component: Halogenated Cycloalkanes

Database: Yes

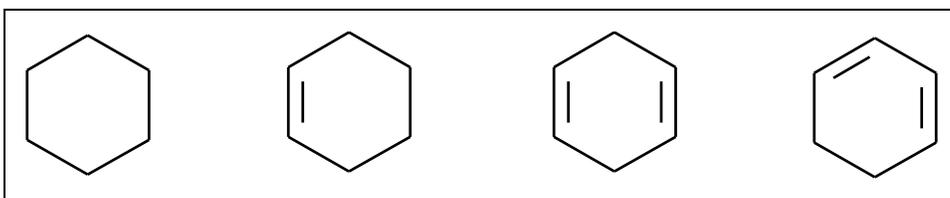
Expert System: Yes

Skeleton Templates:

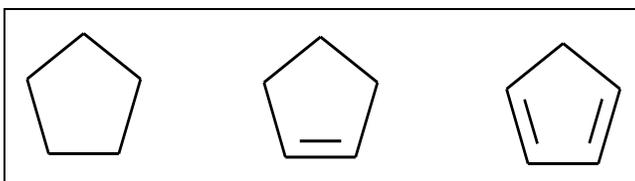
First Menu:



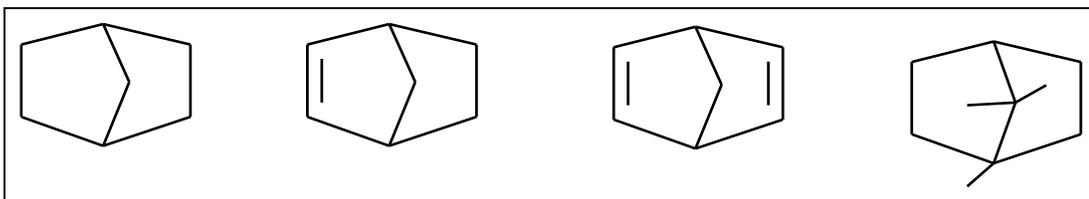
6-membered Rings:

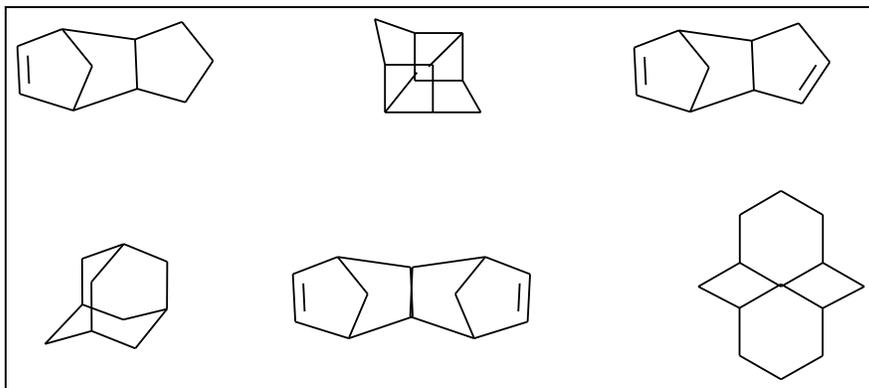


5-membered Rings:



Bicyclic Rings:



Other:

Substituents: Halogens (Cl, Br, I, F).

Exceptions: You are presented with list of halogenated cycloalkane classifications. By selecting the one, the menu of skeletons are displayed. Select the correct one from the menu.

Comments:

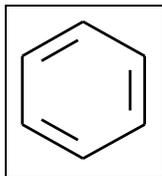
5.3.24 ortho-Halogenated Heterocyclic Type Compounds

Component: ortho-Halogenated Heterocyclic (direct-acting arylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



Ring Substituents: alkyl chains, halogens, hydroxyl, carboxylic acid, and sulfonic acid.

Heteroatoms: Nitrogen

Exceptions: Additional substituents may not be added to the alkyl ring substituents. Any substituents on the original compound are considered as hydrogen. Multi-ring ortho heterocyclics can not be evaluated.

Comments: The ring must contain at least one nitrogen ring atom and a halogen ortho to the nitrogen atom.

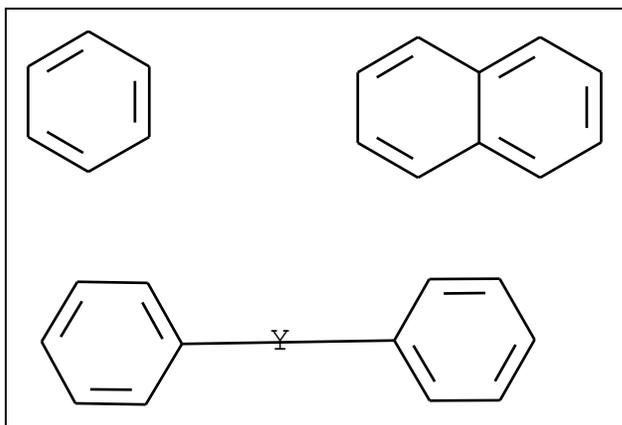
5.3.25 Halogenated Nitroaromatic Type Compound

Component: Halogenated Nitroaromatic (direct-acting arylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



Ring Substituents: alkyl chains, halogens, nitro, hydroxyl, carboxylic acid, and sulfonic acid.

Heteroatoms: Nitrogen

Exceptions: Additional substituents may not be added to the alkyl ring substituents. Any substituents on the original compound are considered as hydrogen. Halogenated Nitroaromatics with more than 2 rings can not be evaluated.

The linkage “Y” need not be defined.

Comments: The ring must contain at least one nitro group and one halogen ortho or para to the nitro group.

5.3.26 Halogenated Linear Aliphatic Type Compounds

Component: Halogenated Linear Aliphatic

Database: Yes

Expert System: Yes

Skeleton Templates:



R1: alkane, alkene, alkyne

X: Halogens (Cl, Br, I, F)

Substituents: None.

Exceptions: Additional substituents may not be added to the alkyl chain.

Comments: The carbon chain must be built and at least one halogen must be added. These compounds are also considered to be direct acting alkylating agents and are sometime known as “alkyl and alkenyl halides”.

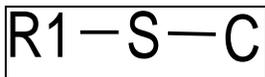
5.3.27 α -Halothioether Reactive Functional Groups

Component: alpha-Halothioether (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)
 other types (H, benzyl, phenylethyl)

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The methylene moiety (S-C) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, and Other. At least one halogen must be placed on the methylene moiety.

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the methylene moiety. Heteroatoms can not be replace the carbon atoms in the R1 alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. Refer to Section 51 for additional information on Direct Acting Alkylating Agents.

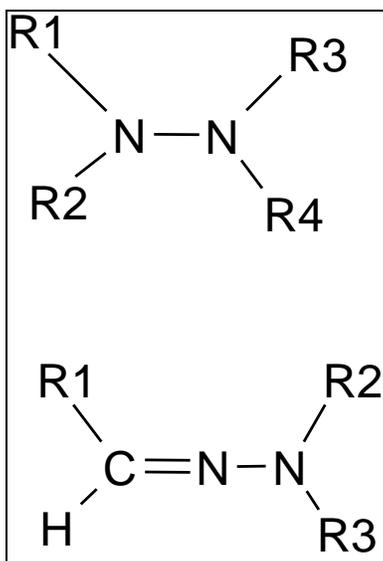
5.3.28 Hydrazo Type Compounds

Component: Hydrazo Compounds

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2/R3/R4: aliphatic (alkyl chain, cycloC6, vinyl, allyl)
 aromatic types (phenyl, benzyl, phenylethyl,)
 acyl type (carbamyl, pyridyl, acyl)
 arylsulfonyl,
 Hydrogen

Substituents : halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), cyano (CN), alkoxy (OR), acyloxy (OC(O)R).

Exceptions: To add substituents to the R group alkyl chains, you first build the carbon chain then add the substituent. The chain must be at least 3 carbon atoms long. If the chain is methyl or ethyl then select CH₃ or C₂H₅ from the menu. Other than the vinyl and allyl R groups on the menu, unsaturated aliphatic chain can not be drawn. If the R group is an aryl or acyl, select the substituent from the menu then answer the number/position questions. Heteroatoms can not replace carbon atoms in the alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, substitute carbon atoms for and heteroatoms in the chain.

Comments: This earlier version of the build screen has the carbon atom and substituents posted on the menu bar not in pull down menus as in later versions.

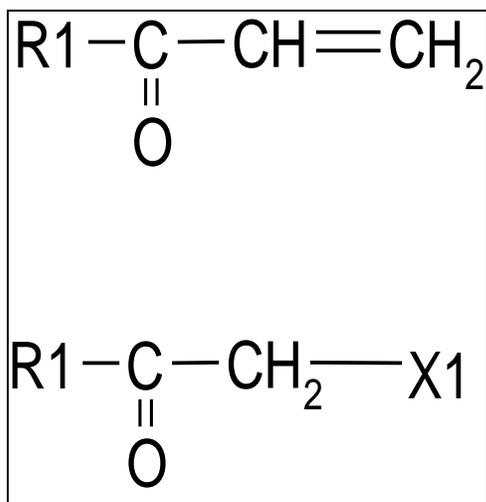
5.3.29 Reactive Ketone Reactive Functional Groups

Component: Reactive Ketones (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)
 other types (benzyl, phenylethyl)

X1: Must be replaced with a halogen.

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The methylene/ethylene moiety (C-X/C=C) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, and Other.

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the methylene/ethylene moiety. Heteroatoms can not be replace the carbon atoms in the R1 alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be

considered. Refer to Section 51 for additional information on Direct Acting Alkylating Agents.

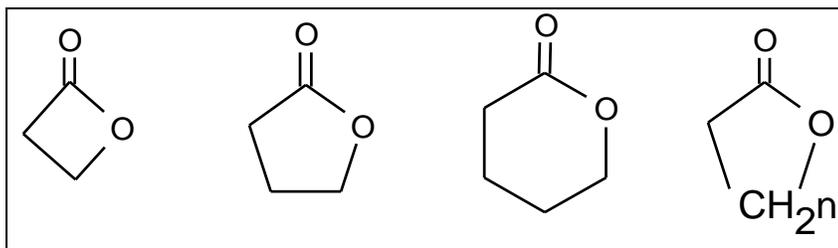
5.3.30 Lactone Type Reactive Functional Groups

Component: Lactones (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



Rings: After selecting a ring skeleton, you will be presented with several skeletons offering a choice of double bond placement.

Substituents: Halogens (Cl, Br, I, F), sulfonic acid (SO₃H), carboxylic acid (COOH), and alkyl chains (C_n) may be placed on the lactone ring. Alkyl ring substituents may also contain substituents may also contain the above substituents including hydroxyl (OH).

Heteroatoms: Nitrogen, oxygen and sulfur may replace the ring carbon atoms.

Exceptions: The carrier molecule need not be defined for lactones.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. Refer to Section 51 for more information on Direct Acting Alkylating Agents.

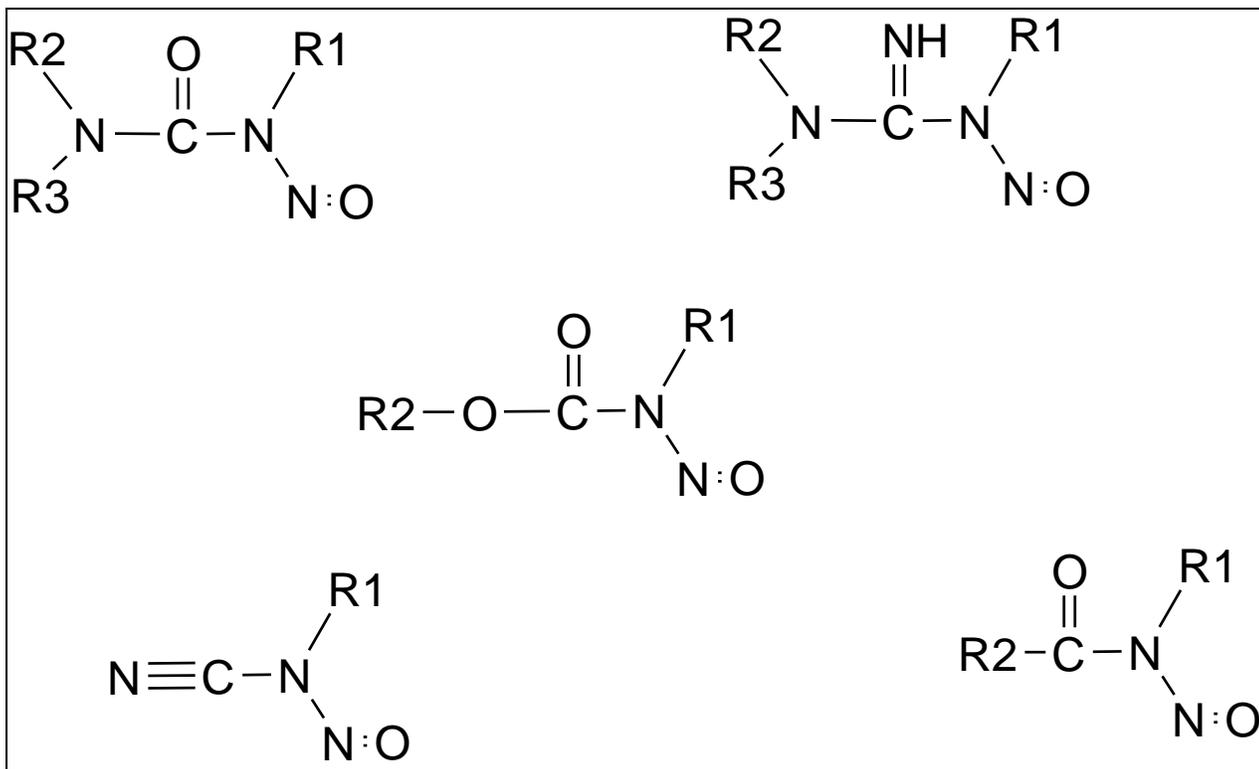
5.3.31 Nitrosamide Type Compounds

Component: Nitrosamide Compounds

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2/R3: aliphatic (alkyl chain, cycloC6, vinyl, allyl)
aromatic types (phenyl, benzyl, phenylethyl)
Other types (hydrogen)

Substituents : halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), alkoxy (OR), phenoxy(OC₆H₅).

Exceptions: To add substituents to the R group alkyl chains, you first build the carbon chain then add the substituent. The chain must be at least 3 carbon atoms long. If the chain is methyl or ethyl then select CH₃ or C₂H₅ from the menu. Other than the vinyl and allyl R groups on the menu, unsaturated aliphatic chain can not be drawn. If the R group is an aryl or acyl, select the substituent from the menu then answer the

number/position questions. Heteroatoms can not replace carbon atoms in the alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, substitute carbon atoms for and heteroatoms in the chain.

Comments:

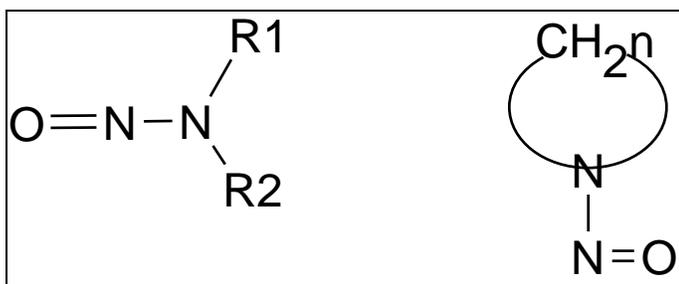
5.3.32 Nitrosamine Type Compounds

Component: Nitrosamine Compounds

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2:

aliphatic (alkyl chain, cycloC6, vinyl, allyl)
 aromatic types (phenyl, benzyl, phenylethyl)
 other types (hydrogen)

CH₂n: Enter the number of atoms in the ring.

Heteroatoms: NH, O, S may replace the carbon atoms in the R1/R2 alkyl groups.

N-R, where R = hydrogen, methyl, or nitroso, O and S may replace ring carbons.

Substituents : halogens (Cl, Br, I, F), hydroxyl (OH) carboxylic acid (COOH), sulfonic acid (SO₃H), sulfate (SO₄H), alkoxy (OR), oxo (=O), cyano (CN), acyloxy (O(O)CR), esters (C(O)OR, and tosylate (TOS).

Exceptions: Outside of vinyl and allyl, unsaturated R groups can not be specifically evaluated. Treat the unsaturated groups as saturated alkyl chain. To add a substituent to a carbon chain, first construct the chain then add the substituents. The chain must be at least three carbon atoms in length. If the alkyl chain is methyl or ethyl then select CH₃ or C₂H₅ from the menu.

Comments: This earlier version of the build screen lists the heteroatoms under a separate menu from the carbon atom.

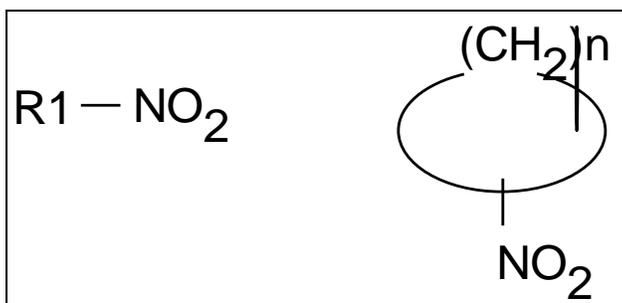
5.3.33 Nitroalkane and Nitroalkene Type Compounds

Component: Nitroalkane and Nitroalkene

Database: No

Expert System: Yes

Skeleton Templates:



Aliphatic R1: Alkyl chains

Cycloaliphatic: Enter a number for “n” representing the number of atoms in the ring. “N” must be greater than 2.

Substituents: Substituents that may be added to an aliphatic chain include halogens (Cl, Br, I, F), cyano (CN), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), acyl (COOR), acyloxy (O(O)CR), and alkoxy (OR) groups, nitroso (N=O), nitro (NO₂), and oxime (NOH).

Exceptions: The nitroso (N=O) or oxime (NOH) are used to build C-Nitroso and Oxime compounds which are converted to nitroalkanes or nitroalkenes as appropriate. The aliphatic compound **must** contain at least one NO₂, NO, or NOH group. The cycloaliphatic ring has one NO₂ group implied.

Comments:

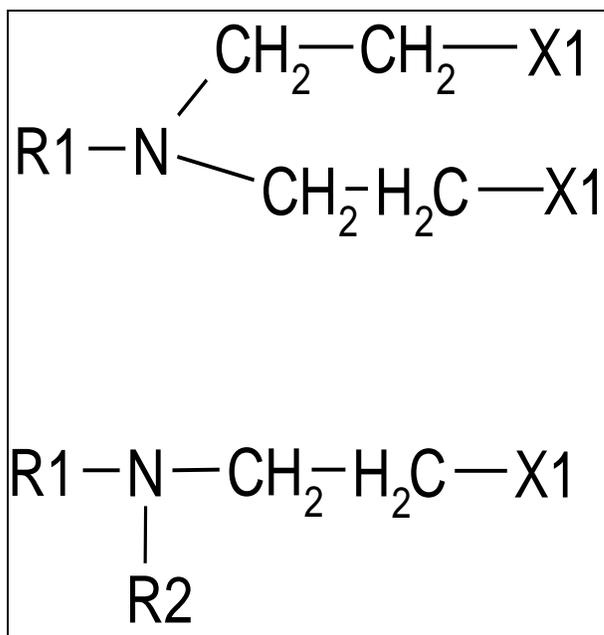
5.3.34 Nitrogen Mustard Reactive Functional Groups

Component: Nitrogen Mustards (direct-acting alkylating agent)

Database: Yes

Expert System: Yes

Skeleton Templates:



R1/R2: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system
 1-4 rings)
 normal body constituent
 (amino acid, purine, etc.)
 other types (H, benzyl,
 phenylethyl)

X1: Must be replaced with a halogen

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The methylene/ethylene moiety (C-X/C=C) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, and Other.

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the methylene/ethylene moiety. Heteroatoms can not be replace the carbon atoms in the R1 alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be

the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. See Section 51 for more details on the Direct Acting Alkylating Agents.

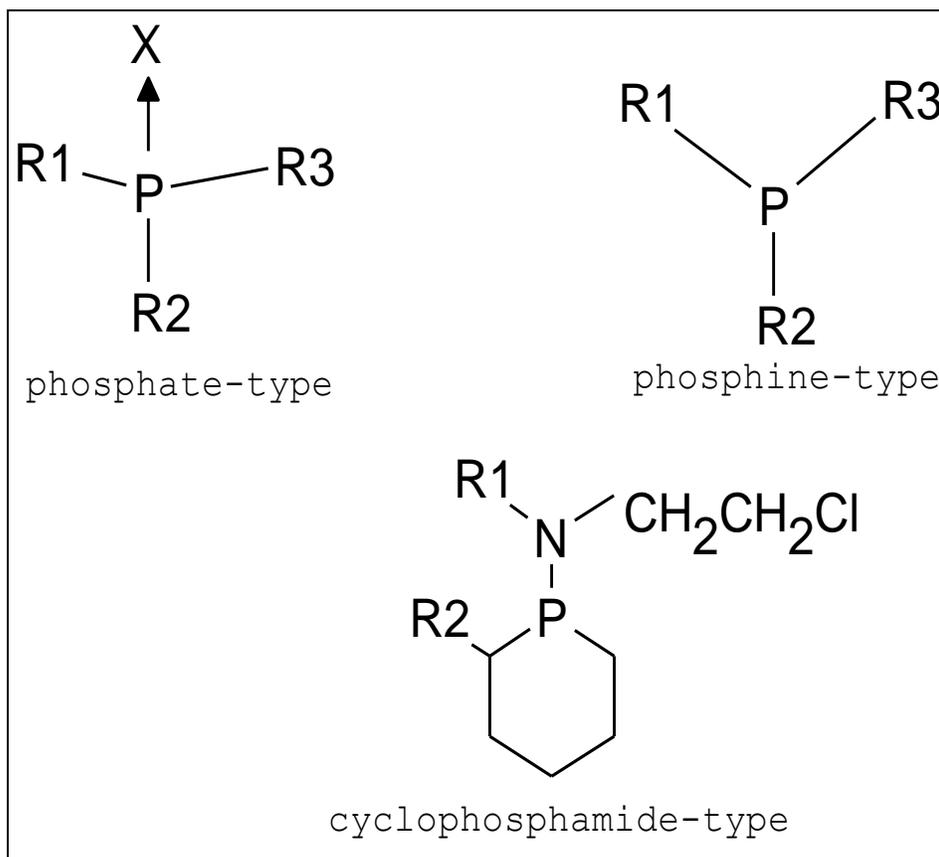
5.3.35 Organophosphorus Type Compounds

Component: Organophosphorus

Database: Yes

Expert System: Yes

Skeleton Templates:



Select the **phosphate-type** skeleton to view 12 additional skeletons. In this generic skeleton R1/R2/R3 stand for, alkyl groups, or aryl groups attached directly to the phosphorus (P), and , X-alkyl or X-aryl where X is oxygen, sulfur or in some cases nitrogen, linking the phosphorus to the alkyl/aryl group. The following types of organophosphates and related compounds are represented: phosphates, phosphonates,

phosphorothioates, phosphorothiolates, phosphorodithioates, phosphoroamidates, phosphoramides.

Select the **phosphine-type** skeleton to view 2 skeletons: phosphine and phosphine-oxide.

Select the **cyclophosphamide-type** skeleton to view 3 skeletons: cyclophosphamide, isophosphamide, trophosphamide.

R1/R2/R3: alkyl (Cn), hydrogen (H), benzyl (CH₂C₆H₅), phenyl (C₆H₅), Morpholino, NR'R'' (where R'R'' can be one of the above).

X1/X2/X3/X4: Oxygen (O), Sulfur (S)

Substituents: Halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H) and additionally alkyl (Cn) on the aryl ring..

Exceptions: In addition to oxygen and sulfur, nitrogen (N) is commonly found in organophosphorus-type compounds. For these types of compounds, the nitrogen heteroatom has been appropriately placed in the skeleton.

The "Other" menu selection, found in most other systems is not offered in this system.

To evaluate di/tri organophosphates, not found in the database, evaluate each degradation product and use the highest concern level for the final concern.

Additional heteroatoms in the alkyl R groups may be entered as carbon atoms or the degradation product may be evaluated separately.

Comments: Phosphoramides and certain phosphorus-containing nitrogen mustards (e.g. cyclophosphamides) may require metabolic activation to alkylating intermediates. Most other alkyl phosphates, i.e. phosphates-type organophosphorus compounds, are direct acting alkylating agents.

5.3.36 Peroxide Type Compounds

Component: Peroxide

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2: aliphatic (alkyl, vinyl, allyl, cycloC6, acyl)
aromatic (phenyl, benzoyl)
hydrogen

Substituents: hydroxyl (OH), sulfite (SO₃), sulfonic acid (SO₃H), carboxylic acid (COOH), esterified carboxylic acid (COOR).

Exceptions:

Comments: The peroxide component assigns the carcinogenicity concern on structure-activity relationship analysis and on available data.

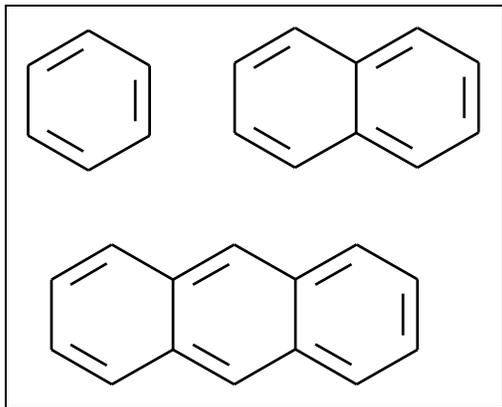
5.3.37 Phenol Type Compounds

Component: Phenol and Phenolic Compounds

Database: Yes

Expert System: Yes

Skeleton Templates:



Ring Substituents: Halogens (Cl, Br, I, F), carboxylic acid (COOH), sulfonic acid, (SO₃H) hydroxyl (OH), vinyl, allyl, alkoxy (OR) and alkyl (Cn) groups.

Substituents: None.

Exceptions: Alkyl groups and alkoxy groups consider the number of carbons in the chain only. If the alkyl group has heteroatoms you may treat the heteroatom as a carbon or if you know the degradation product, evaluate it separately in the appropriate component. The oxygen in the alkoxy group is the only heteroatom considered. Additional substituents that may be on the alkyl or alkoxy group are not considered and can not be added.

Comments: The aromatic ring **must** contain at least one hydroxyl group (OH) to have the compound considered as a phenol or phenolic.

5.3.38 Phosgene Type Compounds

Component: Phosgene and Phosgene-Type

Database: No

Expert System: Yes

Skeleton Templates:



X1/X2: Halogens

Exceptions: Halogens are the only atoms that may be placed on these structures.

Comments:

5.3.39 Polycyclic Aromatic Hydrocarbons - Heterocyclic**Component:** Polycyclic Aromatic Hydrocarbons - Heterocyclic**Database:** Yes**Expert System:** No**Skeleton Templates:**

Exceptions: The Heterocyclic PAH component is a database, without expert system capabilities. The “By Structure” option displays a questionnaire to enter the number of 6-membered rings, 5-membered rings, and the number of nitrogen ring atoms. You are displayed a menu of structures to select the appropriate structure. The Heterocyclic PAH structures are not substituted.

Comments:

5.3.40 Polycyclic Aromatic Hydrocarbons - Homocyclic**Component:** Polycyclic Aromatic Hydrocarbons - Homocyclic**Database:** Yes**Expert System:** Yes**Skeleton Templates:** Aromatic structures containing 3-6 six-membered rings.**Substituents:** The following substituents may be placed on the skeleton templates: hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, F, I), cyano (CN), alkyl (C_n), alkoxy (OC_n), and formyl (C(O)H).**Exceptions:** The “By Structure” option displays a questionnaire asking you to enter the number of 6-membered rings, and the number of 5-membered rings, in addition to other general questions about the structure of the compound.**Comments:**

5.3.41 Siloxane Type Compounds

Component: Siloxane, Siloxene, Silanols

Database: Yes

Expert System: No

Skeleton Templates: None

Exceptions: At the present time, this component does not have an expert system to evaluate new siloxane type compounds. Only the tested compounds in the database can be examined.

Comments:

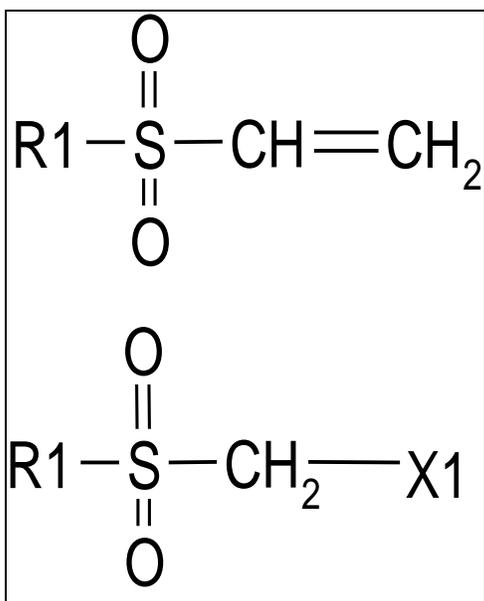
5.3.42 Reactive Sulfone Reactive Functional Groups

Component: Reactive Sulfones (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



R1: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)
 other types (H, benzyl, phenylethyl)

X1: Must be replaced with a halogen (Cl, Br, I, or F).

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The methylene/ethylene moiety (C-X/C=C) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, and Other.

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the methylene/ethylene moiety. Heteroatoms can not be replace the carbon atoms in the R1 alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic,

alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. See Section 51 for additional information on Direct Acting Alkylating Agents.

5.3.43 Sulfur Mustard Reactive Functional Groups

Component: Sulfur Mustards (direct-acting alkylating agent)

Database: Yes

Expert System: Yes

Skeleton Templates:



R1/R2: aliphatic (alkyl chain)
 alicyclic (cycloaliphatic)
 aromatic (aromatic ring system 1-4 rings)
 normal body constituent (amino acid, purine, etc.)
 other types (H, benzyl, phenylethyl)

Substituents: The following substituents may be placed on alkyl R groups : hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), halogens (Cl, Br, I, F), and Other. In addition to these, aryl R group may have vinyl and allyl groups as well as alkyl (C_n) on aromatic rings. The ethylene moiety (C-C) may be substituted with the following: OH, COOH, SO₃H, Cl, Br, I, F, C_n, and Other. At least one halogen must be placed on the beta position of the ethylene moiety.

Exceptions: Unsaturated alkyl chains, other than vinyl and allyl, are treated as saturated alkyl groups. Additional substituents, may not be added to alkyl chains of the methylene moiety. Heteroatoms can not be replace the carbon atoms in the R1 alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately. If the degradation products are not known, replace the heteroatoms with carbon atoms.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be

considered. Refer to Section 51 for more information on Direct Acting Alkylating Agents.

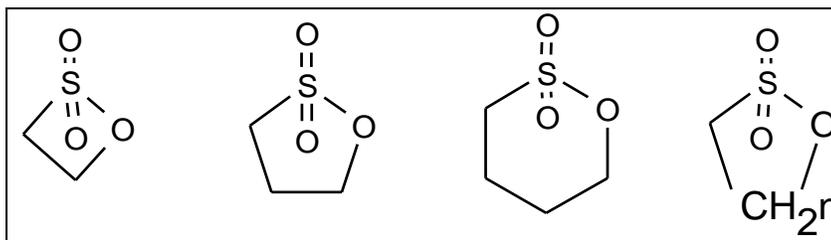
5.3.44 Sultone Reactive Functional Groups

Component: Sultones (direct-acting alkylating agent)

Database: No

Expert System: Yes

Skeleton Templates:



Rings: After selecting a ring skeleton, you will be presented with several skeletons offering a choice of double bond placement.

Substituents: Halogens (Cl, Br, I, F), sulfonic acid (SO₃H), carboxylic acid (COOH), and alkyl chains (C_n) may be placed on the sultone ring. Alkyl ring substituents may also contain substituents may also contain the above substituents including hydroxyl (OH).

Heterotoms: Nitrogen, oxygen and sulfur may replace the ring carbon atoms.

Exceptions: The carrier molecule need not be defined for sultones.

Comments: The evaluation of any direct-acting alkylating agent considers 1 or more reactive functional group on a carrier molecule. The carrier molecule is considered to be the molecule to which the reactive group is attached. It may be aromatic, aliphatic, alicyclic, etc. It is important to remember that you are drawing the reactive functional group and not the entire molecule but its attachment to the carrier molecule must be considered. Refer to Section 51 for additional information on Direct Acting Alkylating Agents.

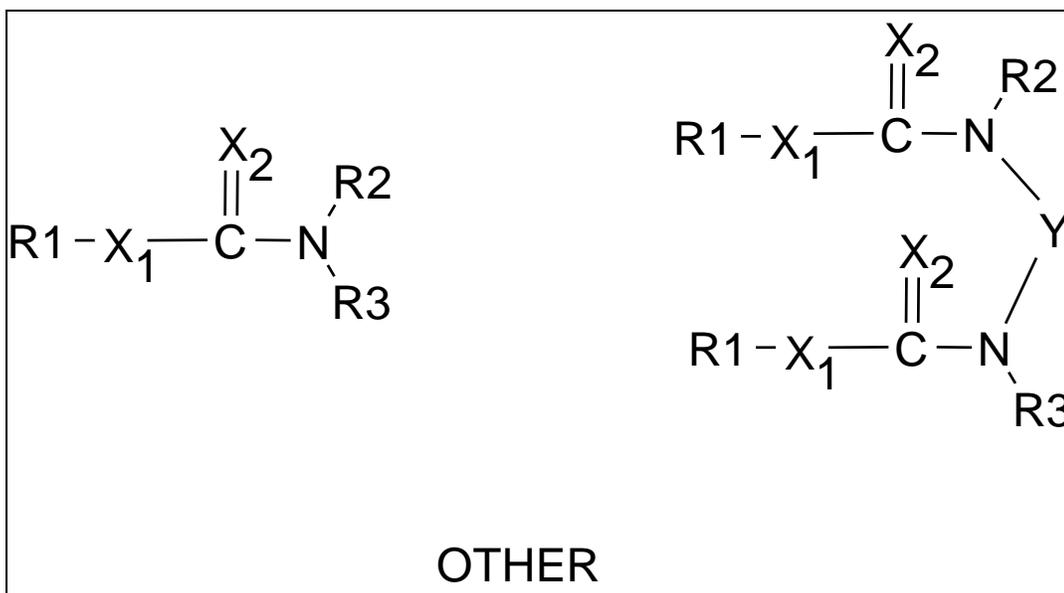
5.3.45 Thiocarbamate Type Compounds

Component: Thiocarbamates

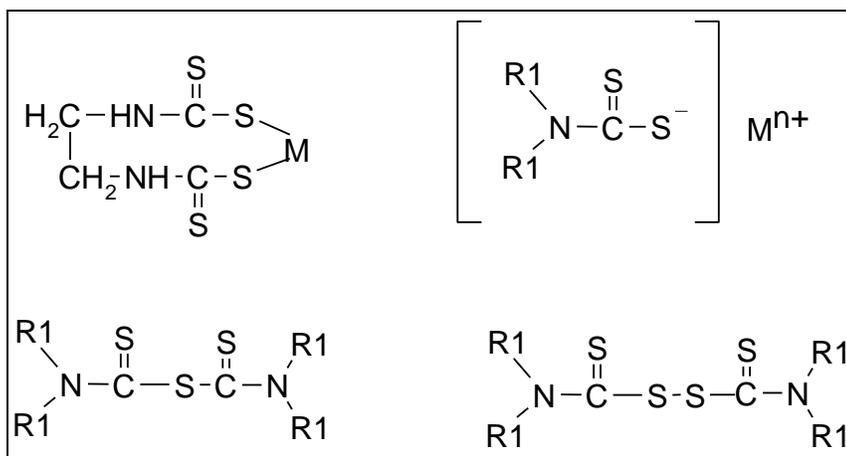
Database: Yes

Expert System: Yes

Skeleton Templates:



Other:



R1: Refer to the carbamates to view the R groups that may replace the acetylenic R1 group.

M: Indicates some metal which does not need to be defined.

R'/R''/R2/R3: These R groups may be defined using menus containing various alkyl groups, aryl groups, halogens, hydroxyl, etc. Substituents may be added to these R groups.

X1/X2: Oxygen or Sulfur atoms.

Y: One of four linkages are provided in a menu to define the linkage for dicarbamates.

Substituents: Refer to the Carbamate Component section on substituents.

Exceptions: For the dicarbamate skeleton, note that the R1 groups will be identical to each other as will the X1 heteroatoms and the X2 heteroatoms.

In some cases, the menu item you have selected to define one of the R groups may not be allowed. You will be given a message to that effect. For example, the hydroxyl (OH) is not valid on R' or R'' positions. It may be placed only at R2 or R3.

Comments: For some menu selections, you will be transferred to the carbamate component.

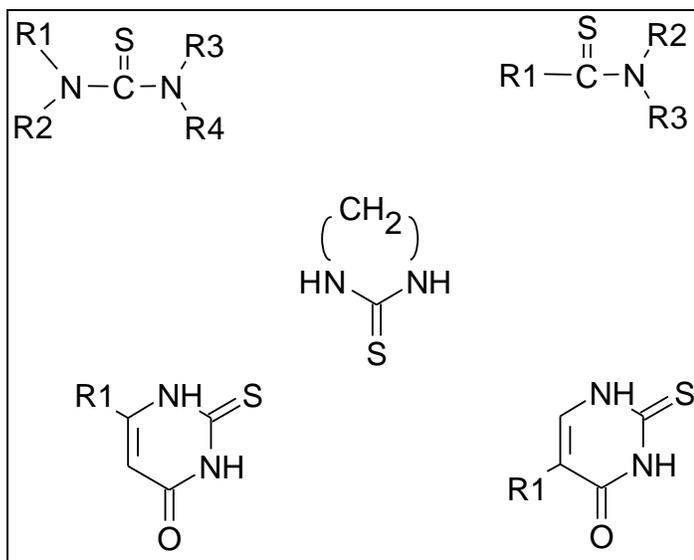
5.3.46 Thiocarbonyl Type Compounds

Component: Thiocarbonyls

Database: No

Expert System: Yes

Skeleton Templates:



R1/R2/R3/R4 aliphatic (alkyl chains, vinyl, cycloC6, allyl)
aromatic (phenyl, phenylethyl, benzyl, carbamyl)

Substituents: None.

Exceptions: Specific substituents are not considered in this component. You are asked to answer a question regarding the presence on any substituents.

Comments:

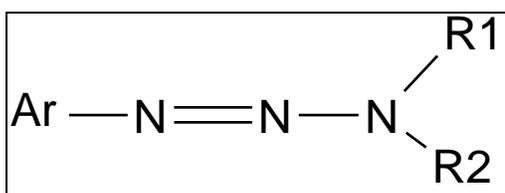
5.3.47 Triazene Type Compounds

Component: Triazene

Database: No

Expert System: Yes

Skeleton Templates:



other types (hydrogen)

R1/R2: aliphatic (alkyl chain,
cycloC6, vinyl,
allyl)
aromatic types (benzyl,
phenylethyl,)

Substituents : halogens (Cl, Br, I, F) , hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO₃H), cyano (CN), alkoxy (OR), acyloxy (OC(O)R).

Exceptions: To place substituents on alkyl R groups, you must first build the carbon chain then add the substituent. The chain must be at least 3 carbon atoms long. If the chain is methyl or ethyl then select CH₃ or C₂H₅ from the menu. Other than the vinyl and allyl R groups on the menu, other unsaturated aliphatic chain can not be drawn. To add substituents to aryl R groups, select the substituent from the menu, then answer the number/position questions. Heteroatoms can not replace carbon atoms in the alkyl chain nor can keto groups be added. The degradation products of these compounds should be considered separately.

Triazenes with aryl ring systems consisting of more than 2 aromatic rings should be evaluated in the PAH component.

Comments: This earlier version of the build screen has the carbon atom and substituents posted on the menu bar not in pull down menus as in later versions.

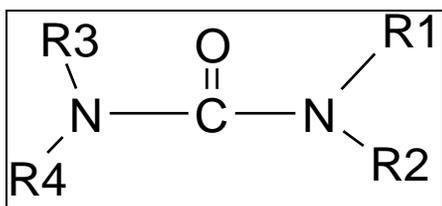
5.3.48 Urea Type Compounds

Component: Ureas

Database: Yes

Expert System: Yes

Skeleton Templates:



R1/R2: alkyl chain
hydrogen
aryl (nonspecific)
alkoxy

Exceptions: If the R groups of the urea are substituted, you are given a list of reactive functional group to examine. If the substituents are among the list, you are instructed to evaluate the compound as a direct-acting agent.

If one or more of the R groups is a type of aryl group, then you are instructed to evaluate the degradation products.

Comments:

6. Direct-Acting Alkylating Agents - A Guided Tour

The Direct-acting Alkylating Agents Component of the Organic Subsystem evaluates alkylating agents which do not require metabolic activation to exert carcinogenic action. Some molecules are unlikely to have more than one direct-acting alkylating agent are referred to as stand-alone compounds, whereas others more commonly have more than one reactive functional groups (RFGs) of the same or of different types. The carcinogenicity concern is first determined for each of the RFGs; the concern for the entire molecule is determined by the combination of RFGs.

6.1 Stand-alone Compounds

The direct-acting alkylating agents that are stand-alone compounds are listed below:

- Aldehydes
- Alkyl and Alkenyl Halides (Halogenated Linear Aliphatics)
- Alkyl Phosphates (most Organophosphate Compounds)
- Alkyl Sulfates and Alkyl Alkanesulfonates
- Dicarbonyls

These compounds are all evaluated by either selecting the compound from a database or building the compound by selecting the appropriate skeleton of the compound and adding substituents, etc. to the skeleton. For more information about each type of direct-acting alkylating agent that is a stand-alone compound, refer the 'User's Guide to the Organic Subsystem'.

6.2 Reactive Functional Groups

The direct-acting alkylating agents that are reactive functional groups are listed below:

- Acrylamides

- Acrylates
- Epoxides
- Ethyleneimines
- alpha-Haloalkylamines
- alpha-/beta-Haloethers
- alpha-Halothioethers
- Ketones, Reactive
- Lactones
- Nitrogen Mustards
- Sulfones, Reactive
- Sulfur Mustards
- Sultones

These RFGs must be attached to some type of carrier molecule to form the compound to be evaluated. A carrier molecule is used to refer to the entire compound minus the specific reactive functional group being evaluated. The compound can be monofunctional, meaning there is only one RFG attached to the carrier molecule, or polyfunctional, meaning there is more than one RFG attached to the carrier molecule. In either case, general information about the compound must be entered and both the RFG(s) and the corresponding carrier molecule must be defined.

7. Steps For Evaluating an RFG

The following are step-by-step instructions for evaluating one or more RFGs attached to a carrier molecule.

7.1 Step 1

First, one or more questions about the compound as a whole are asked. The questions displayed are dependent upon the previous answers. These questions pertain to the bioavailability of the compound, the molecular weight of the compound, the RFG equivalent weight, the presence of covalently linked repeating subunits, and the

anticipated route or routes of exposure of the compound. Simply answer the questions presented. If you need clarification, help is available by pressing the F1 key.

7.2 Step 2

If the RFG is an acrylamide, acrylate, alpha-halothioether, or sulfur mustard, the RFG skeleton is known and will be displayed directly on the screen.

If the RFG is not one of the aforementioned, a menu of RFG skeletons is displayed and the appropriate skeleton must be selected from the menu.

Remember, the skeleton represent the one RFG that you are evaluating at this time. You will be able to evaluate all RFGs during this session. The R1/R2 groups represent the “carrier molecule” which you will also have the opportunity to describe in general terms.

7.3 Step 3

Once the skeleton of the RFG has been chosen, the “carrier molecule” must be defined and substituents may be added to the atoms which make up the RFG skeleton. These can be defined in any order. The “carrier molecule” selections can be found under the ‘R-groups/Substituents’ option under the ‘Add’ menu. The possibilities for the “carrier molecule” include: Aliphatic, Aromatic, Alicyclic, Normal body constituents and Other groups. Look at the selections available under each. Press the Escape key to leave the menu without selecting an item. The last option offered on the ‘R-groups/Substituents’ menu is Substituents. The items from the ‘Substituent’ menu can only be placed on atoms that make the RFG skeleton; they can not be used to define the carrier molecule, which is denoted as R1 and/or R2.

When defining the “carrier molecule”, the remaining RFGs can be defined as simple substituents. To do this simply indicate the RFG with “Other” or as an alkyl chain, which ever is more representative. Remember, you will have the opportunity to completely define this RFG later in the evaluation.

7.4 Step 4

When this RFG and the “carrier molecule” has been completely defined, select the ‘Exit’ option from the main menu and the ‘Evaluate Compound’ option from the ‘Exit’ menu. The final level of concern for this RFG will then be established.

7.5 Step 5

If there is another RFG attached to the compound that needs to be evaluated, then enter another code number (filename) for the evaluation of that RFG, select the type of RFG from the menu, and repeat Step 2 - Step 4.

If each RFG has been evaluated and the compound is monofunctional, then the final level of concern for the compound is displayed and the evaluation ends.

If each RFG has been evaluated and the compound is polyfunctional, enter a unique code name for the overall line of reasoning. Then, if asked, answer the questions regarding the distance between each pair of RFGs . Once all the information has been supplied, the final level of concern for the compound is displayed and the evaluation ends.

Keep a record of the code numbers (filenames) used for each RFG evaluated. These code numbers are referred to in the final justification report. In addition to the final report, you can view (or print) the justification report for each RFG through the report

utility. Select the Reports from the Main Menu, then select the code number (filename) from the displayed list.

8. Tutorials

This section provides step by step tutorials for various subsystems of the OncoLogic™ program in order that the user might become familiar with the basic approach for performing an evaluation. The samples include a polymer, a metal, a fiber, and an organic. The examples should be robust enough for the user to get a feel for how to perform an evaluation in any of the OncoLogic™ subsystems. If you are having difficulty with a particular subsystem, refer to the General Tips on page 14.

Each sample session begins with an “Information Summary”. The questions asked by OncoLogic™ can be answered by entering the information in the summary. Each sample evaluation will begin from the main menu of options.

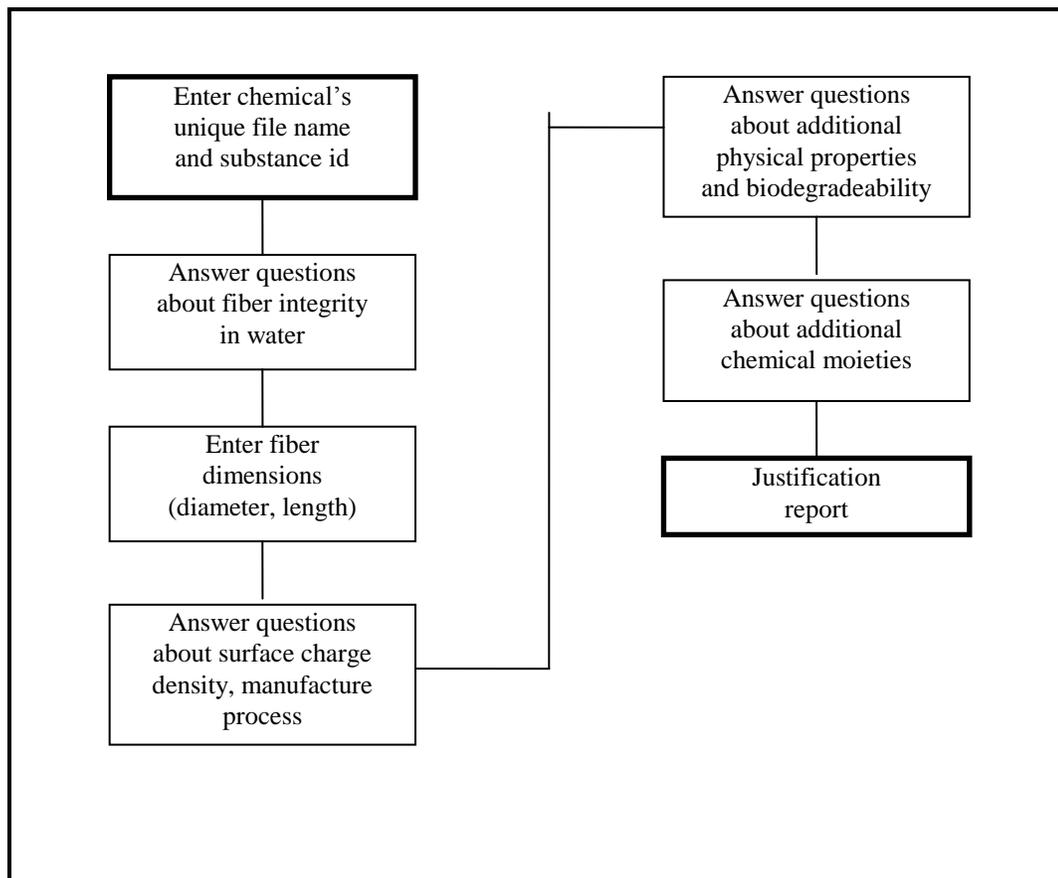
8.1 Fiber Sample

The following is a sample evaluation for a fiber.

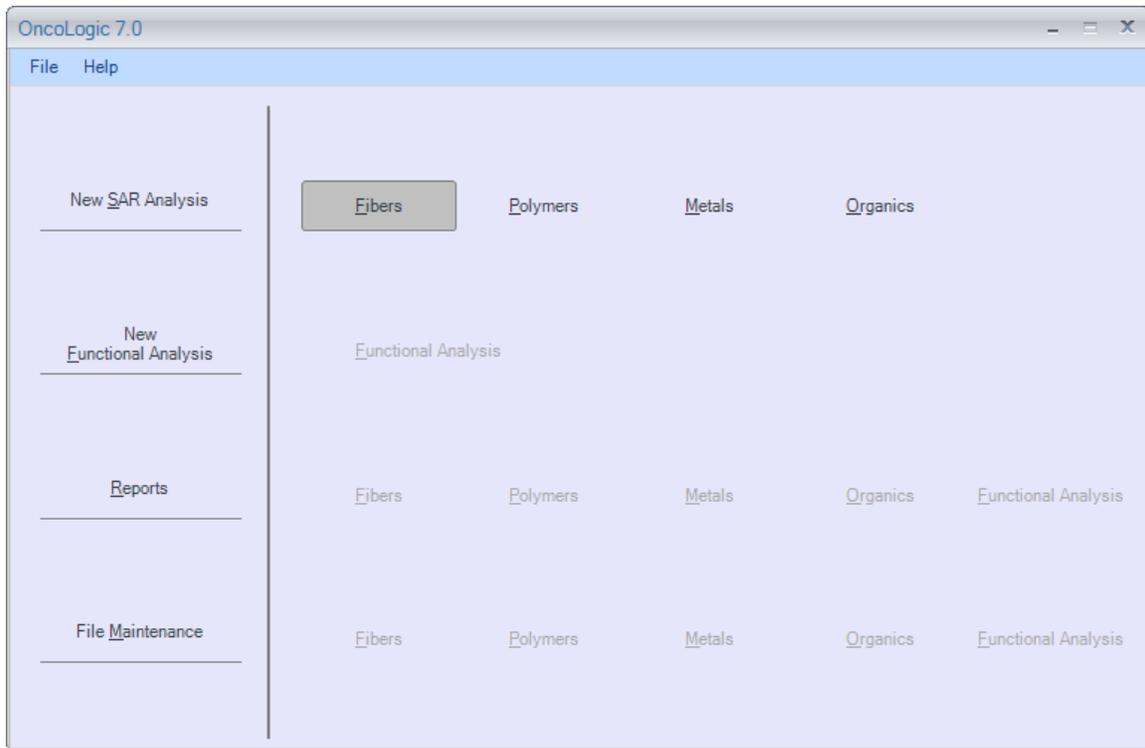
Information summary:

1. Filename: Fiber1
2. Fiber Identification: Kaolin Clay Fiber
3. Manufacturing Process: Melting kaolin clay at temperature of 1200 C and drawing the molten clay through orifices with a diameter of .22 um.
4. Physical Properties:
 - a) Diameter range: 0.22 microns
 - b) Length range: 5.5 microns
 - c) High durability

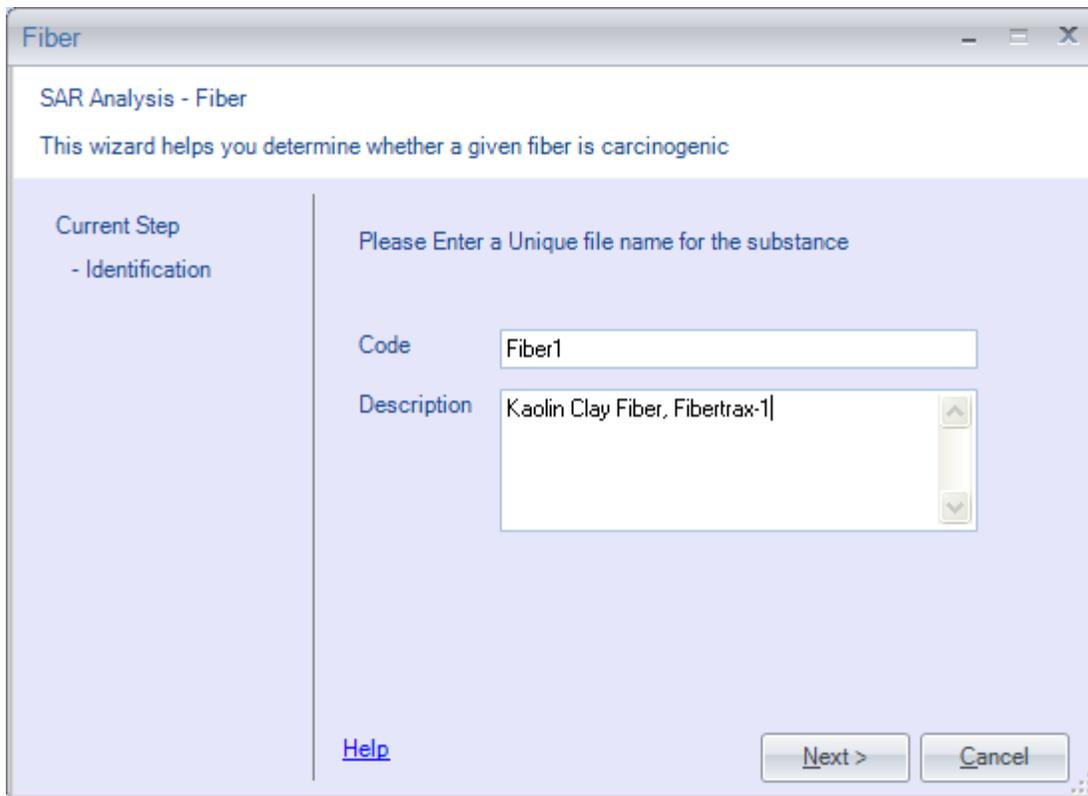
General Input Flow Diagram:



The screens that follow are provided to walk you through this sample evaluation. Each screen will be presented and the instructions for answering that screen will follow. Press the <F1> key for the help text on any screen. The first screen presented will be the OncoLogic™ main menu screen.



Select Fibers.



Enter code: Fiber1.

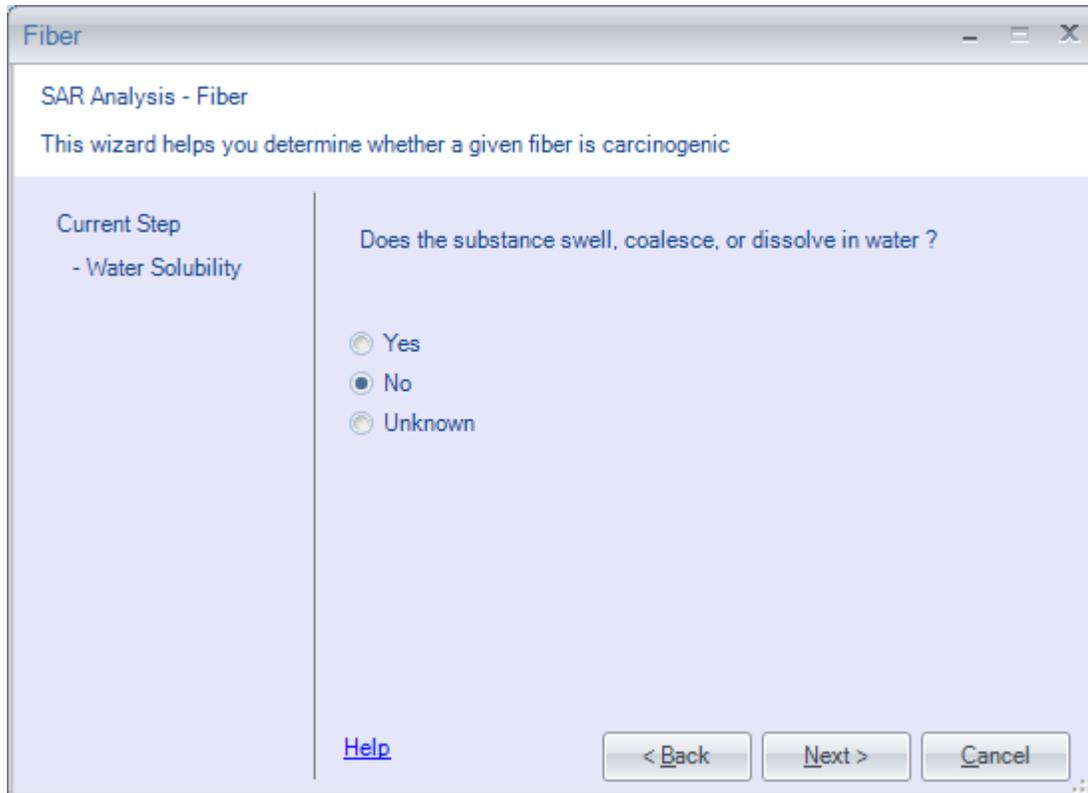
Enter Description: Kaolin Clay Fiber, Fibertrax 1

If a filename was used before, you will be asked to enter a different filename.

You may change what you have typed by using the <Backspace> key.

Press: <Next> when you are ready to continue.

You may enter any type of character for the substance identification. There is a limit of 240 letters, numbers, etc. that may be entered. Any more than 240 characters will not be accepted.



The screenshot shows a window titled "Fiber" with a subtitle "SAR Analysis - Fiber". Below the subtitle is the text "This wizard helps you determine whether a given fiber is carcinogenic". The main area is divided into two sections. On the left, under "Current Step", it says "- Water Solubility". On the right, the question is "Does the substance swell, coalesce, or dissolve in water?". There are three radio button options: "Yes", "No", and "Unknown". The "No" option is selected. At the bottom left is a "Help" link. At the bottom right are three buttons: "< Back", "Next >", and "Cancel".

Select: No, and press "Next"

Fiber

SAR Analysis - Fiber

This wizard helps you determine whether a given fiber is carcinogenic

Current Step
- Diameter

The diameter of the substance, if known, can be given as a single value or the range of values. Please select the appropriate option.

Single Value
 Range Of Values
 Unknown

Please enter the diameter of the substance in microns

0.22

[Help](#) < Back Next > Cancel

Select: Single Value

Enter 0.22 and **press** <Next>.

Fiber

SAR Analysis - Fiber

This wizard helps you determine whether a given fiber is carcinogenic

Current Step
- Length

The length of the substance, if known, can be given as a single value or the range of values. Please select the appropriate option.

Single Value
 Range Of Values
 Unknown

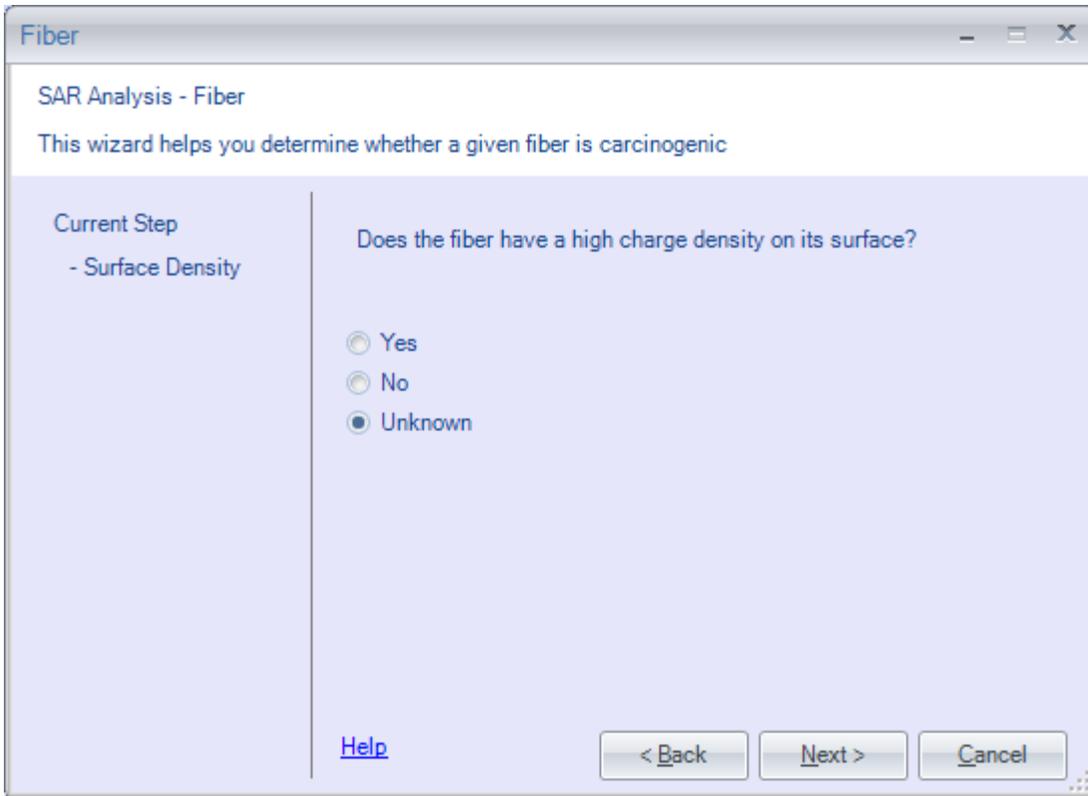
Please enter the length of the substance in microns

5.5

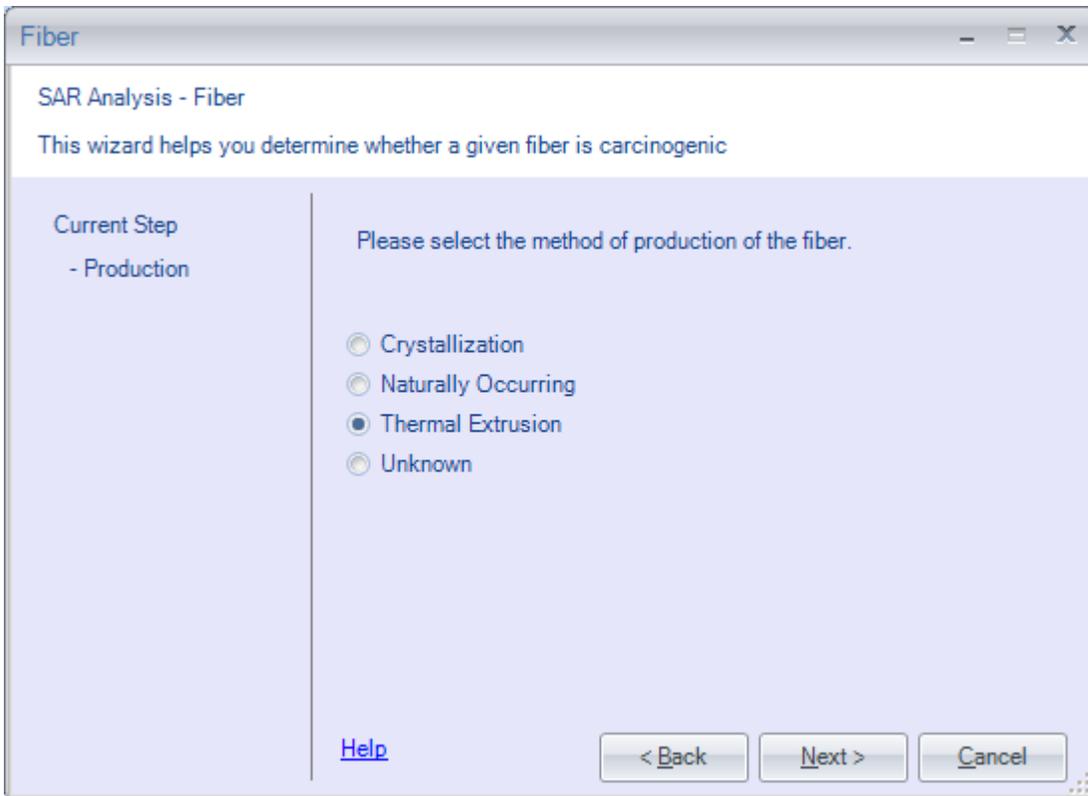
[Help](#) < Back Next > Cancel

Select: Single Value

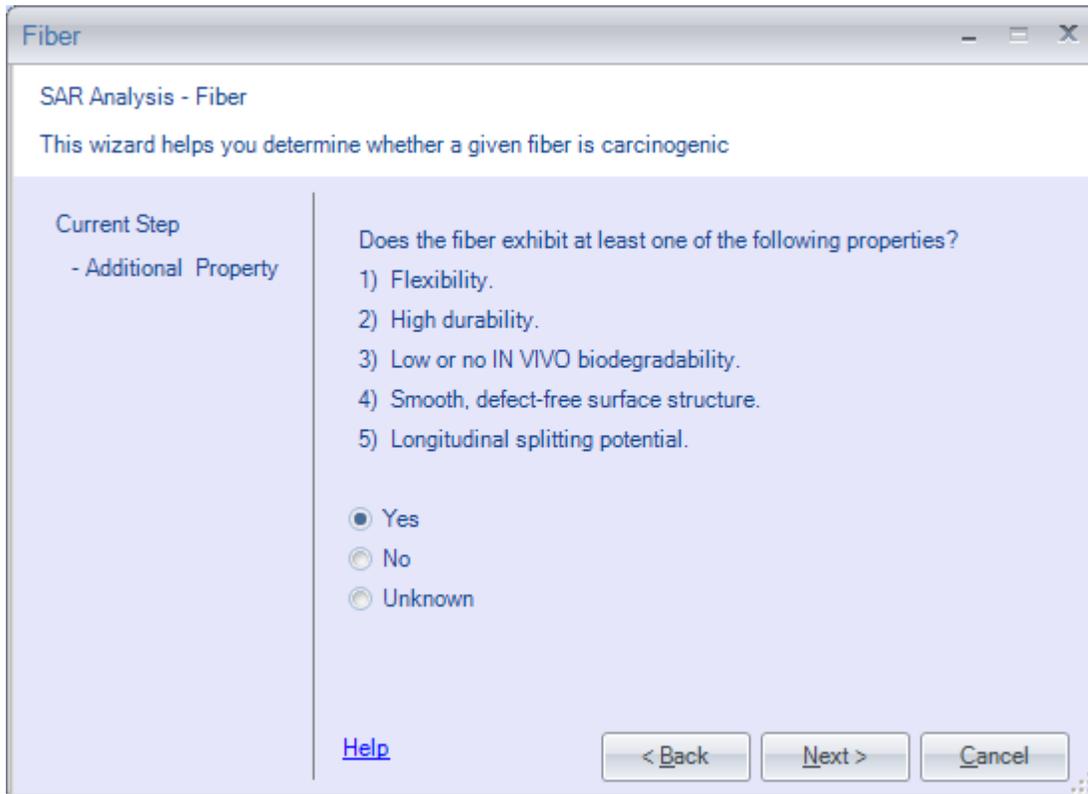
Enter 5.5 and **press** <Next>.



Since the given does not specify a charge density, **select** Unknown. , and press “Next”

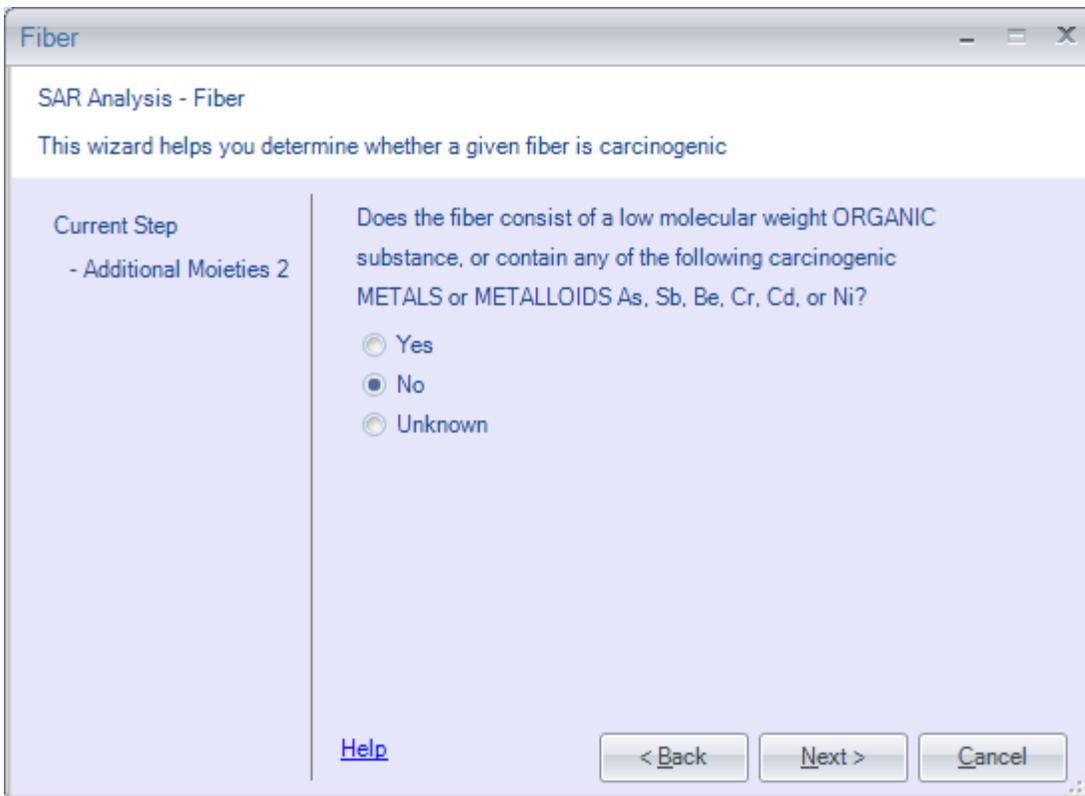


Select: Thermal Extrusion, and press “Next”



The screenshot shows a software window titled "Fiber" with a subtitle "SAR Analysis - Fiber". Below the subtitle, it states "This wizard helps you determine whether a given fiber is carcinogenic". The main content area is divided into two sections. On the left, under "Current Step", it says "- Additional Property". On the right, it asks "Does the fiber exhibit at least one of the following properties?" followed by a numbered list: 1) Flexibility, 2) High durability, 3) Low or no IN VIVO biodegradability, 4) Smooth, defect-free surface structure, and 5) Longitudinal splitting potential. Below the list are three radio button options: "Yes" (which is selected), "No", and "Unknown". At the bottom left is a "Help" link, and at the bottom right are three buttons: "< Back", "Next >", and "Cancel".

Select Yes, and press “Next”



The screenshot shows a window titled "Fiber" with a subtitle "SAR Analysis - Fiber". Below the subtitle is the text: "This wizard helps you determine whether a given fiber is carcinogenic". On the left side, under "Current Step", it says "- Additional Moieties 2". The main area contains the question: "Does the fiber consist of a low molecular weight ORGANIC substance, or contain any of the following carcinogenic METALS or METALLOIDS As, Sb, Be, Cr, Cd, or Ni?". There are three radio button options: "Yes", "No", and "Unknown". The "No" option is selected. At the bottom, there is a "Help" link and three buttons: "< Back", "Next >", and "Cancel".

Select No, and press “Next”

At this point, the evaluation will be complete, and the justification report displayed. Because the justification report is more than one page long, you will need to scroll down to read the entire report.

Justification Report	
OncoLogic Justification Report	
SUMMARY	:
Filename	: Fiber1
Substance ID	: Kaolin Clay Fiber, Fibertrax-1
Diameter Used	: 0.22 microns
Length Used	: 5.5 microns
Aspect Ratio	: 25 microns
The level of concern for carcinogenic potential of this fiber is MODERATE.	
JUSTIFICATION	
The unifying concept of fiber carcinogenesis is the Stanton Hypothesis. This hypothesis states that the dimensions of a fiber are the major criteria for establishing the concern for its carcinogenic potential.	
Since the diameter of the fiber is less than 0.25 microns, its length is less than or equal to 8 microns, and its aspect ratio is greater than 5, the initial level of concern for carcinogenic potential of this fiber is MODERATE.	
Fibers that are produced by extrusion, especially thermal/melting treatment, are assumed to have low charge density on their surface since these conditions do not allow time for orderly build-up of surface structure. This decreases the level of concern to LOW-MODERATE.	
The fiber exhibits one or more of the following properties: 1) Flexibility 2) Durability 3) Low or no IN VIVO biodegradability (Note: There is insufficient evidence the IN VITRO biodegradability	
<ESC> = Exit	

Justification Report

is a valid indicator for IN VIVO biodegradability.) 4) Smooth, defect-free surface 5) Longitudinal splitting potential These characteristics make minor modifications to the concern level and many are inter-related. Thus, regardless of the number of these characteristics the fiber exhibits, the level of concern is increased by only one step to MODERATE.

The final level of concern for the carcinogenic potential of this fiber is MODERATE.

<ESC> = Exit

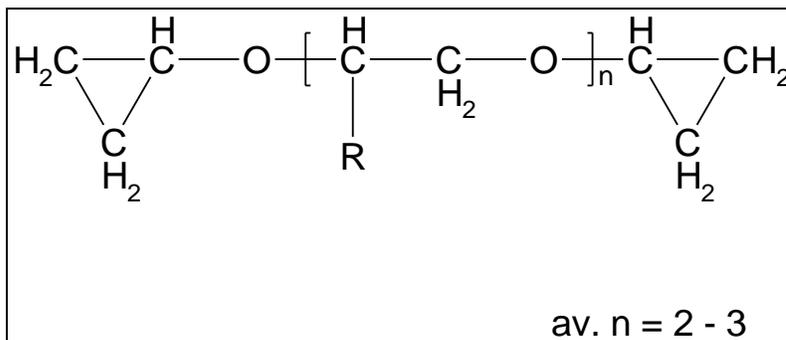
Press <Close> to return to main menu.

8.2 Polymer Sample

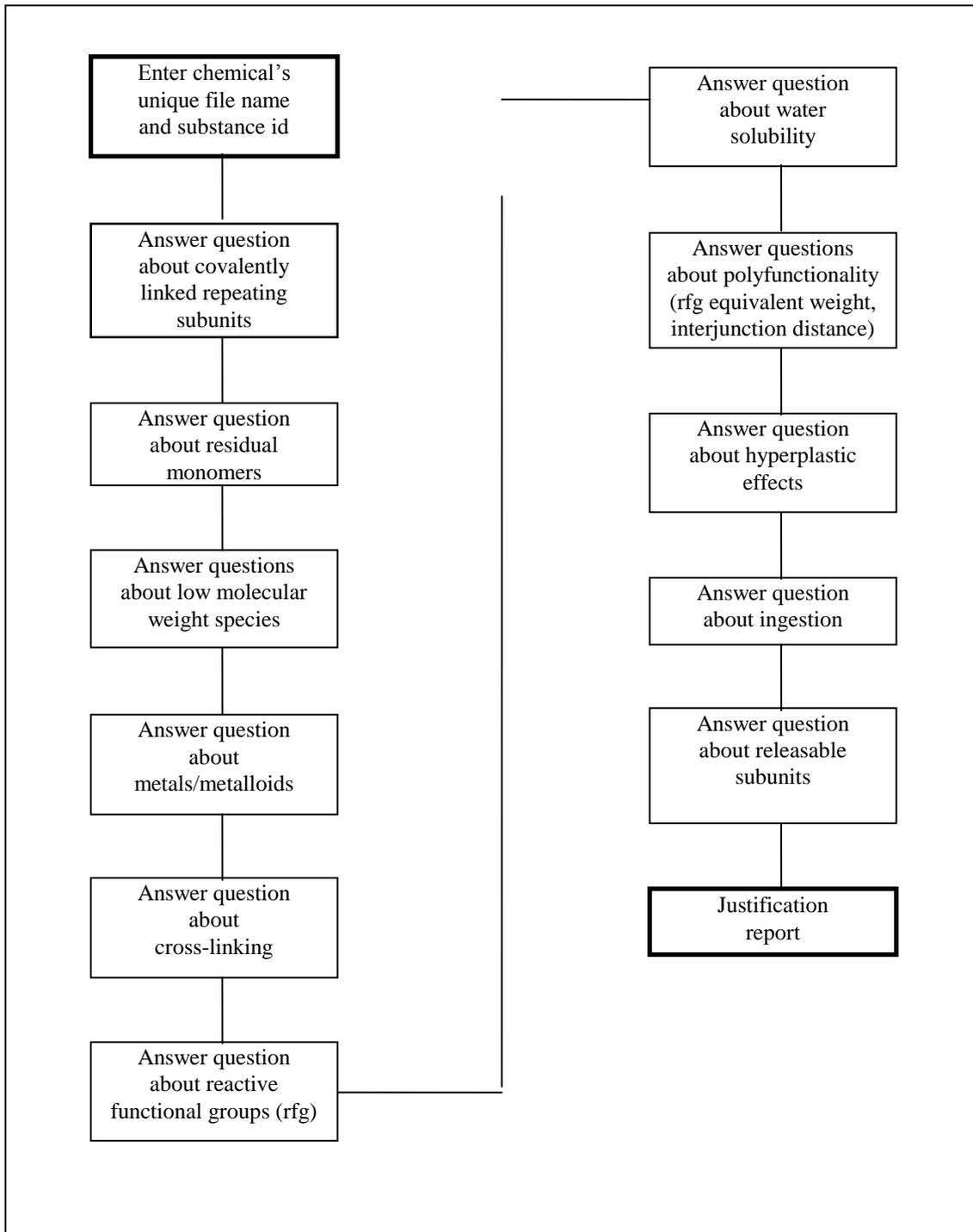
The following is a sample evaluation for a polymer.

Information summary:

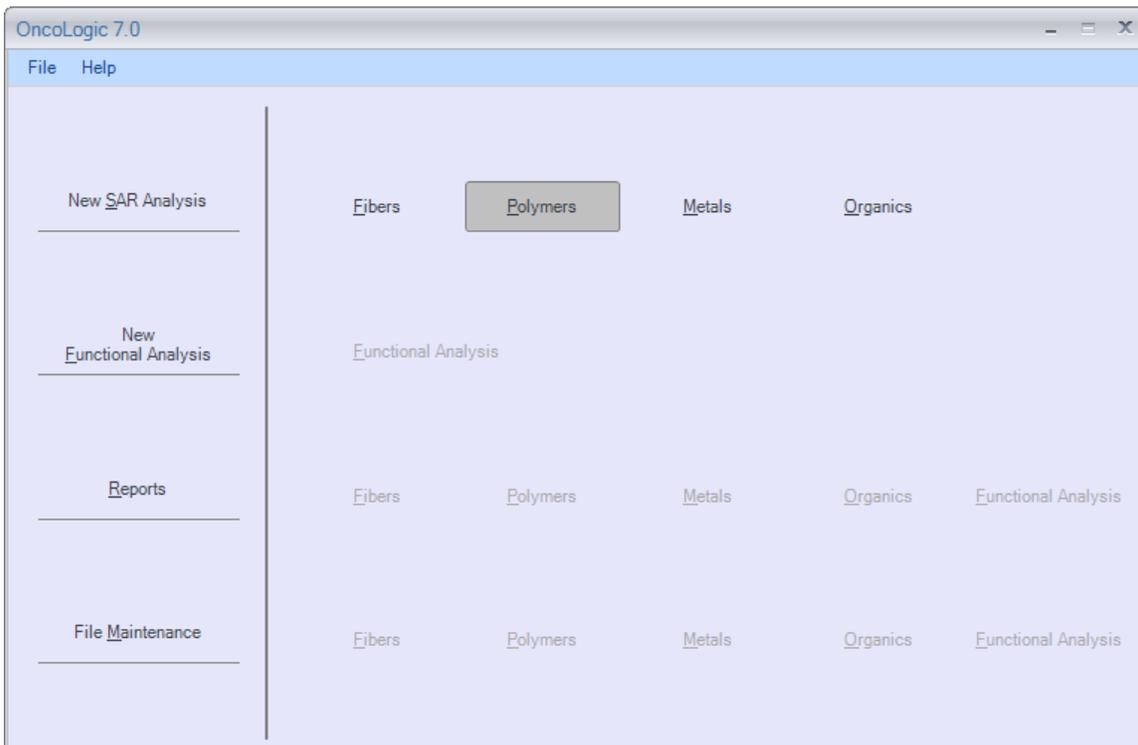
1. Filename: Polymer1
2. Polymer Identification: Polymer substance A
3. Physical State: liquid
4. Molecular Weight: 1,100 daltons
5. Residual Monomers: negligible
6. Low MW Species: 5% < 500 MW, 35% < 1000 MW
7. Metals: NA
8. Functional Group Equivalent Weight: 550
9. Solubility: .2%
10. Usage:
11. Exposure: Unspecified; may lead to oral exposure
12. Test Data: NA
13. Structure:



General Input Flow Diagram for polymer sample



The screens that follow are provided to walk you through this sample evaluation. Each screen will be presented and the instructions for answering that screen will follow. If at anytime you make a mistake but are at the next screen, simply press the <Esc> key /"Back" Button to return to the previous screen. Also, feel free to press the <F1> key for the help text on any screen. The first screen presented will be the OncoLogic™ main menu screen.



Select Polymers.

Polymer

SAR Analysis - Polymer

This wizard helps you determine whether a given polymer is carcinogenic

Current Step
- Identification

Please Enter a Unique file name for the substance

Code: Polymer1

Description: Polymer substance A

[Help](#)

Enter the filename: Polymer1.

If a filename was used before, you will be asked to enter a different filename.

Enter: Polymer substance A

Press: <Next> when you are ready to continue.

You may enter any type of character for the substance identification. There is a limit of 240 letters, numbers, etc. that may be entered. Any more than 240 characters will not be accepted.

The screenshot shows a window titled "Polymer" with a subtitle "SAR Analysis - Polymer". Below the subtitle is the text "This wizard helps you determine whether a given polymer is carcinogenic". On the left side, under "Current Step", it says "- Number screen". The main area contains the instruction "Please enter the number average molecular weight." and a text input field containing the value "1000". At the bottom, there is a "Help" link, a "< Back" button, a "Next >" button, and a "Cancel" button.

Enter the molecular weight: 1100.

Press: <Next>.

The screenshot shows the same "Polymer" window, now at a different step. The "Current Step" is "- Covalently link". The main area contains the question "Does the substance consist of covalently linked repeating subunits?". There are two radio button options: "Yes" (which is selected) and "No". At the bottom, there is a "Help" link, a "< Back" button, a "Next >" button, and a "Cancel" button.

Select: Yes, and press "Next".

The screenshot shows a window titled "Polymer" with a subtitle "SAR Analysis - Polymer". Below the subtitle is the text "This wizard helps you determine whether a given polymer is carcinogenic". On the left side, under "Current Step", it says "- Two percent". The main area contains the question "Does the polymer contain residual monomers exceeding 2 percent?". There are three radio button options: "Yes", "No", and "Unknown". The "No" option is selected. At the bottom, there is a "Help" link, a "< Back" button, a "Next >" button, and a "Cancel" button.

Select: No, and press “Next”

The screenshot shows the same "Polymer" window, now at a different step. The "Current Step" is "- Weight less than 500". The question is "Do more than 2 percent of the polymer molecules have a molecular weight less than 500?". The radio button options are "Yes", "No", and "Unknown". The "Yes" option is selected. The "Help" link and navigation buttons ("< Back", "Next >", "Cancel") are also present at the bottom.

Select: Yes, and press” Next”

Polymer

SAR Analysis - Polymer

This wizard helps you determine whether a given polymer is carcinogenic

Current Step
- RFG Species

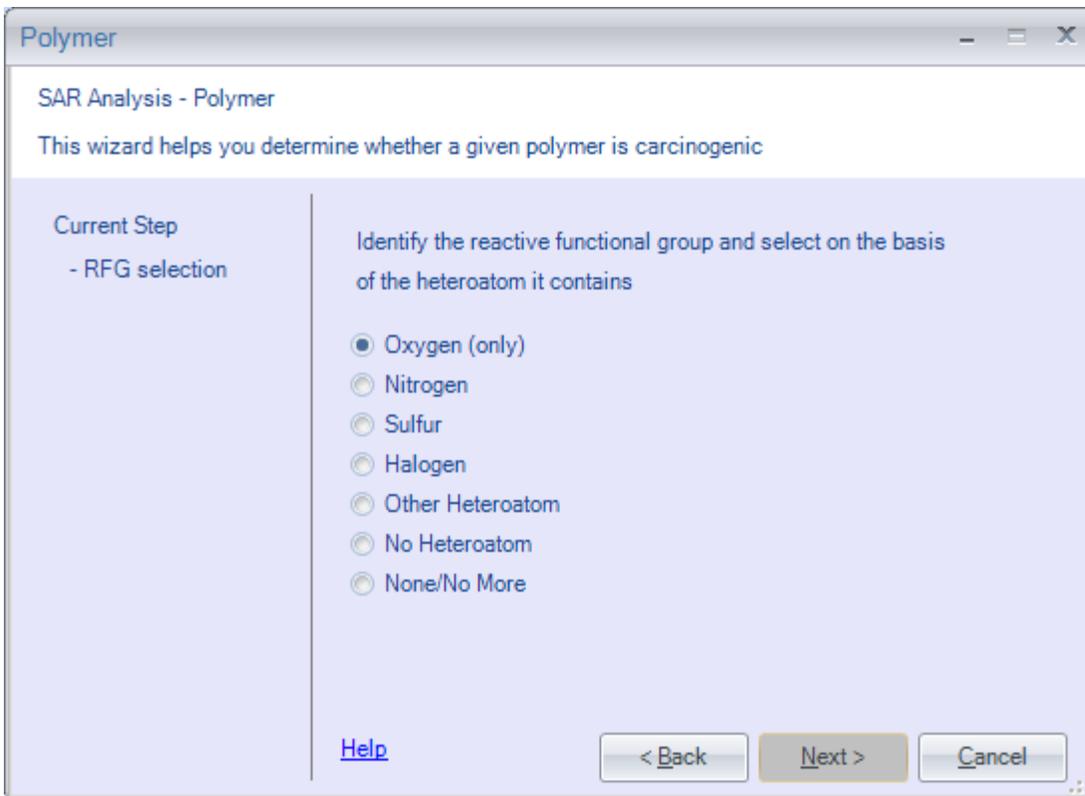
Does the low molecular weight species contain any reactive functional groups ?

Yes
 No
 Unknown

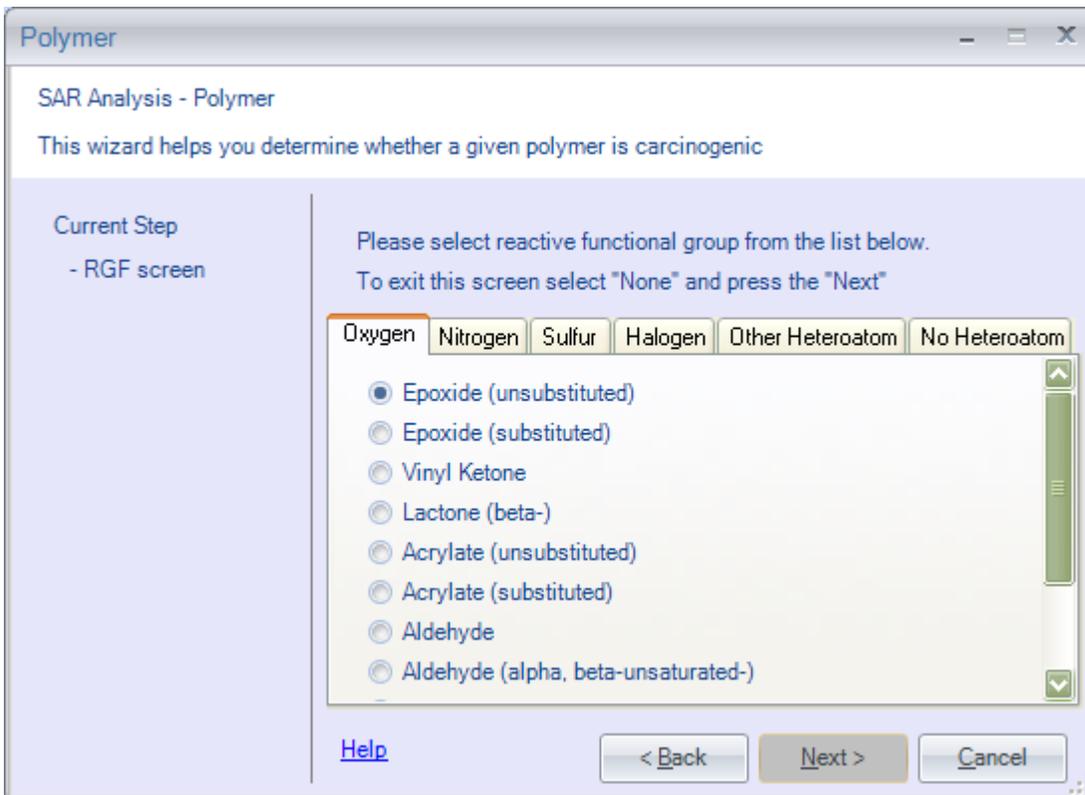
[Help](#)

< Back Next > Cancel

Select Yes, and press “Next”

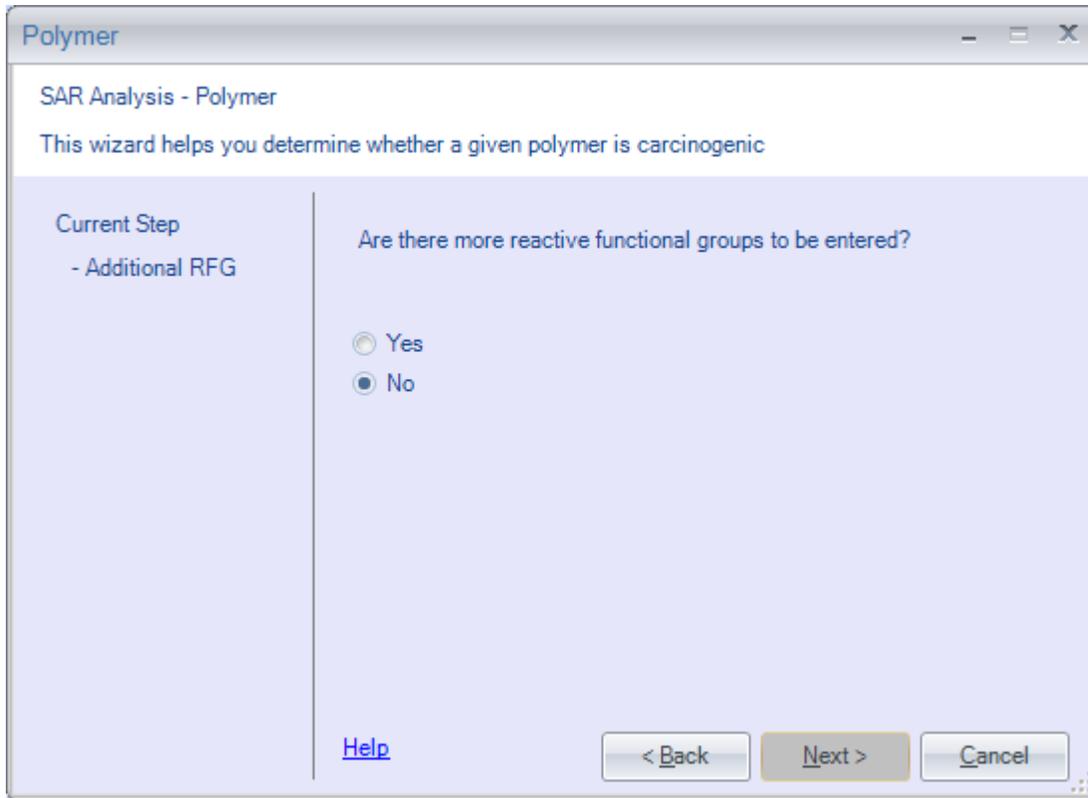


Select: Oxygen, and press Next



Select: Epoxide, and press “Next”

Note: On some of the RFG menus, it may be necessary to press the <Page Down> key in order to view all of the options.



The screenshot shows a software window titled "Polymer" with a subtitle "SAR Analysis - Polymer". Below the subtitle, it states "This wizard helps you determine whether a given polymer is carcinogenic". The window is divided into two main sections. On the left, under "Current Step", it says "- Additional RFG". On the right, the question "Are there more reactive functional groups to be entered?" is displayed. Below this question are two radio button options: "Yes" (which is unselected) and "No" (which is selected). At the bottom left of the window is a blue "Help" link. At the bottom right are three buttons: "< Back", "Next >" (which is highlighted in a darker grey), and "Cancel".

Select: No, and press “Next”

Polymer

SAR Analysis - Polymer

This wizard helps you determine whether a given polymer is carcinogenic

Current Step
- Metals

If the polymer contains one or more of the following metals/metalloids, select the one that appears first in the list; otherwise, select "Next"

- None
- Beryllium (Be)
- Cadmium (Cd)
- Chromium (Cr)
- Nickel (Ni)
- Arsenic (As)
- Antimony (Sb)

[Help](#)

< Back Next > Cancel

Select: None, and press "Next"

Polymer

SAR Analysis - Polymer

This wizard helps you determine whether a given polymer is carcinogenic

Current Step
- Cross linked

Is the polymer cross-linked?

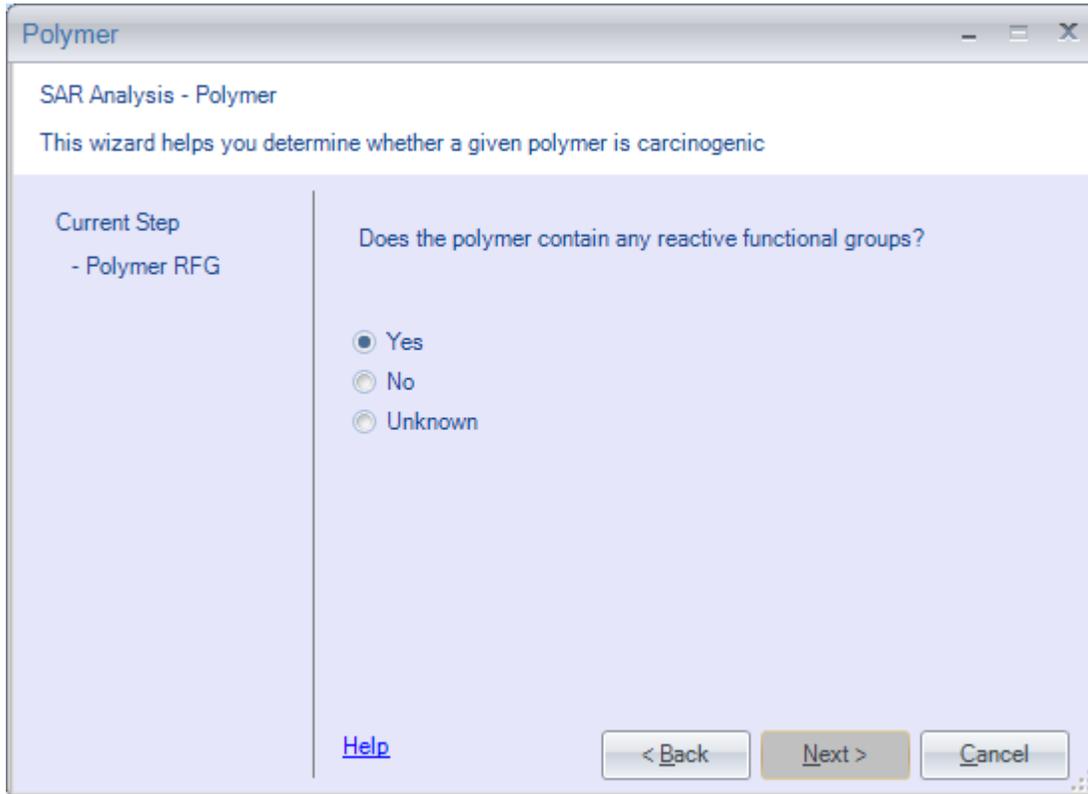
- Yes
- No
- Unknown

[Help](#)

< Back Next > Cancel

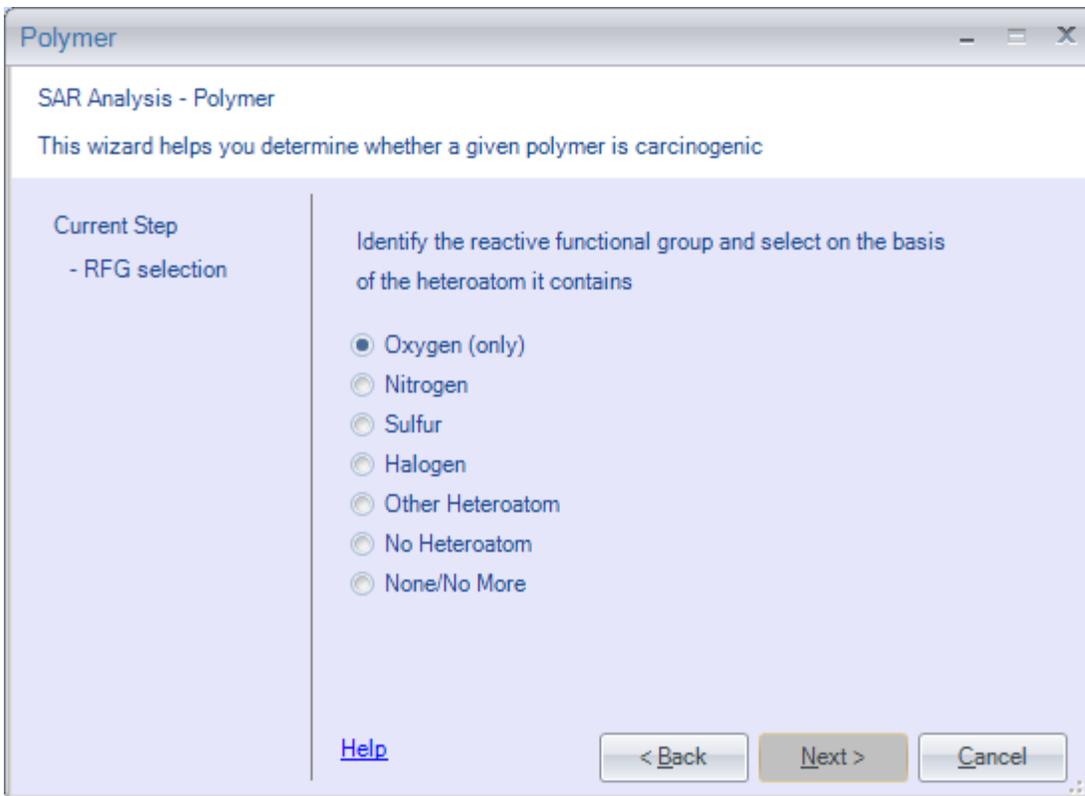
Select: No, and press "Next"

Note: Usually crosslinking can be determined by examining the structure of the polymer.

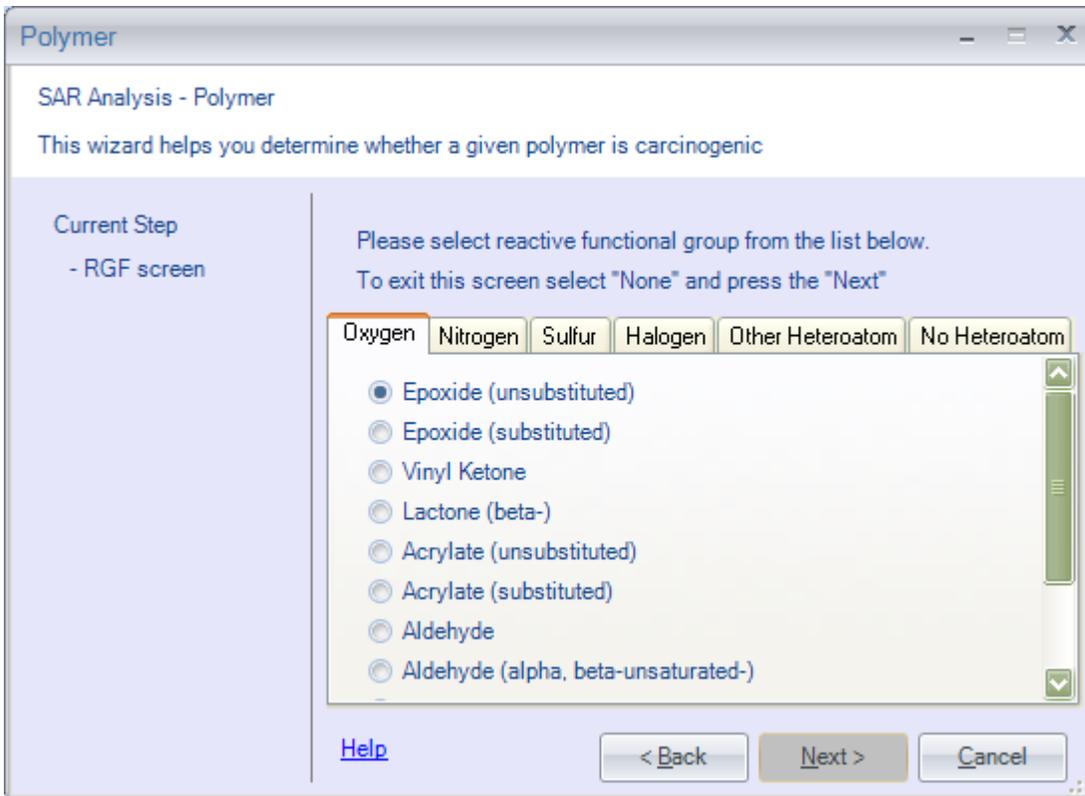


The screenshot shows a software window titled "Polymer" with a subtitle "SAR Analysis - Polymer". The main text reads "This wizard helps you determine whether a given polymer is carcinogenic". On the left, a sidebar indicates the "Current Step" is "- Polymer RFG". The main area contains the question "Does the polymer contain any reactive functional groups?" with three radio button options: "Yes" (selected), "No", and "Unknown". At the bottom, there is a "Help" link and three buttons: "< Back", "Next >" (highlighted), and "Cancel".

Select: Yes, and press "Next"



Select: Oxygen, and press “Next”



Select: Epoxide, and press “Next”

The screenshot shows a software window titled "Polymer" with a subtitle "SAR Analysis - Polymer". Below the subtitle, it states "This wizard helps you determine whether a given polymer is carcinogenic". The window is divided into two main sections. On the left, a vertical sidebar indicates the "Current Step" as "- Additional RFG". The main area of the window contains the question "Are there more reactive functional groups to be entered?". Below this question are two radio button options: "Yes" (which is unselected) and "No" (which is selected). At the bottom of the window, there are three buttons: "< Back", "Next >", and "Cancel". A blue "Help" link is also visible in the bottom left corner of the main area.

Select: No, and press “Next”

Polymer

SAR Analysis - Polymer

This wizard helps you determine whether a given polymer is carcinogenic

Current Step
- Water solubility

Enter the water solubility of the polymer as weight percent. If water solubility is given in ppm, convert to percent by dividing the number by 10,000. If the weight percent is unknown, enter 0.

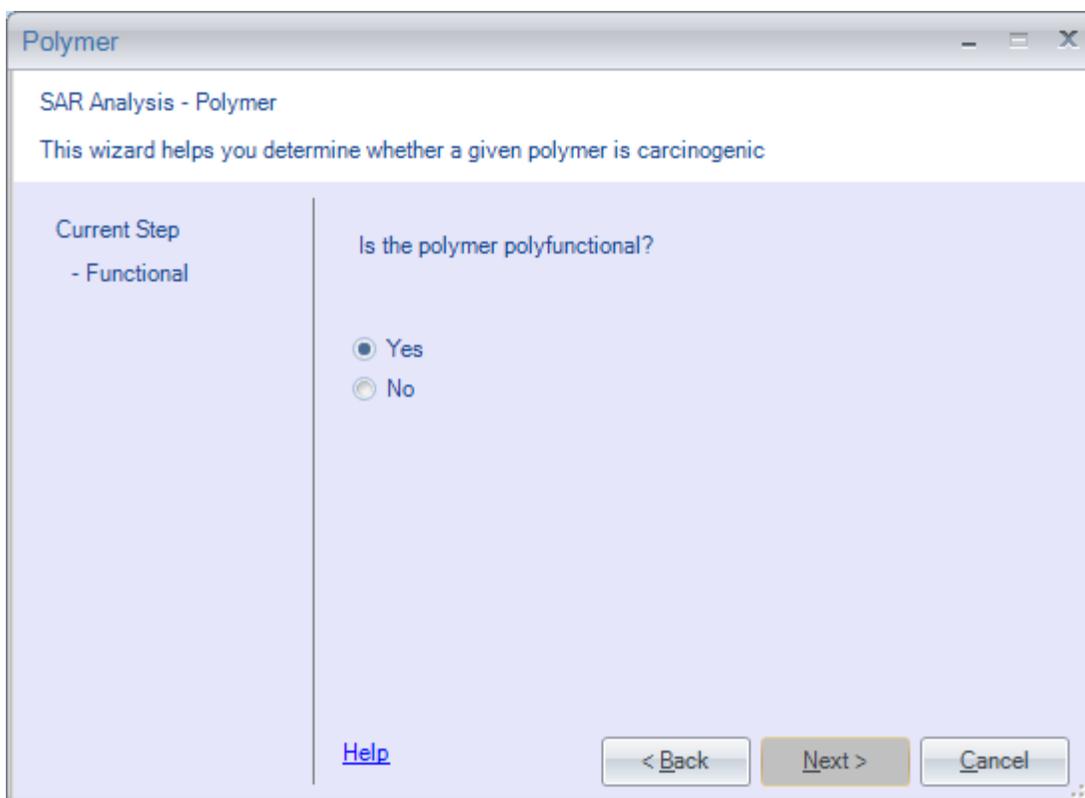
0.2

[Help](#)

< Back Next > Cancel

Enter: 0.2

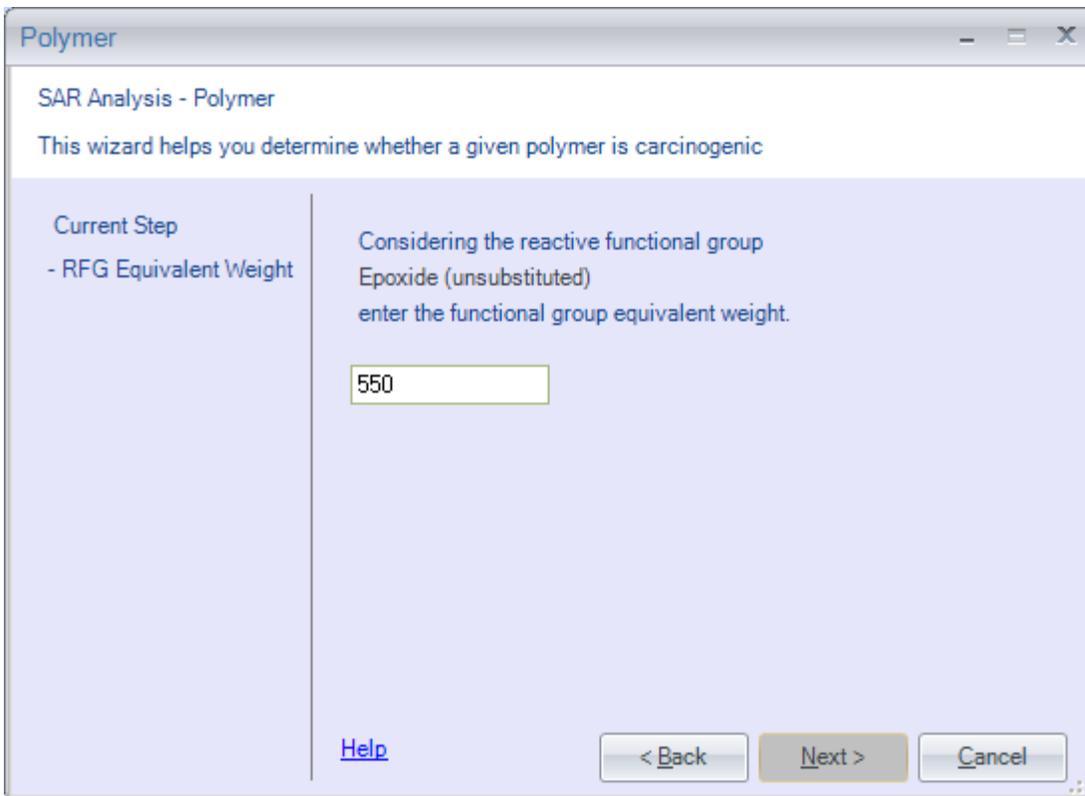
Press: <Next>



The screenshot shows a software window titled "Polymer" with a subtitle "SAR Analysis - Polymer". Below the subtitle, it states "This wizard helps you determine whether a given polymer is carcinogenic". The window is divided into two main sections. On the left, a vertical sidebar indicates the "Current Step - Functional". The main area on the right asks the question "Is the polymer polyfunctional?". There are two radio button options: "Yes" (which is selected) and "No". At the bottom of the window, there is a blue "Help" link, and three buttons: "< Back", "Next >" (highlighted in a darker color), and "Cancel".

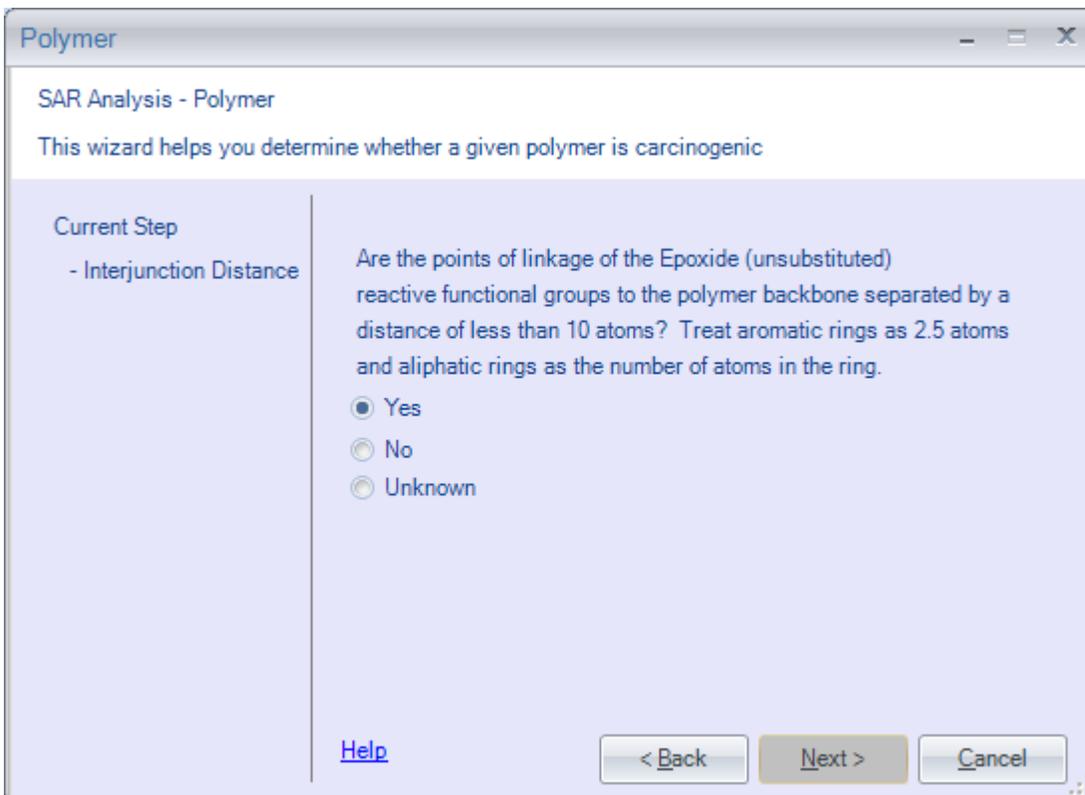
Select: Yes, and press "Next"

Note: Refer to the structure to determine if the reactive functional group occurs more than once in the polymer.



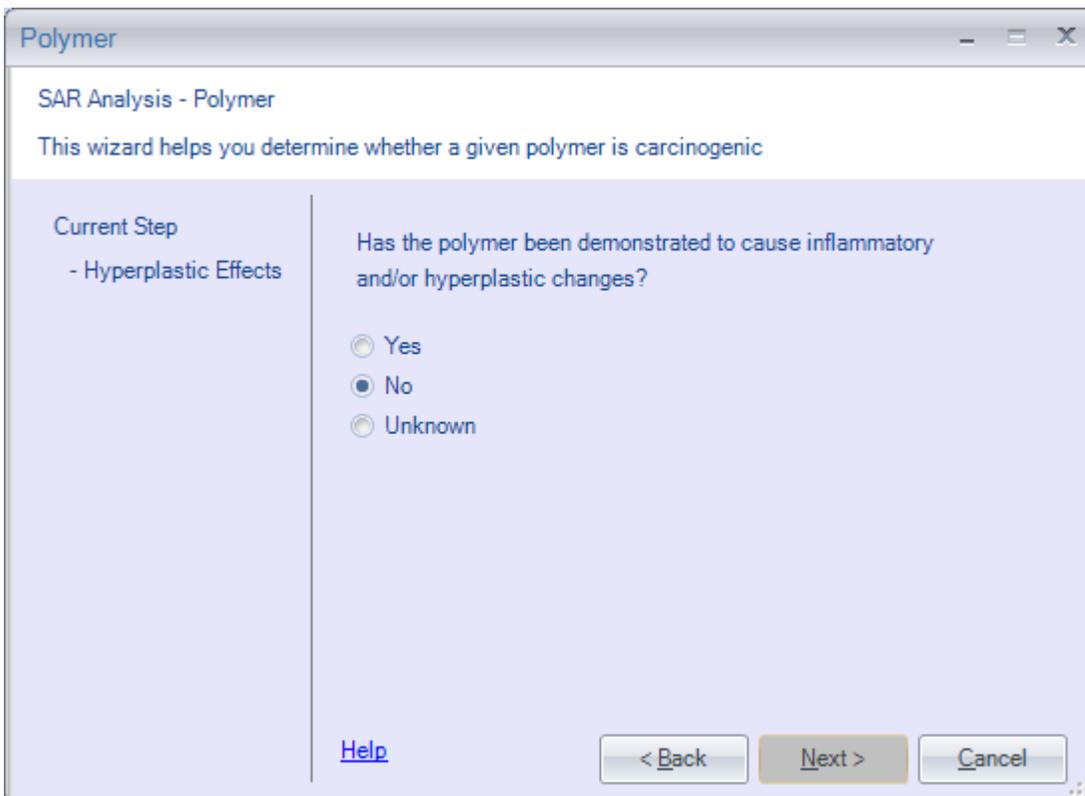
Enter: 550

Press: <Next>



Because the size of the polymer backbone is given as a range, we will use the average distance between the reactive functional groups. So, for $n = 2$, we get 7 atoms, and when for $n = 3$, we get 10 atoms. Averaging, we have 8.5 atoms. So, we will answer yes to the current question.

Select: Yes, , and press “Next”



Polymer

SAR Analysis - Polymer

This wizard helps you determine whether a given polymer is carcinogenic

Current Step
- Hyperplastic Effects

Has the polymer been demonstrated to cause inflammatory and/or hyperplastic changes?

Yes
 No
 Unknown

[Help](#)

< Back Next > Cancel

Select: No, and press “Next”

The screenshot shows a window titled "Polymer" with a subtitle "SAR Analysis - Polymer". Below the subtitle is the text "This wizard helps you determine whether a given polymer is carcinogenic". The window is divided into two main sections. On the left, under "Current Step", it says "- Absorption Potential". On the right, the question is "Does the polymer have a demonstrated ability to be absorbed and to accumulate in soft tissue?". There are three radio button options: "Yes", "No", and "Unknown". The "Unknown" option is selected. At the bottom left is a "Help" link. At the bottom right are three buttons: "< Back", "Next >", and "Cancel".

Select: Unknown, and press “Next”

The screenshot shows the same "Polymer" window, now at the second step. The "Current Step" is "- Ingestion". The question is "Is the polymer likely to be ingested?". There are two radio button options: "Yes" and "No". The "Yes" option is selected. The "Help" link and navigation buttons ("< Back", "Next >", "Cancel") are in the same positions as in the previous screenshot.

Select: Yes, and press “Next”

The screenshot shows a window titled "Polymer" with a subtitle "SAR Analysis - Polymer". Below the subtitle is the text "This wizard helps you determine whether a given polymer is carcinogenic". The window is divided into two main sections. On the left, under "Current Step", it says "- Internal Releasable Subunits". On the right, the question is "Does the polymer contain any internal releasable subunits?". There are three radio button options: "Yes", "No", and "Unknown". The "No" option is selected. At the bottom left is a "Help" link. At the bottom right are three buttons: "< Back", "Next >", and "Cancel".

Select: No, and press “Next”

The screenshot shows the same "Polymer" window, now at the second step. The "Current Step" is "- Terminal/Pendant Releasable Subunits". The question is "Does the polymer contain any terminal and/or pendant releasable subunits?". The "No" option is selected. The "Help" link and navigation buttons ("< Back", "Next >", "Cancel") are also present at the bottom.

Select: No, and press “Next”

At this point, the evaluation will be complete, and the justification report displayed. Because the justification report is more than one page long, you will need to scroll down to read the entire report. This can be accomplished in two ways. You may press the <Page Down> key or you can use the mouse and move the pointer to the right hand side of the window and click on the arrows to scroll the text. The screens that follow will contain the justification report a page at a time as if someone was using the <Page Down> key to scroll.

Justification Report	
OncoLogic Justification Report	
SUMMARY	:
Filename	: Polymer1
Substance ID	: Polymer substance A
The final level of carcinogenicity concern for this polymer is LOW-MODERATE.	
Based on the reactive functional group Epoxide (unsubstituted), the level of concern for the low molecular weight species is LOW-MODERATE.	
CAUTIONARY NOTES: 1. Plasticizers and other additives, if present, should be evaluated separately in the Organics Subsystem. 2. Counterions of polymers with ionic backbones should be evaluated separately.	
JUSTIFICATION:	
Because the substance consists of covalently linked repeating units and has a molecular weight greater than or equal to 1000, the substance is classified as a high molecular weight polymer.	
Since the polymer contains less than 2% residual monomer(s), the carcinogenicity concern for any residual monomers is LOW.	
The polymer contains low molecular weight species (>2% below 500), with a reactive-functional-group-bearing sidechain. The level of carcinogenicity concern for the low molecular weight species is based on the reactive functional group: Epoxide (unsubstituted). The level of carcinogenicity concern for the low molecular weight species is LOW-MODERATE.	
The polymer is not cross-linked.	

Justification Report

Since the percent water solubility is greater than or equal to 0.1%, the polymer is considered to be soluble in water.

The reactive functional group (RFG) which was used during the evaluation of the polymer is: Epoxide (unsubstituted).

This water soluble polymer is polyfunctional. Based on the expert-assigned inherent carcinogenic potential of the RFG(s) that you have entered and the entered information on the functional group equivalent weight of 550 daltons, which is low enough to cause concern, and the interjunction distance of less than ten atoms, which is within the favorable distance for potential cross-linking, the RFG which is retained for the evaluation of the polymer is: Epoxide (unsubstituted). Since the polymer has been demonstrated not to cause (or is not known to have caused) inflammatory and/or hyperplastic changes, carcinogenicity concerns arising from these pathophysiological changes can be eliminated. The RFG which is contained in this polymer is known to be stable in solution or as an emulsion in water. The current level of carcinogenicity concern based on the RFG is retained.

The water soluble polymer has a molecular weight less than or equal to 2500. The polymer contains reactive-functional-group-bearing sidechains but has not (or is not known to have) demonstrated an ability to be absorbed and to accumulate in soft tissue. Therefore, the level of carcinogenicity concern for this polymer is LOW-MODERATE.

The final concern for this polymer is LOW-MODERATE.

Press: <Close>. This will return you to the main menu.

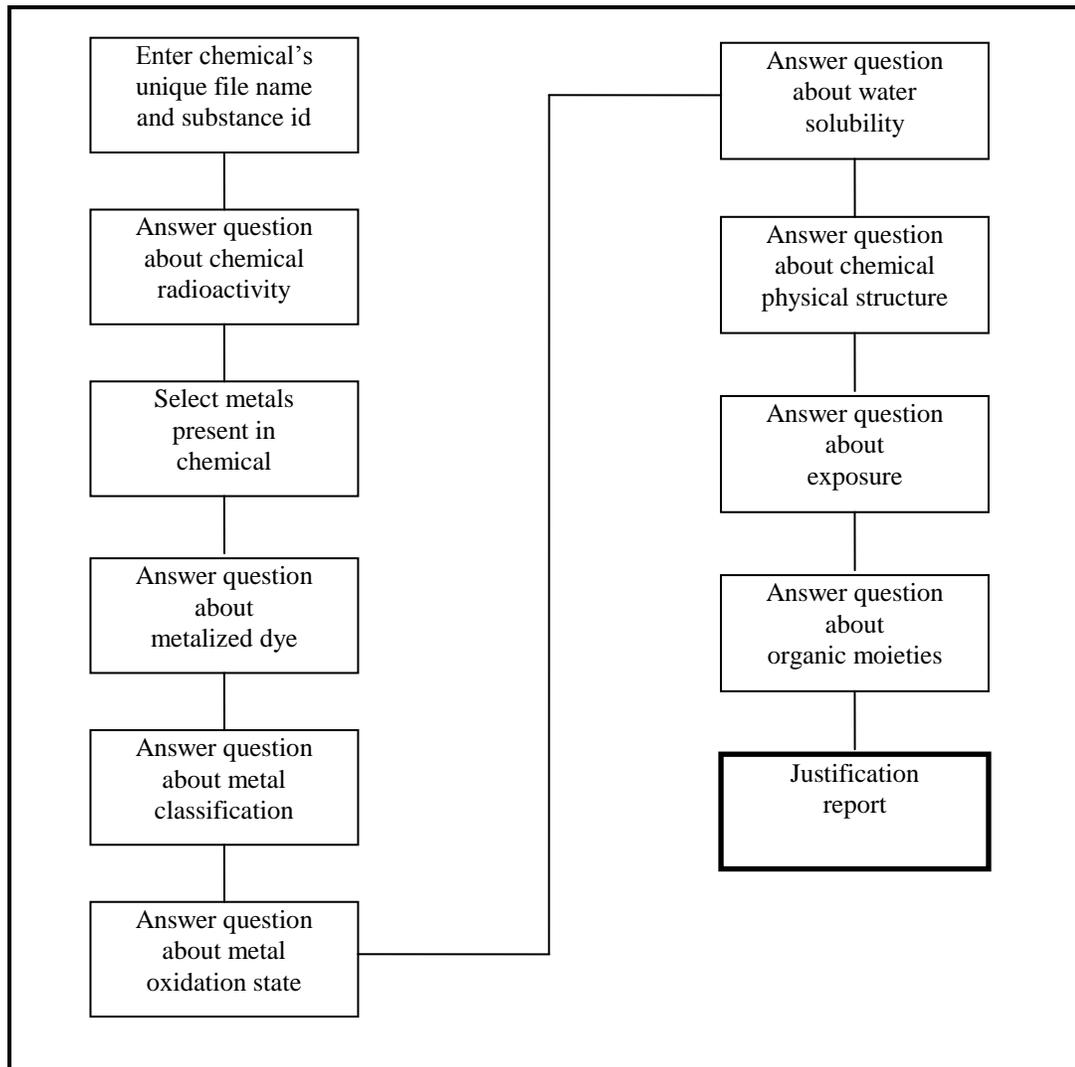
8.3 Metal Sample

The following is a sample evaluation for a metal.

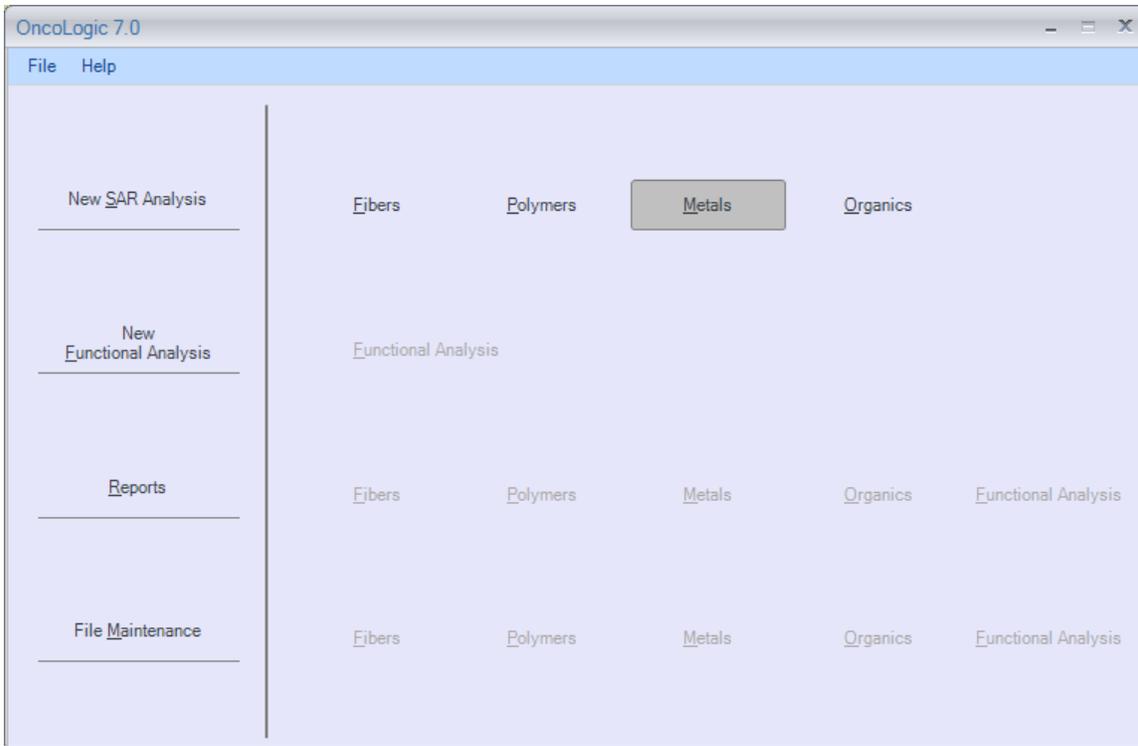
Information summary:

1. Filename: Metal1
2. Metal Identification: Metal Substance #1
3. $ZrCrO_4 \cdot 6H_2O$
4. M.W.: 402
5. Physical state: white crystal
6. Crystal structure: rhomboid
7. Solubility: sparingly soluble
8. Usage: to be incorporated into abrasive sanding paper
9. Test Data: NA

General Input Flow Diagram for metal compound:



The screens that follow are provided to walk you through this sample evaluation. Each screen will be presented and the instructions for answering that screen will follow. Feel free to press the <F1> key for the help text on any screen. The first screen presented will be the OncoLogic™ main menu screen.



Select: Metals

Metal

SAR Analysis - Metal

This wizard helps you determine whether a given metal is carcinogenic

Current Step
- Identification

Please Enter a Unique file name for the substance

Code: Metal1

Description: Metal substance #1

[Help](#)

Enter the filename: Metal1.

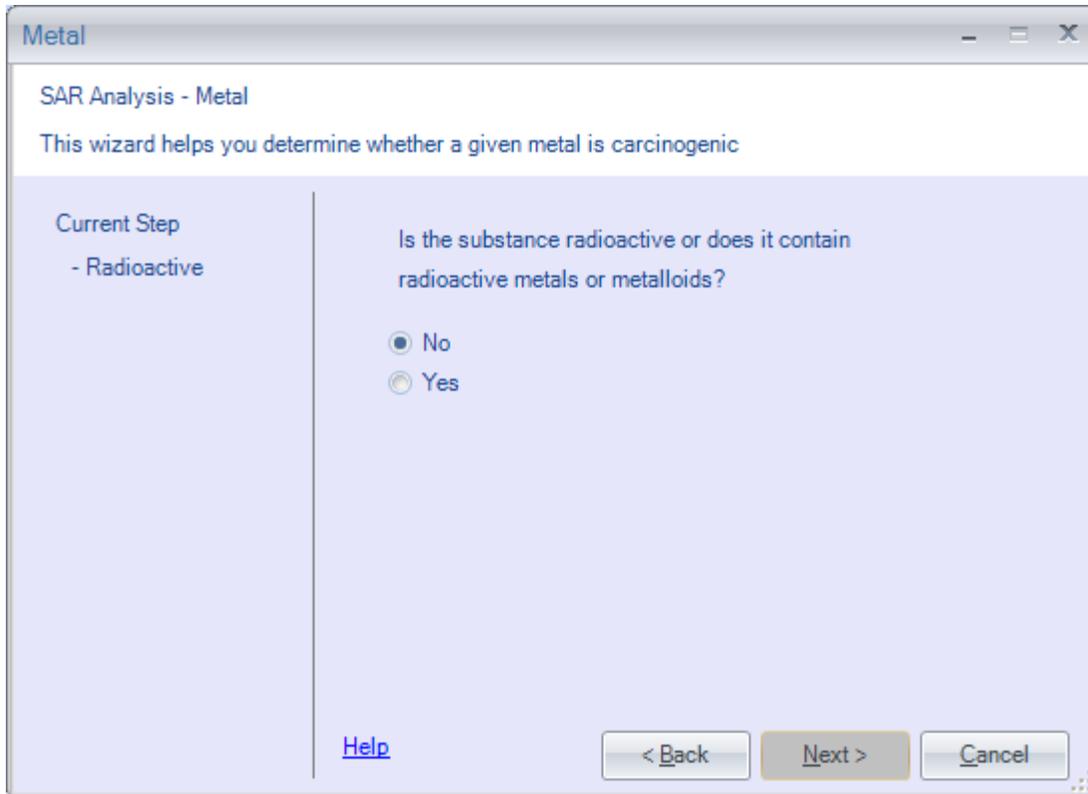
If a filename was used before, you will be asked to enter a different filename.

Enter: Metal substance #1

You may change what you have typed by using the <Backspace> key.

Press: <Next> when you are ready to continue.

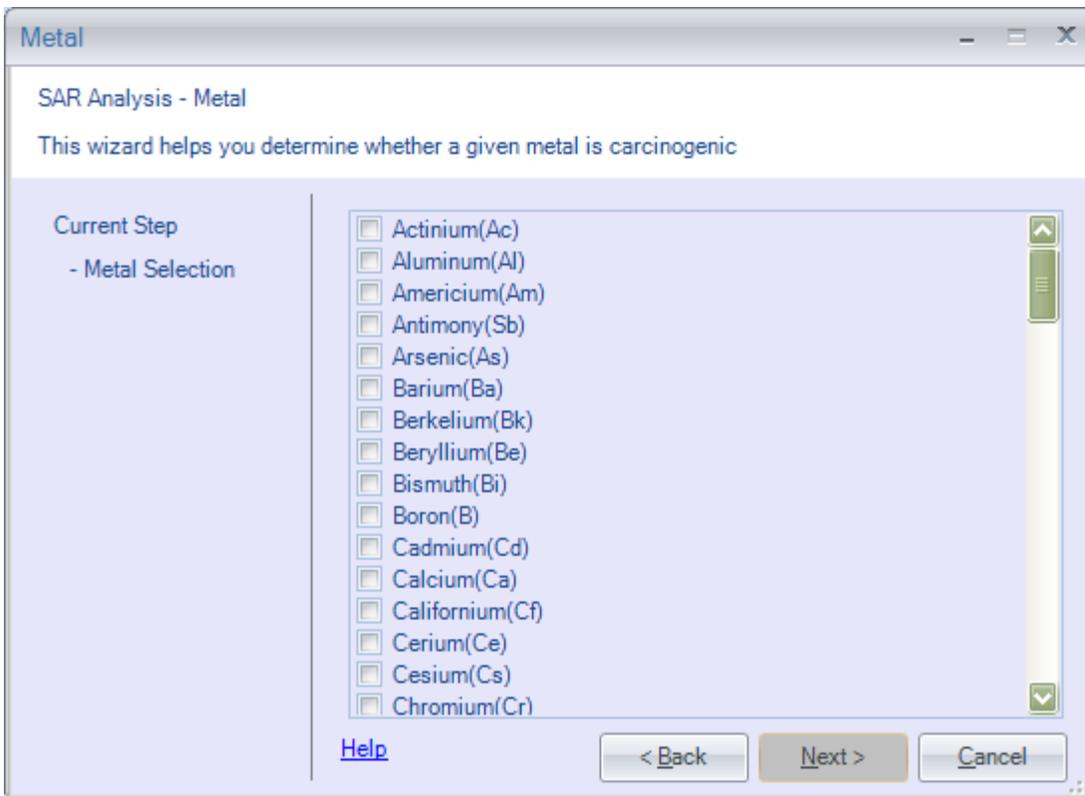
You may enter any type of character for the substance identification. There is a limit of 240 letters, numbers, etc. that may be entered. Any more than 240 characters will not be accepted.



The screenshot shows a software window titled "Metal" with a subtitle "SAR Analysis - Metal". Below the subtitle, it reads "This wizard helps you determine whether a given metal is carcinogenic". The window is divided into two main sections. On the left, under "Current Step", it says "- Radioactive". The main area contains the question "Is the substance radioactive or does it contain radioactive metals or metalloids?". There are two radio button options: "No" (which is selected) and "Yes". At the bottom of the window, there is a "Help" link, and three buttons: "< Back", "Next >", and "Cancel".

Select: No.

If you had answered Yes, the evaluation would have end. The metals subsystem is not designed to evaluate radioactive substances.



Select Chromium and Zirconium and press “Next”

Metals which do not appear in the initial window screen can be viewed by scrolling down. To scroll down either press the <Page Down> key or use the mouse to click the arrows on the right hand side of the screen. Another way to quickly move near a desired metal is to press the first letter of the metal name. The highlighted box will then move to the first metal containing the pressed letter. Continuing to press the first letter will cause the highlight bar to advance through the metals beginning with that letter.

The screenshot shows a window titled "Metal" with a subtitle "SAR Analysis - Metal". Below the subtitle is the text: "This wizard helps you determine whether a given metal is carcinogenic". On the left side, under "Current Step", it says "- Metallized dye". The main area contains the question: "Is the substance in the form of a metallized dye or pigment?". There are two radio button options: "Yes" (unselected) and "No" (selected). At the bottom, there is a "Help" link, and three buttons: "< Back", "Next >" (highlighted), and "Cancel".

Select: No

The screenshot shows the same "Metal" window, now at a different step. The subtitle is "SAR Analysis - Metal" and the text is "This wizard helps you determine whether a given metal is carcinogenic". The "Current Step" on the left is "- Metal substance classification". The main area contains the question: "Classify the type of metal-containing substance.". There are four radio button options: "Metal dust", "Carbonyl-type compound", "Complex or Coordination compound", and "Inorganic or Other Organic compound" (selected). At the bottom, there is a "Help" link, and three buttons: "< Back", "Next >" (highlighted), and "Cancel".

Select: Inorganic or Other compound.

Since the compound being evaluated does not fall into the first three categories, the fourth category, Inorganic/Other, is selected.

Metal

SAR Analysis - Metal

This wizard helps you determine whether a given metal is carcinogenic

Current Step
- Chromium oxidation state

Select the oxidation state of the Chromium.

Divalent
 Trivalent
 Hexavalent

[Help](#)

< Back Next > Cancel

Select: Hexavalent.

The screenshot shows a window titled "Metal" with a subtitle "SAR Analysis - Metal". Below the subtitle is the text "This wizard helps you determine whether a given metal is carcinogenic". The window is divided into two main sections. On the left, under "Current Step", it says "- Water solubility". On the right, the instruction is "Select the water solubility of the substance." Below this instruction are four radio button options: "Soluble", "Sparingly Soluble" (which is selected), "Insoluble", and "Unknown". At the bottom left is a blue "Help" link. At the bottom right are three buttons: "< Back", "Next >" (highlighted), and "Cancel".

Select: Sparingly.

The screenshot shows the same "Metal" window, now at the second step. The "Current Step" section on the left now says "- Physical structure". The instruction on the right is "Indicate the presence or absence of a crystal lattice structure in the substance." Below this are three radio button options: "Crystalline" (which is selected), "Amorphous", and "Unknown". The "Help" link and navigation buttons ("< Back", "Next >", "Cancel") are in the same positions as in the previous screenshot.

Select: Crystalline.

Metal

SAR Analysis - Metal

This wizard helps you determine whether a given metal is carcinogenic

Current Step
- Anticipated routes of exposure

Please identify the expected routes of exposure of this compound from the list below. Select the appropriate route(s)
When the appropriate routes have been selected, press "Next"

Inhalation
 Injection
 Oral
 Dermal

[Help](#) < Back Next > Cancel

Select Inhalation and Dermal

Press <Next>.

Metal

SAR Analysis - Metal

This wizard helps you determine whether a given metal is carcinogenic

Current Step
- Organic moiety

Is the substance expected to release an organic moiety under physiological conditions, including the acidic condition of the stomach?

Yes
 No
 Unknown

[Help](#)

Select: No.

At this point, the evaluation will be complete, and the justification report displayed. Because the justification report is more than one page long, you will need to scroll down to read the entire report. This can be accomplished in two ways. You may press the <Page Down> key or you can use the mouse and move the pointer to the right hand side of the window and click on the arrows to scroll the text. The screens that follow will contain the justification report a page at a time as if someone was using the <Page Down> key to scroll.

Justification Report

OncoLogic Justification Report

SUMMARY

:

Filename

:

Metall

Substance ID

:

Metal substance #1

The final level of concern for this Cr-containing inorganic or organic compound , when the anticipated exposure is via the inhalation route , is HIGH.

JUSTIFICATION

Since this substance contains more than one metal, Cr, Zr, the system has considered all metals present. The level of concern and the line of reasoning are based on the metal which provides the highest level of carcinogenicity concern. When more than one metal gives the same highest level of concern, the line of reasoning is given for only one of the metals.

In general, virtually all Cr-containing compounds are of some carcinogenicity concern unless they can be clearly shown to be not bioavailable. Exposure to these compounds by inhalation or injection is of greater concern than exposure by the oral or dermal route.

The carcinogenic potential of inorganic chromium compounds is affected by their oxidation state, crystallinity, and solubility, which affect the extent of compound uptake by cells. Hexavalent compounds are more easily taken up by cells than trivalent; and crystalline compounds are more easily taken up than amorphous compounds. Sparingly soluble and insoluble compounds are more likely than soluble compounds to be retained at the site of exposure, and thus have more of an opportunity to be taken up by the cells. Organic chromium compounds containing a Cr-C covalent bond are treated as inorganic compounds because the Cr-C covalent bond is expected to be easily hydrolyzed in aqueous solution.

Justification Report

Since the substance is a(an) inorganic or organic compound, and the oxidation state of chromium is hexavalent, and exposure to this sparingly soluble, crystalline substance is expected to be by the inhalation route, the level of carcinogenicity concern is HIGH.

The final level of concern for this Cr-containing inorganic or organic compound , when the anticipated exposure is via the inhalation route , is HIGH.

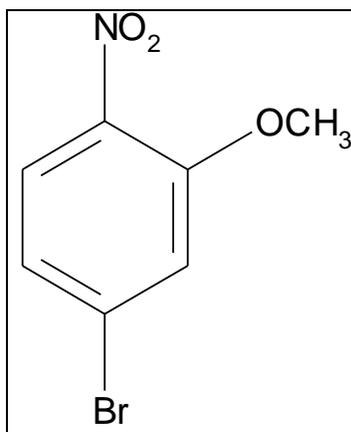
Press: <Close> will return you to the main menu.

8.4 Organic Sample

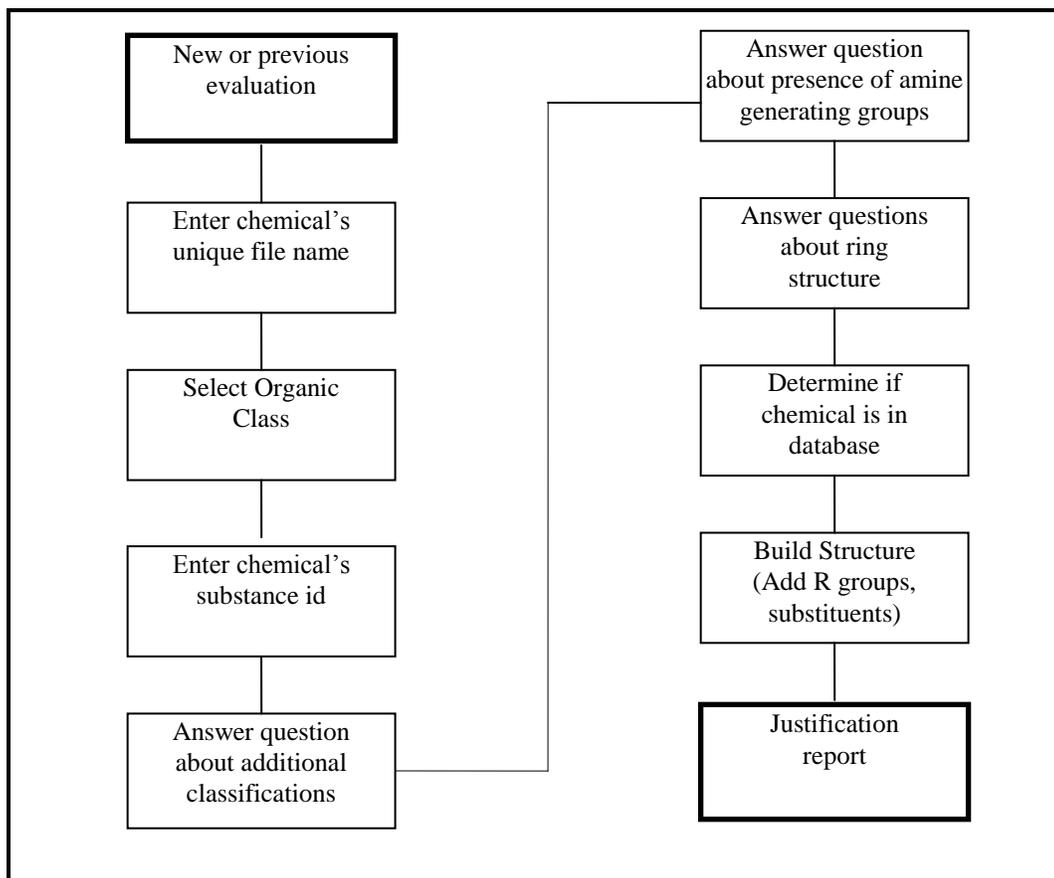
The following is a sample evaluation for an aromatic amine.

Information summary:

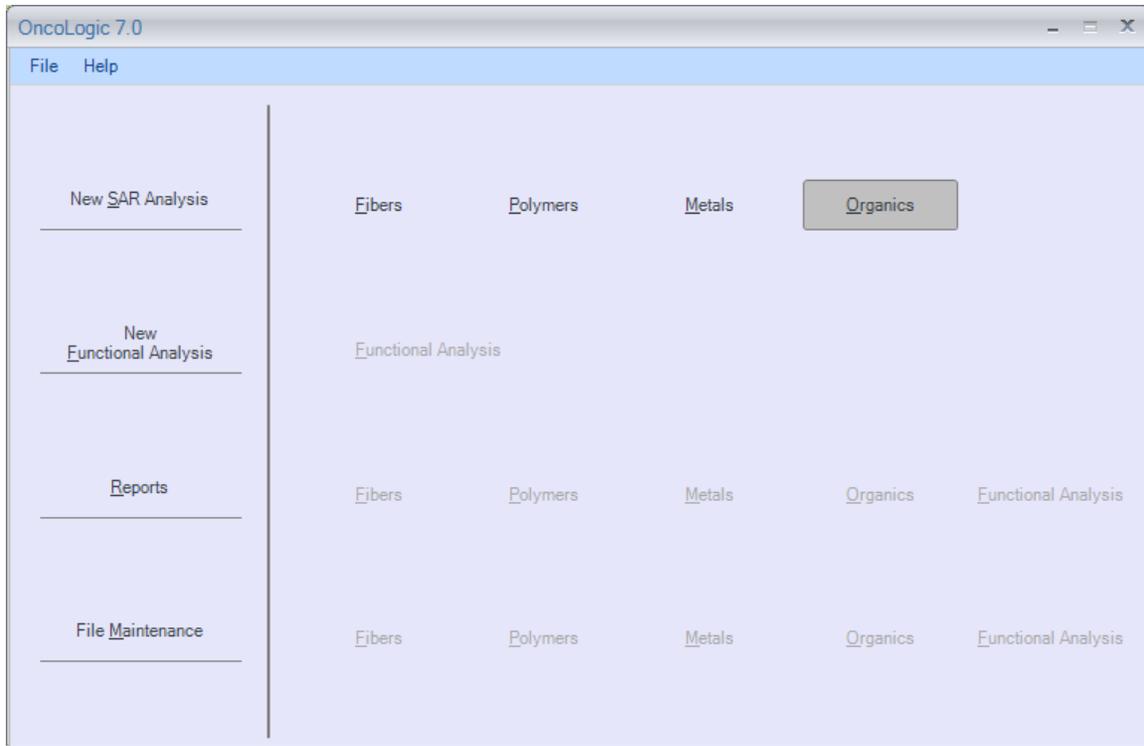
1. Code Number: Arom1
2. Substance Identification: Aromatic Amine #1



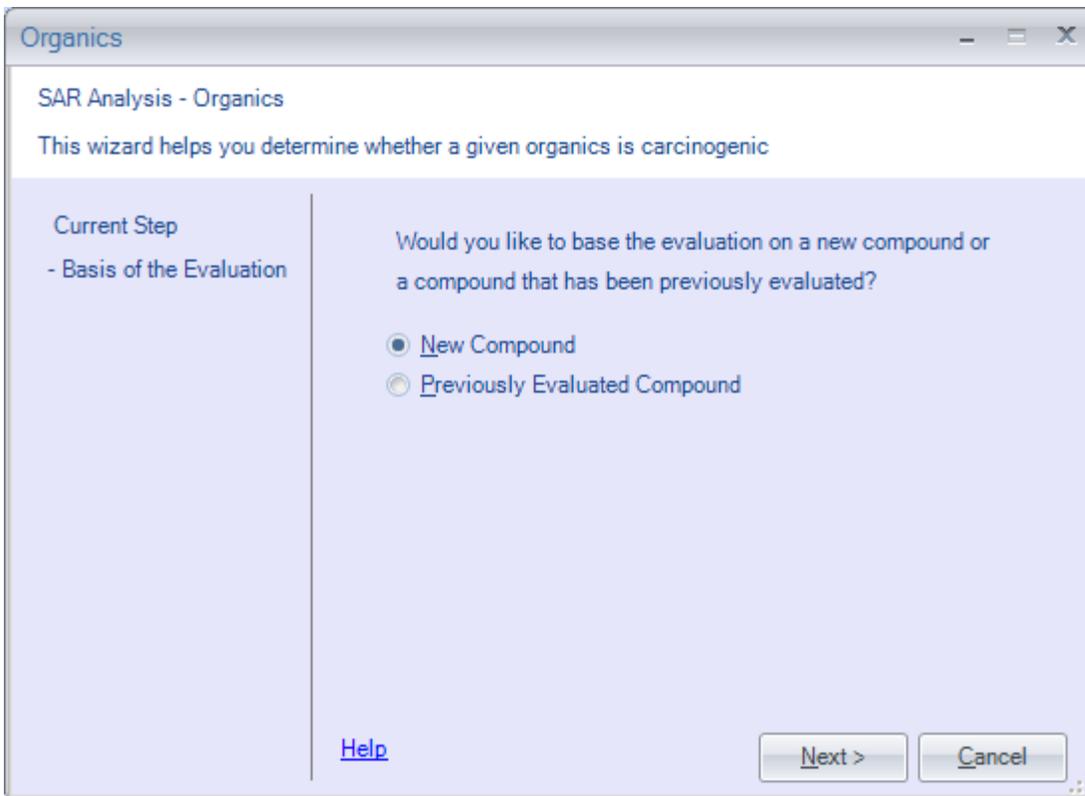
General Input Flow Diagram for aromatic amine example.



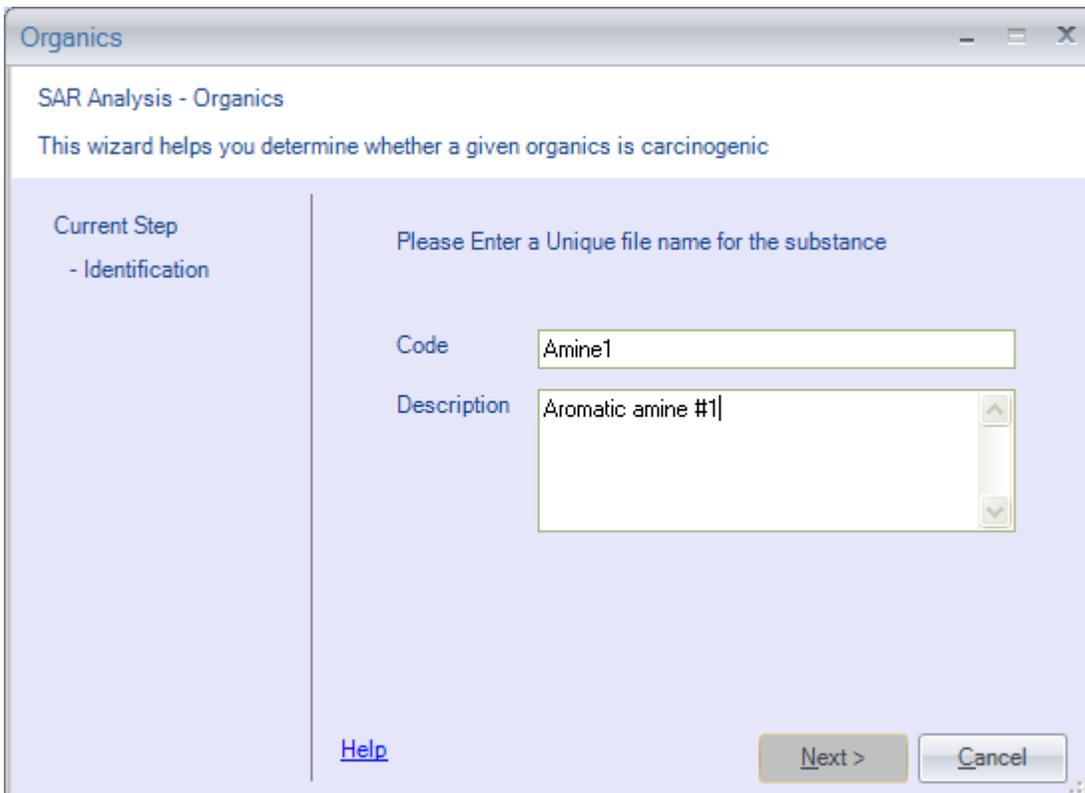
The screens that follow are provided to walk you through this sample evaluation. Each screen will be presented and the instructions for answering that screen will follow. The first screen presented will be the OncoLogic™ main menu screen.



Select: Organics



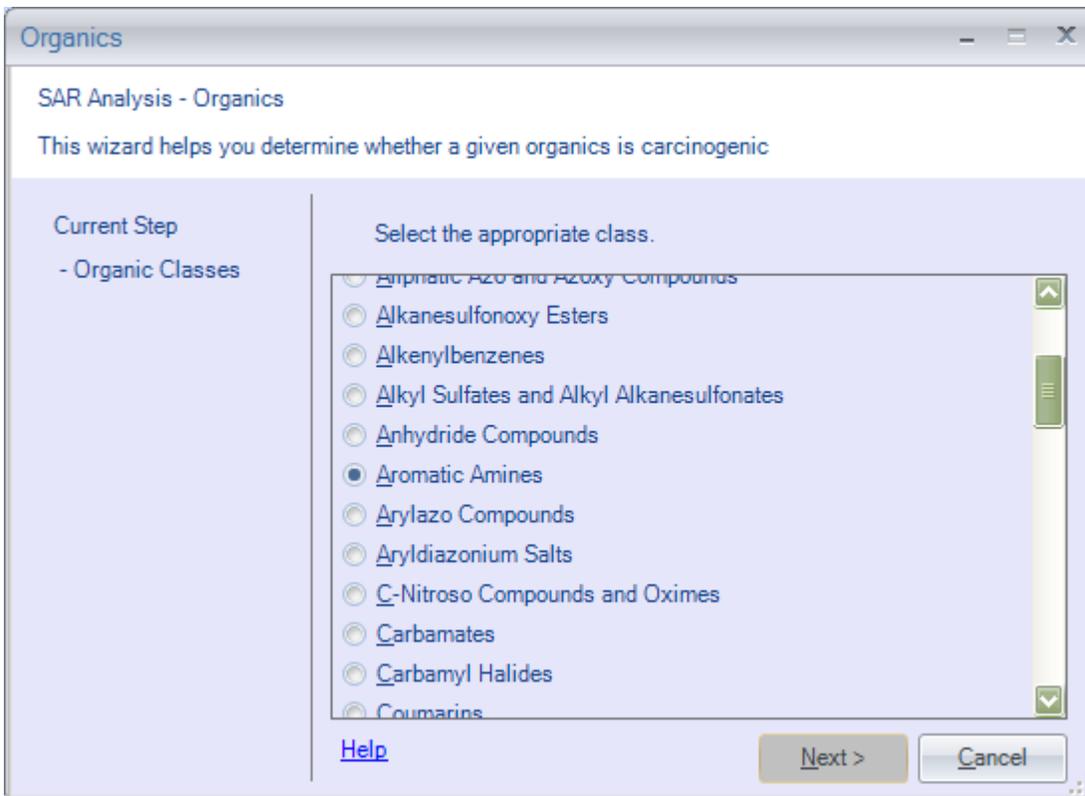
Select: New Compound



Enter the filename: Amine1.

Press: <Next>

If a filename was used before, you will be asked to enter a different filename.



Select: Aromatic Amines.

Note: In order to see the other organic classes, you need to scroll down. This can be done by either pressing the <Page Down> key or using the mouse to click the arrows on the right hand side of the window. Also, by pressing the first letter of the organic class, the highlight bar will jump to the first class starting with that letter. By continually pressing that letter, the highlight bar will cycle through all of the organic classes beginning with that letter.

Organics

SAR Analysis - Organics

This wizard helps you determine whether a given organics is carcinogenic

Current Step
- Aromatic amine related compounds

If your compound falls into any of the classes listed below, it may need to be evaluated in another component. Please select following classes. When all classes have been selected, press "Next" button. If your compound is not a member of any of these classes, choose "None" and press "Next" button.

None
 Arylazo compound
 Azomethine compound
 Diarylamine
 Triarylamine
 Cycloalkylimine

[Help](#) Next > Cancel

Select: NONE and press <Enter>.

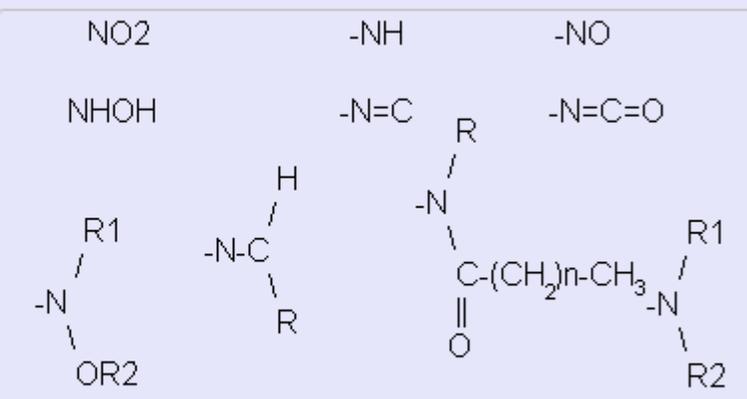
Organics

SAR Analysis - Organics

This wizard helps you determine whether a given organics is carcinogenic

Current Step
- Amino and Amine generating groups

NO₂ -NH -NO
 NHOH -N=C -N=C=O



Does the compound to be evaluated contain one or more of the amino or amino-generating groups shown?

Yes No

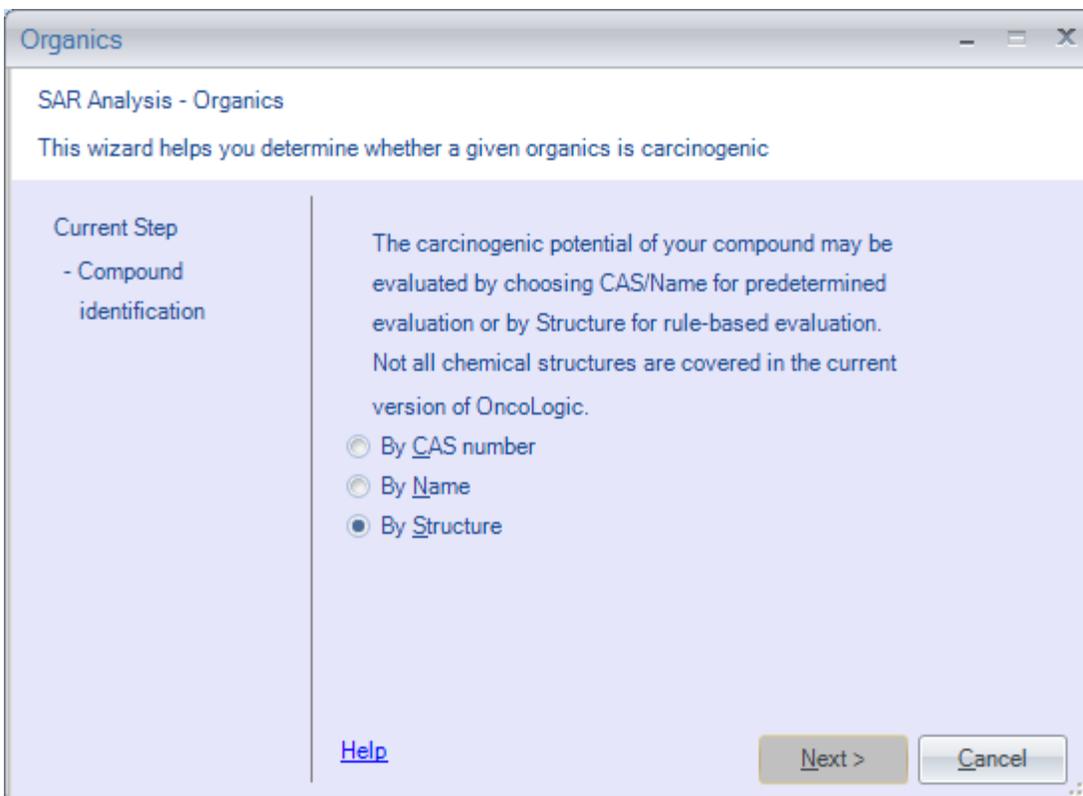
[Help](#) < Back Next > Cancel

Select: Yes and **press** <Return>.

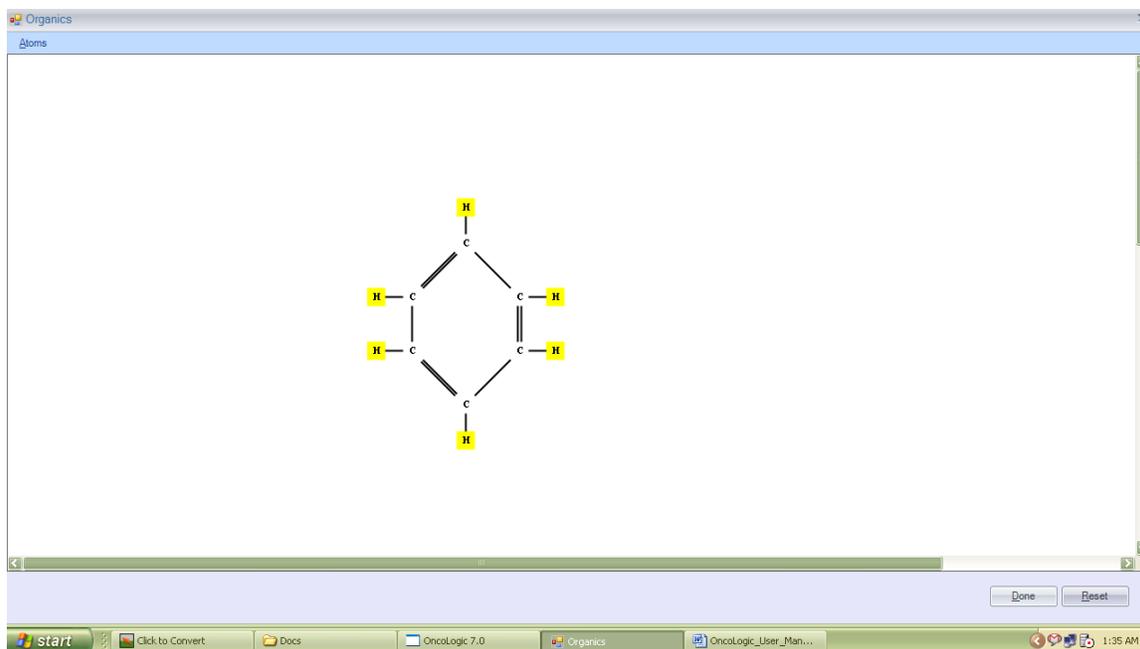
Highlight CONTINUE and **press** <Return> or **click** left mouse button.

The screenshot shows a software window titled "Organics" with a close button (X) in the top right corner. The main content area is titled "SAR Analysis - Organics" and contains the text "This wizard helps you determine whether a given organics is carcinogenic". On the left side, there is a sidebar with the text "Current Step" and "-Aromatic Amines Questionnaire". The main area contains three input fields: "Enter the number of 6-membered rings in the compound" with a value of "1", "Enter the number of 5-membered rings in the compound" with a value of "0", and "Enter the number of 4-membered rings in the compound" with a value of "0". Below these fields are radio buttons for "Yes" and "No", with "No" selected. A "Confirm" dialog box is overlaid on top, featuring a question mark icon and the text "Are answers to all questions correct?". It has two buttons: "Yes" and "No". At the bottom of the main window, there is a "Help" link and three buttons: "< Back", "Next >", and "Cancel". The "Next >" button is highlighted.

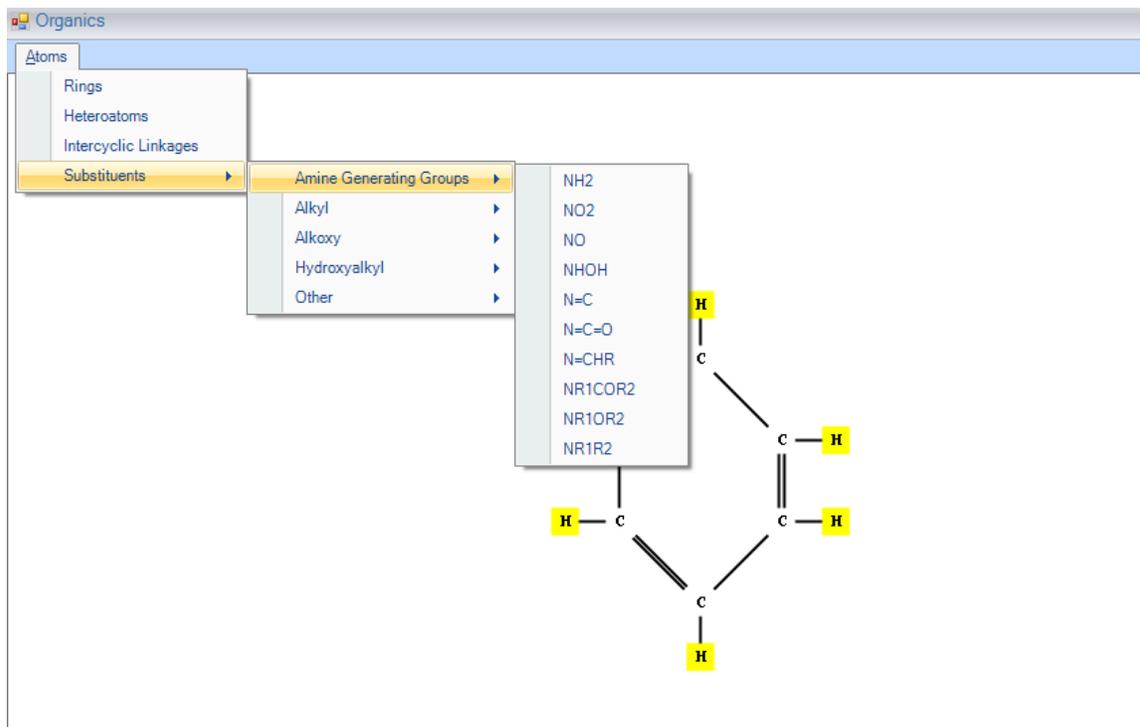
Fill the proper ring data and give answers to the Questionnaires.



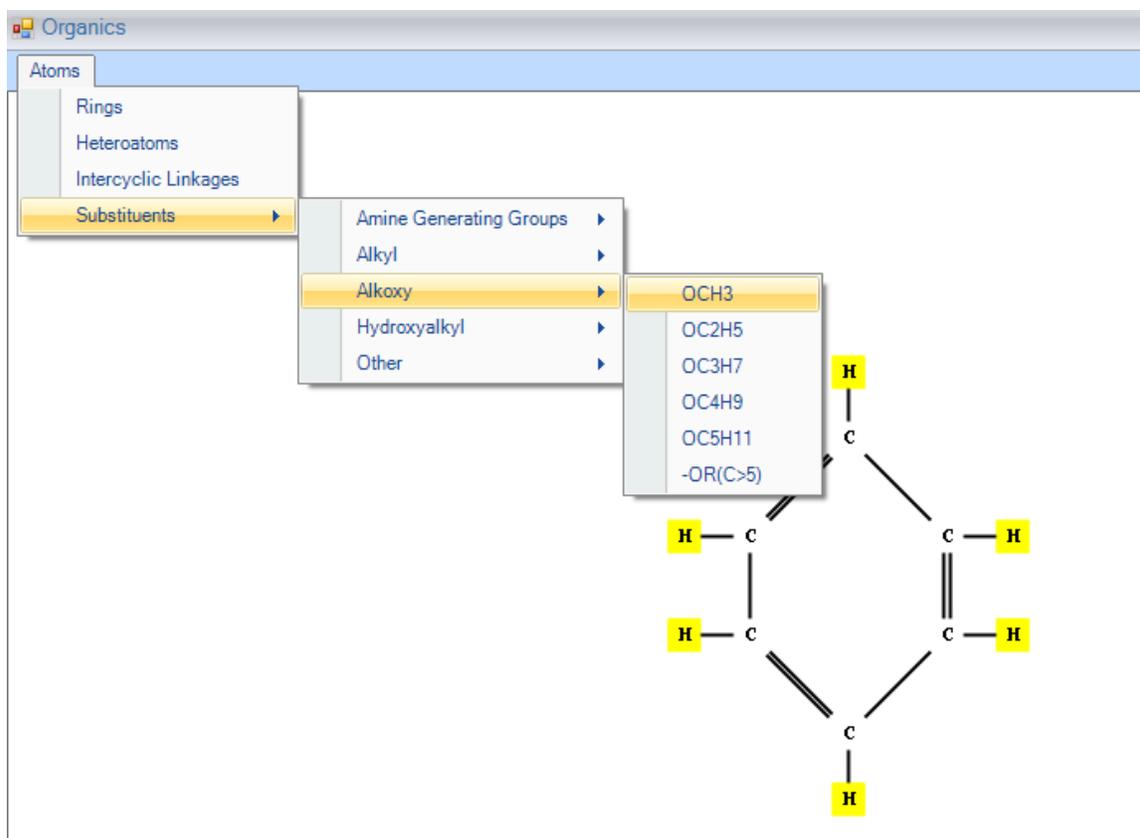
Because we do not have the name or CAS number for the compound, we will **select 'BY STRUCTURE'**. However, if the CAS number or name had been known, use of the database would have been the first course of action.



As before, the method using commands is accomplished through the use of pull down menus. For us to build the compound, we will begin by **selecting the 'Atoms' menu option and clicking** with the left mouse button.



As you will see, there are now four more options which can be selected. We will **highlight Substituents** and **click** the mouse button.

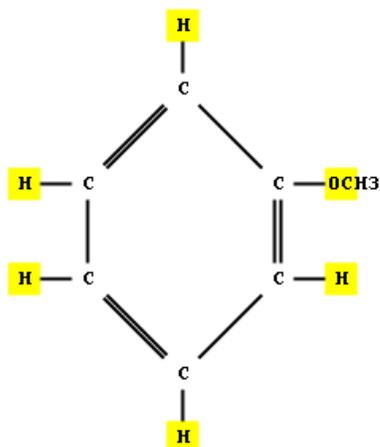


From here we will **highlight and select -OCH₃** by clicking the mouse button in order to add the substituent to the ring structure.

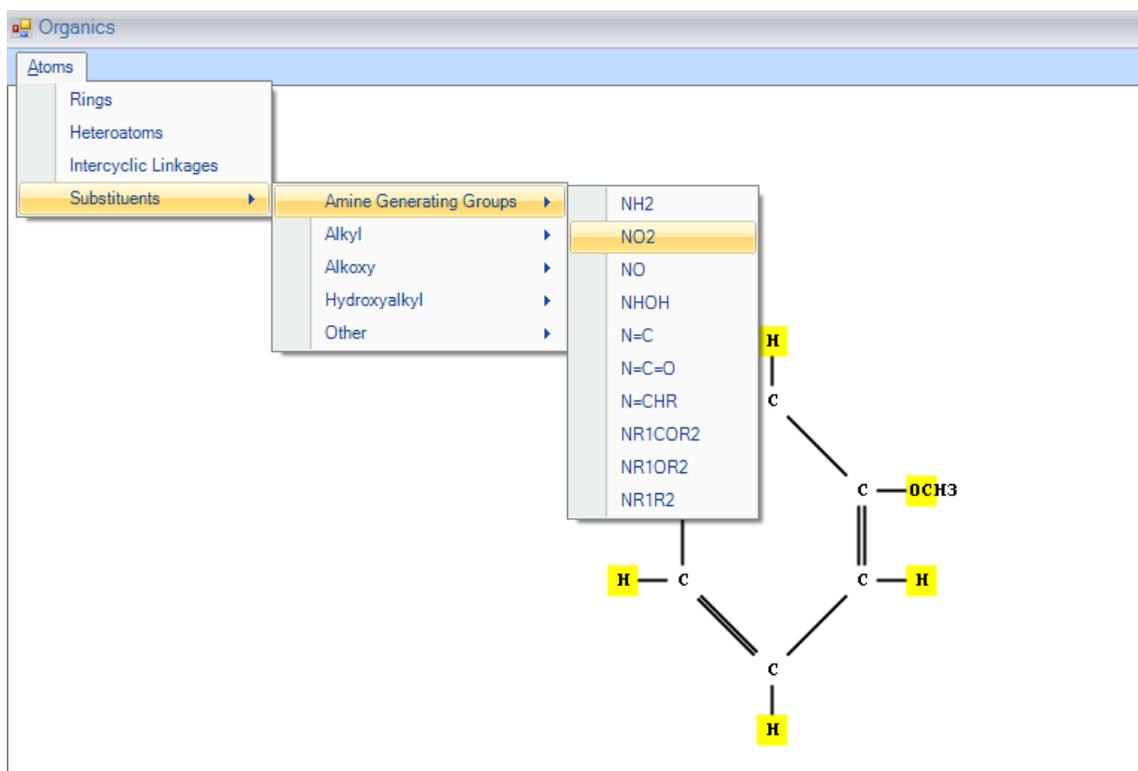
Once you have selected the substituent, you can then place it onto the skeleton using the mouse. First pick a location to add the substituent onto by **moving the mouse pointer over the appropriate atom, click** the left mouse button.

Organics

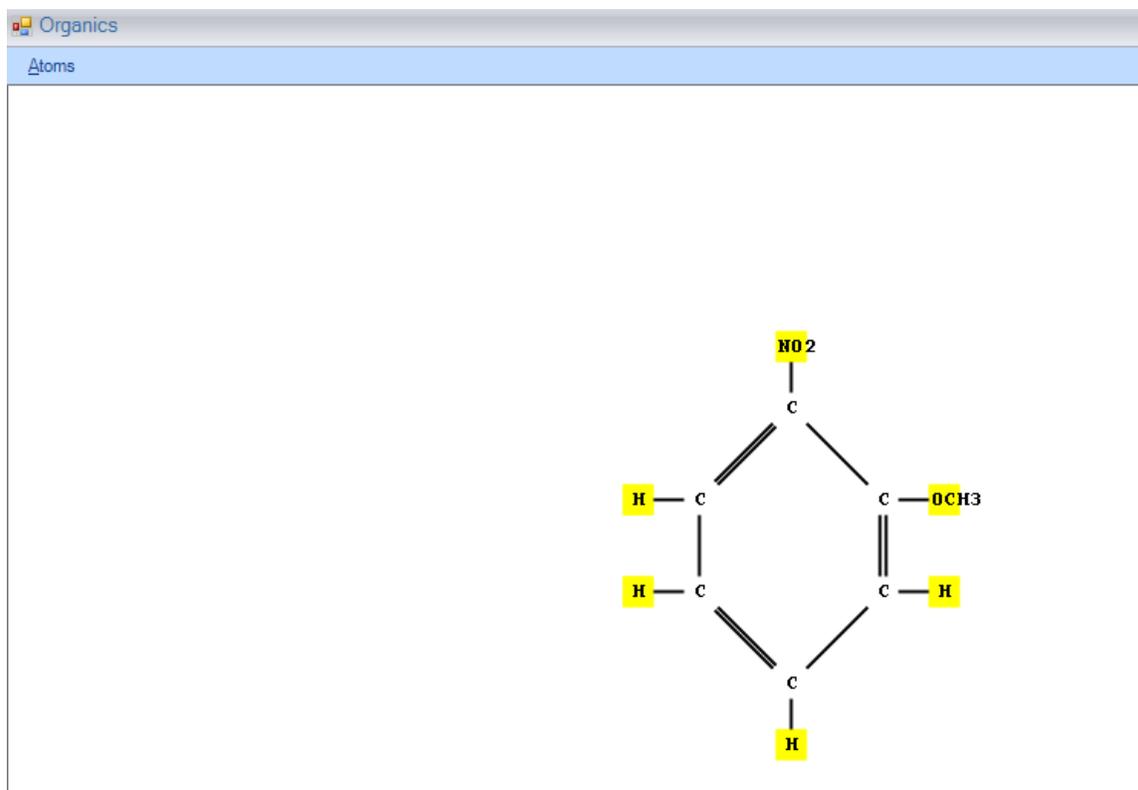
Atoms



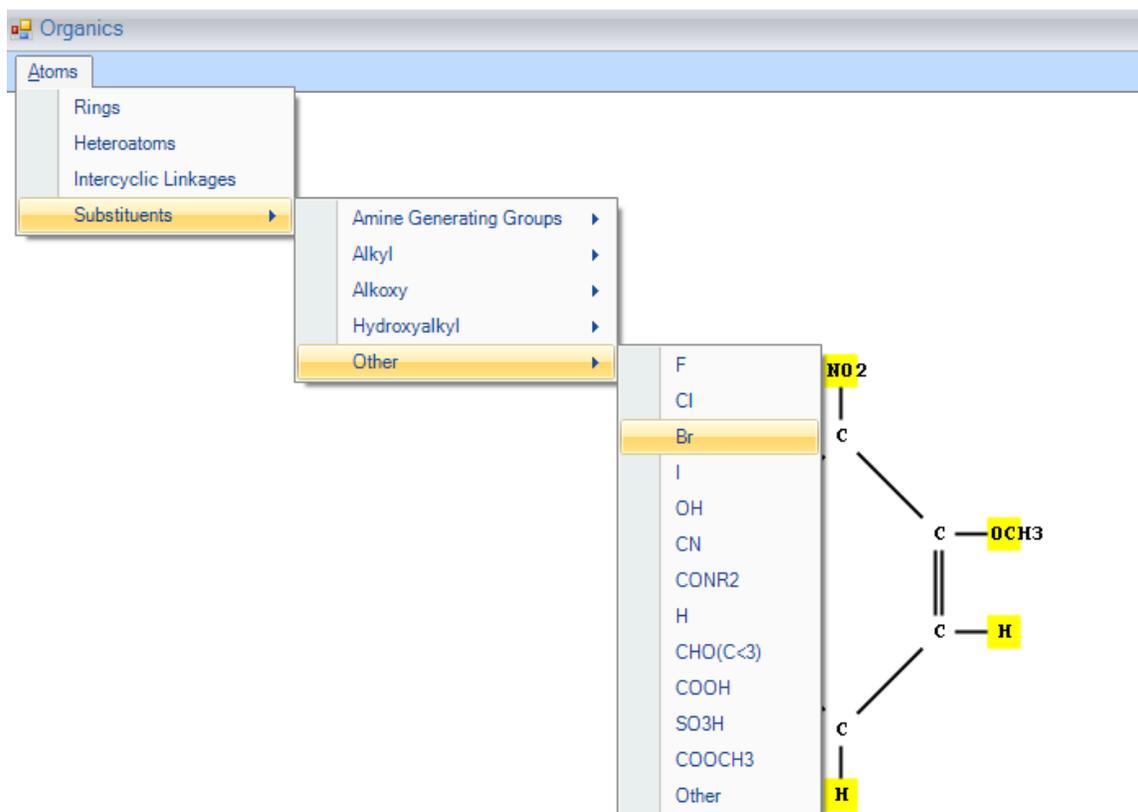
Since we have no other methoxy substituents to add to the compound. We will now **select Amine Generating Groups** from the menu.



Select: -NO₂ by **highlighting** the group and **clicking** the mouse button or pressing



Highlight the appropriate atom and **click** the mouse button.

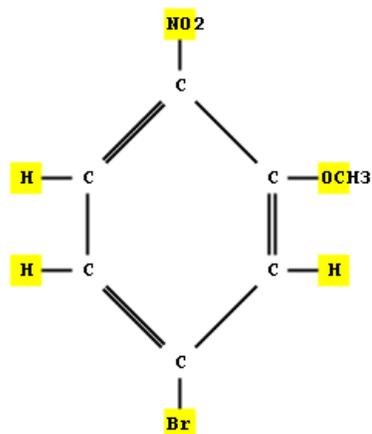


Select: Other.

Highlight -Br and click the left mouse button in order to place the substituent onto structure.

Organics

Atoms



Now Press “Done” Button

At this point, the evaluation will be complete, and the justification report displayed.

Justification Report

OncoLogic Justification Report

SUMMARY :

CODE NUMBER : Aminel

SUBSTANCE ID : Aromatic amine #1

The level of carcinogenicity concern for this compound is HIGH-MODERATE

JUSTIFICATION:

In general, the level of carcinogenicity concern of an aromatic amine

Press <Page Down> key to scroll through text.

is determined by considering the number of rings, the presence or absence of heteroatoms in the rings; the number and position of amino groups; the nature, number and position of other nitrogen-containing 'amine-generating groups'; and the type, number and position of additional substituents. Aromatic amine compounds are expected to be metabolized to N-hydroxylated/N-acetylated derivatives which are subject to further bioactivation, producing electrophilic reactive intermediates that are capable of interaction with cellular nucleophiles (such as DNA) to initiate carcinogenesis.

Nitro groups of aryl compounds can be reduced by nitro reductase to amino groups yielding aromatic amine compounds. The evaluation of this compound proceeds as if the nitro group were a free amine group.

An aromatic compound containing one benzene ring, one amino group, and one methyl or methoxy group ortho- to the amino group, has a carcinogenicity concern of HIGH-MODERATE.

The additional chloro and/or bromo group(s) generally raise(s) the level of concern, but they also impose an upper limit of HIGH-MODERATE on the concern level of the compound. Therefore, the level of concern remains HIGH-MODERATE.

The final level of carcinogenicity concern for this compound is HIGH-MODERATE.

Press <Close> key to return to main menu.