OncoLogic™ - The Cancer Expert System – An Overview

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

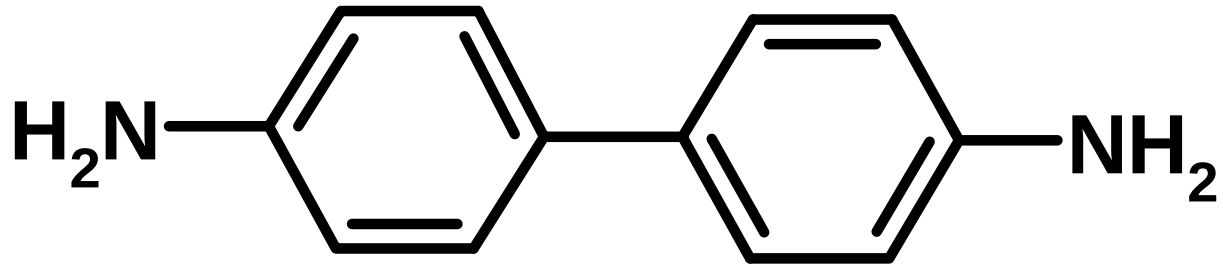
Concern Levels

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

Critical Factors for SAR Consideration

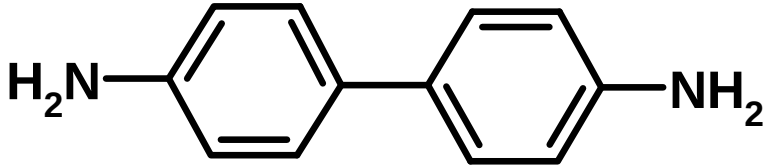
- **Electronic and Steric Factors**
  - **Resonance stabilization, Steric hindrance**
- **Metabolic Factors**
  - **Blocking of detoxification, Enhancement of activation**
- **Mechanistic Factors**
  - **Electrophilic vs. receptor- mediated**
  - **Multistage process**
- **Physicochemical Factors**

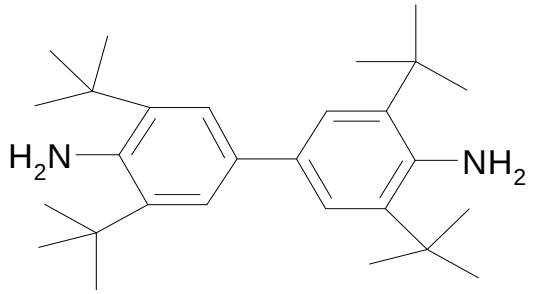
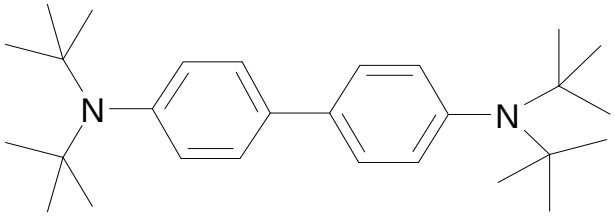
Examples of How “Knowledge Rules” Can be Used in Chemical Design



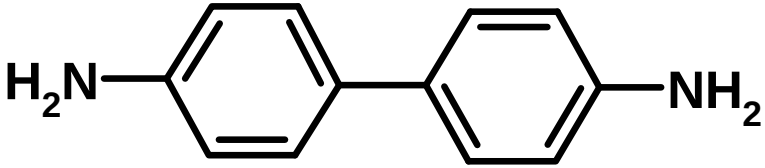
OncoLogic Cancer Concern = High

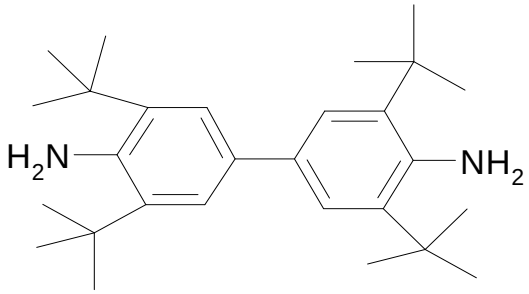
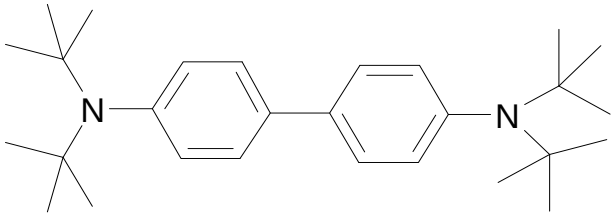
Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential



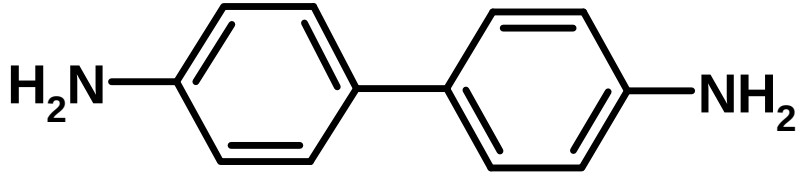
Example	Action	Effect on Cancer Concern/Justification
	**Introduce bulky substituent(s) <u>ortho</u> to amino / amine-generating group(s).**	
	**Introduce bulky N-substituent(s) to amino / amine-generating group(s).**	

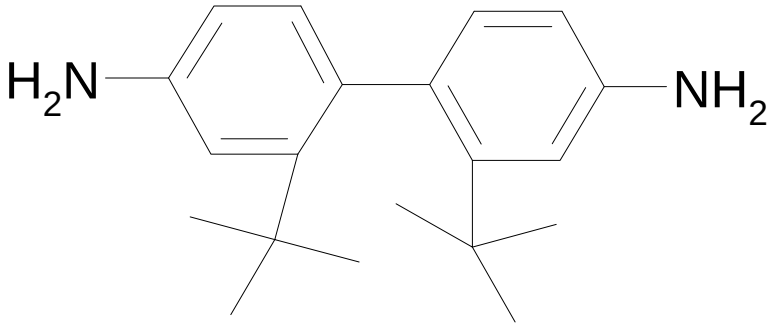
Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential



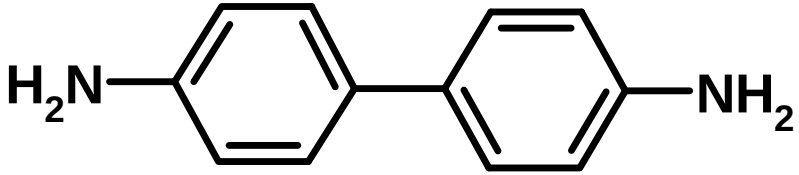
Example	Action	Effect on Cancer Concern/Justification
	Introduce bulky substituent(s) ortho to amino / amine-generating group(s).	Provide steric hindrance to inhibit bioactivation. Concern = Marginal
	Introduce bulky N-substituent(s) to amino / amine-generating group(s).	Make it a poor substrate for the bioactivation enzymes. Concern = Marginal

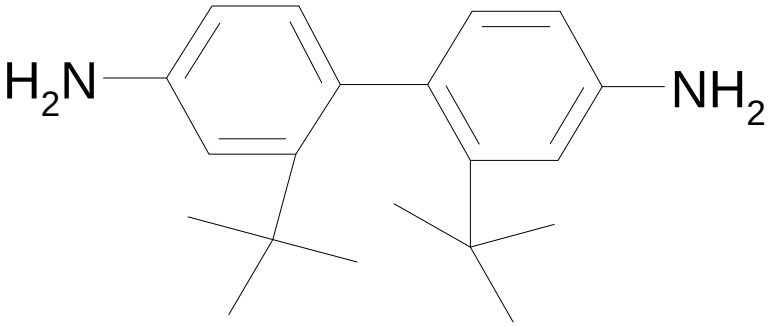
Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential (Cont.)



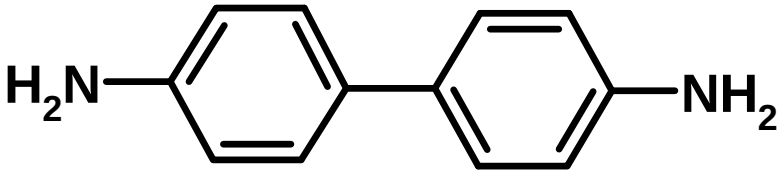
Example	Action	Effect on Cancer Concern/Justification
	**Introduce bulky groups <u>ortho</u> to intercyclic linkages.**	

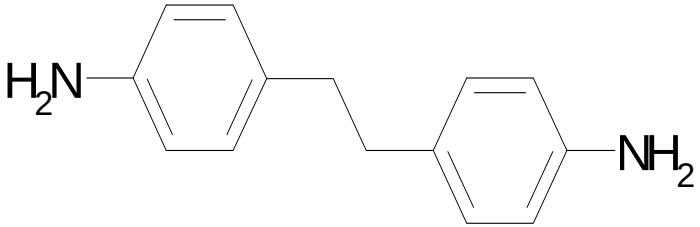
Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential (Cont.)



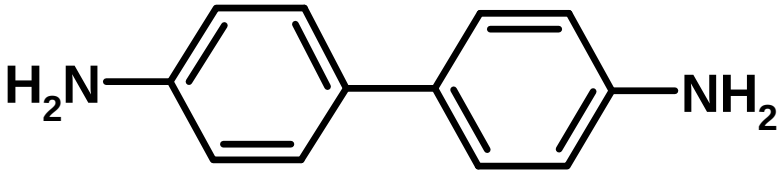
Example	Action	Effect on Cancer Concern/Justification
	Introduce bulky groups <u>ortho</u> to intercyclic linkages.	Distort the planarity of the molecule making it less accessible and a poorer substrate for the bioactivation enzymes. **Concern = Marginal**

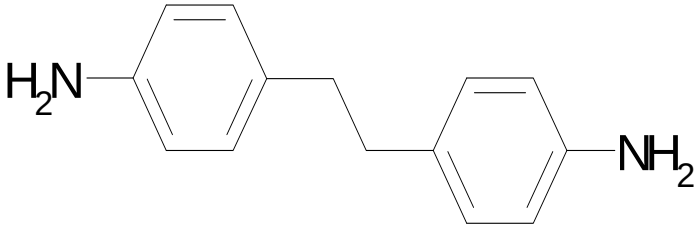
Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential (Cont.)



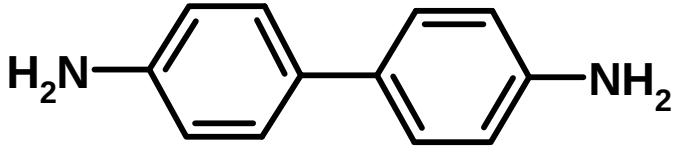
Example	Action	Effect on Cancer Concern/Justification
	**Replace electron-conducting intercyclic linkages by electron-insulating intercyclic linkages.**	

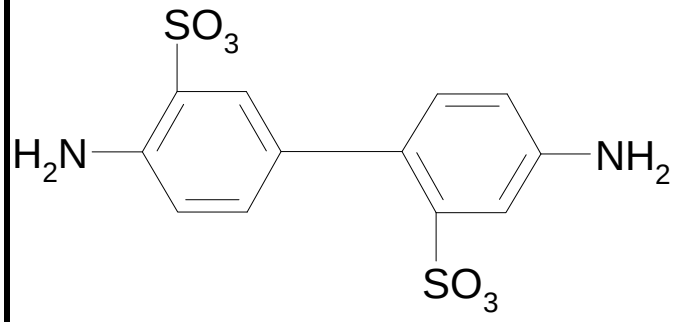
Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential (Cont.)



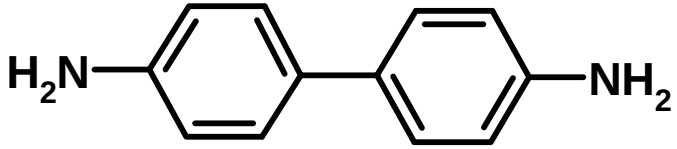
Example	Action	Effect on Cancer Concern/Justification
	Replace electron-conducting intercyclic linkages by electron-insulating intercyclic linkages.	1. Reduce length of conjugation path and thus the force of conjugation, which facilitates departure of acyloxy anion. 2. Less resonance stabilization of electrophilic nitrenium ion. Concern = Marginal

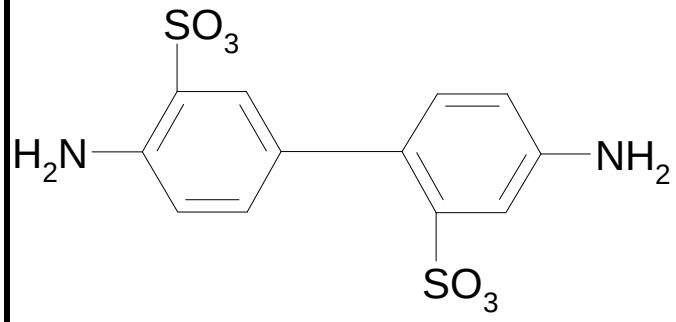
Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential (Cont.)



Example	Action	Effect on Cancer Concern/Justification
	**Ring substitution with hydrophilic groups (e.g., sulfonic acid); especially at ring(s) bearing amino / amine-generating group(s).**	

Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential (Cont.)



Example	Action	Effect on Cancer Concern/Justification
	**Ring substitution with hydrophilic groups (e.g., sulfonic acid); especially at ring(s) bearing amino / amine-generating group(s).**	**Render molecule more water-soluble thus reducing absorption and accelerating excretion.** **Concern Level = Low**

Major Data Sources Used to Develop Cancer Knowledge Rules

- Chemical Induction of Cancer monograph series
- IARC monograph series
- NCI/NTP technical reports
- Survey of compounds which have been tested for carcinogenic activity, PHS Publ. 149
- Non-classified EPA submission data from various EPA program offices

OncoLogic™ Prediction vs. NTP Bioassays Aromatic Amines and Related Compounds

NTP #	Chemical	Bioassay Results			Oncologic Evaluation
		Rat	Mouse	"Call"	
24	4,4'-Diamino-2,2'-stilbene disulfonic acid	N/N	N/N	--	L
42	p-Nitroaniline	NT	E/N	Eq	mar
26	p-Nitrobenzoic acid	N/S	N/N	+	mar
9	p-Nitrophenol	NT	N/N	--	LM
33	4-Hydroxyacetanilide	N/E	N/N	Eq	LM
32	2,4-Diaminophenol dihydrochloride	N/N	S/N	+	M
40	3,3'-Dimethylbenzidine	C/C	NT	+	HM
43	o-Nitroanisole	C/C	C/C	+	HM

C = Clear evidence of carcinogenicity
S = Some evidence of carcinogenicity
N = No evidence of carcinogenicity
NT = Not tested
+ = At least one test = C or S
Eq = No C or S, and E must appear at least once
-- = No C, S, or E

Conclusion from NTP Predictive Exercises

- **Most of the best performers are predictive systems that incorporate human expert judgment and biological information**
- **OncoLogic was one of the best performers among more than 15 methods**

OncoLogic™ - Benefits

- **Allow non-experts to reach scientifically supportable conclusions**
- **Expedites the decision making process**
- **Allows sharing of knowledge**
- **Reduces/eliminates error and inconsistency**
- **Formalize knowledge rules for cancer hazard identification (SAT-style)**

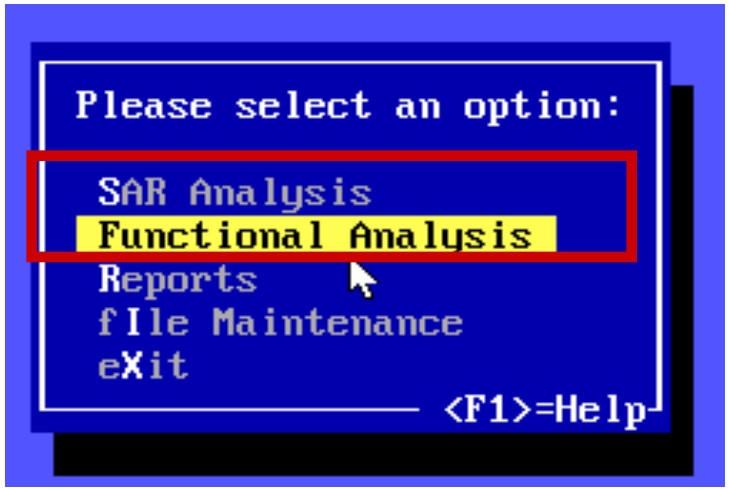
OncoLogic™ - Benefits (Cont.)

- **Provide guidance to industries on elements of concern for developing safer chemicals**

- **Bridge expertise of chemists and toxicologists for most effective hazard evaluation**

Running OncoLogic™

- Two methods to predict carcinogenicity
  - SAR Analysis
    - Knowledge rules
  - Functional Analysis
    - Uses results of specific mechanistic/non-cancer studies



SAR Analysis

- **Four modules**
  - **Organics**
  - **Metals**
  - **Polymers**
  - **Fibers**
- **Different method used to evaluate each type**

Running OncoLogic™
Organics Module

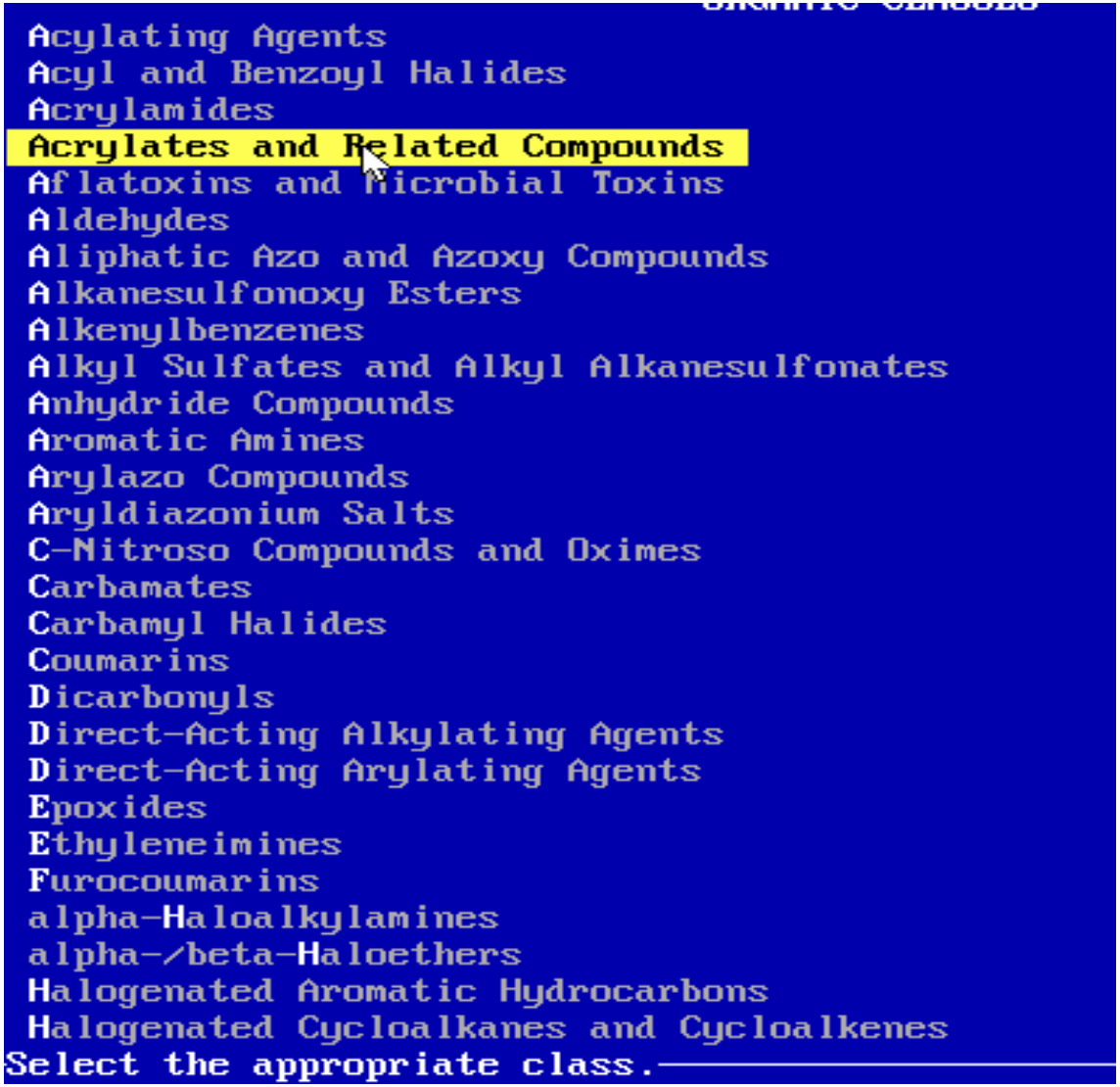
Organics

- **Enter information on chemical identity**
- **Choose appropriate chemical class**
- **Enter chemical name, CAS#, or chemical structure**

Running OncoLogic™
Organics Module

- **Select chemical class**
  - **48 total**
  - **Description in Manual**
  - **Hit “F1” to view sample structures**

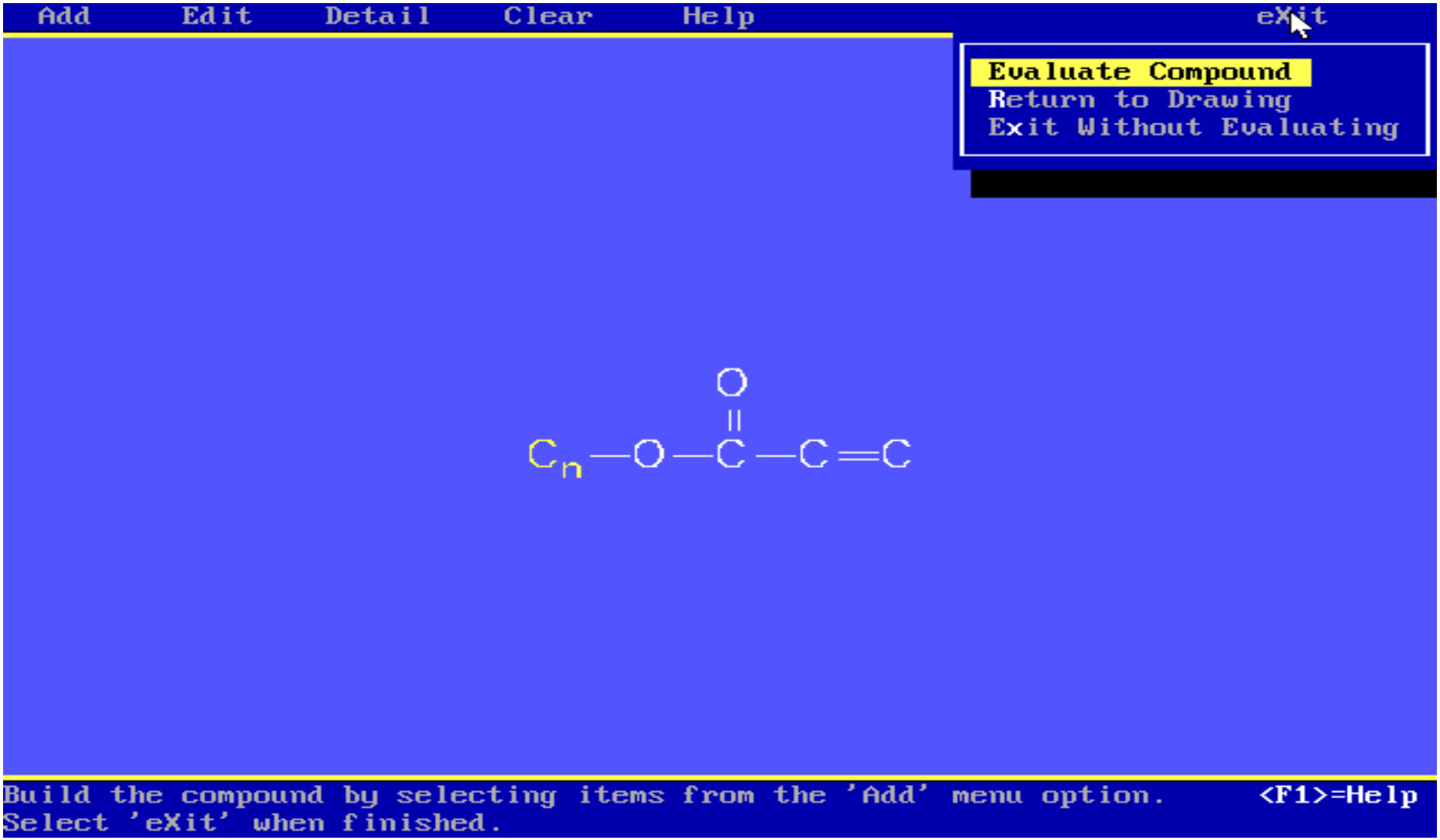
- **Absence of structure in OncoLogic provides suggestive, *but not definitive*, evidence of low cancer concern**



Running OncoLogic™
Organics Module

- **Pick Correct Backbone Structure if Provided**

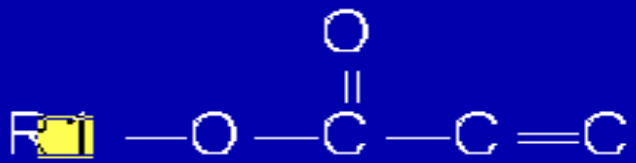
Running OncoLogic™
Organics Module



Running OncoLogic™
Organics Module

Perform evaluation

Compound Display



Justification Report

SUMMARY:

CODE NUMBER: SFEx

SUBSTANCE ID: SF Ex

The final level of carcinogenicity concern for this acrylate when the anticipated route of exposure is inhalation or injection is MARGINAL.

JUSTIFICATION:

<F1>=Help <ESC>=Exit

OncoLogic™ Justification for Organics Module

OncoLogic Justification Report

CODE NUMBER: Isodecyl Acrylate Example

SUBSTANCE ID: 1330-61-6

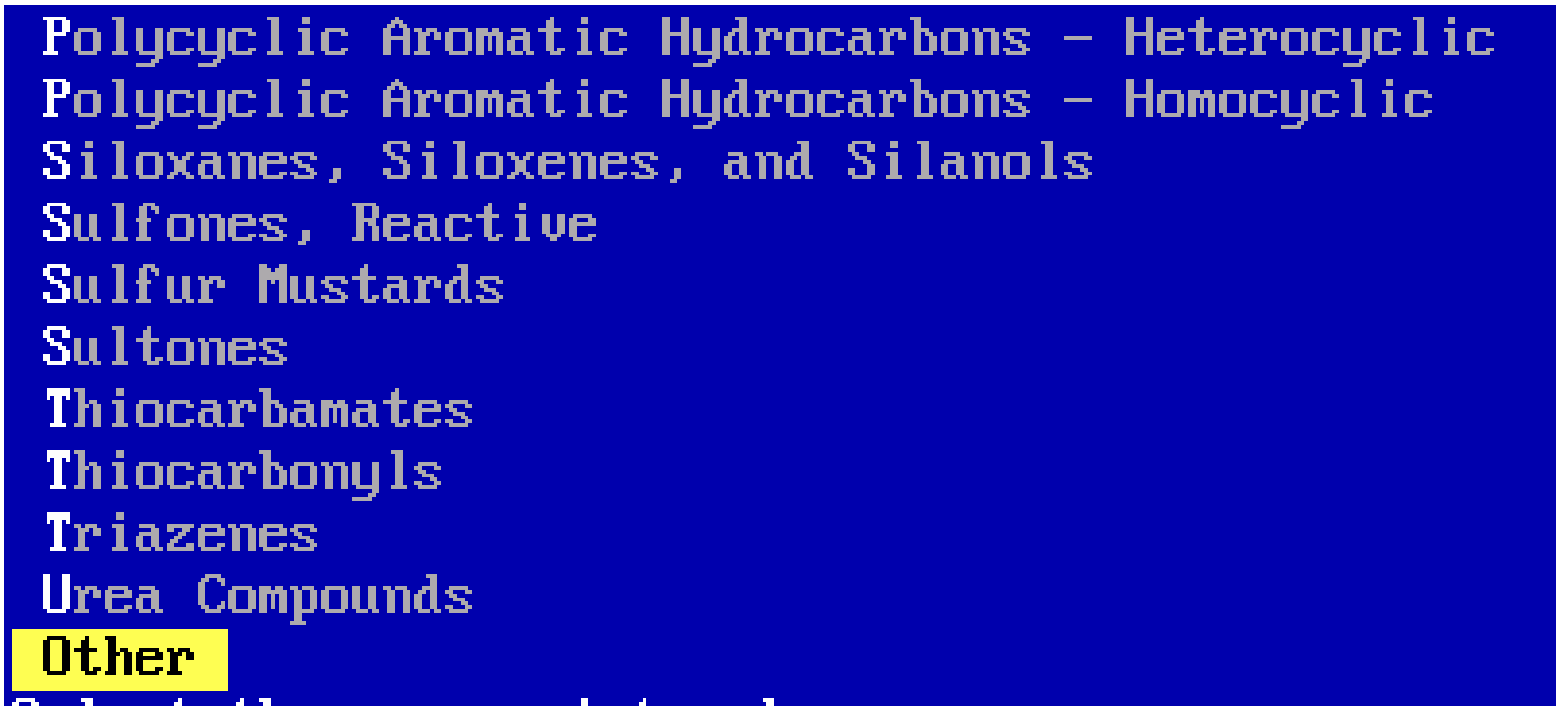
The final level of carcinogenicity concern for this acrylate when the anticipated route of exposure is inhalation or injection is MARGINAL.

JUSTIFICATION:

An acrylate is a potential alkylating agent which may bind, via Michael addition, to key macromolecules to initiate/exert carcinogenic action. The alkylating activity of acrylates can be substantially inhibited by substitution at the double bond, particularly by bulky or hydrophilic groups.....

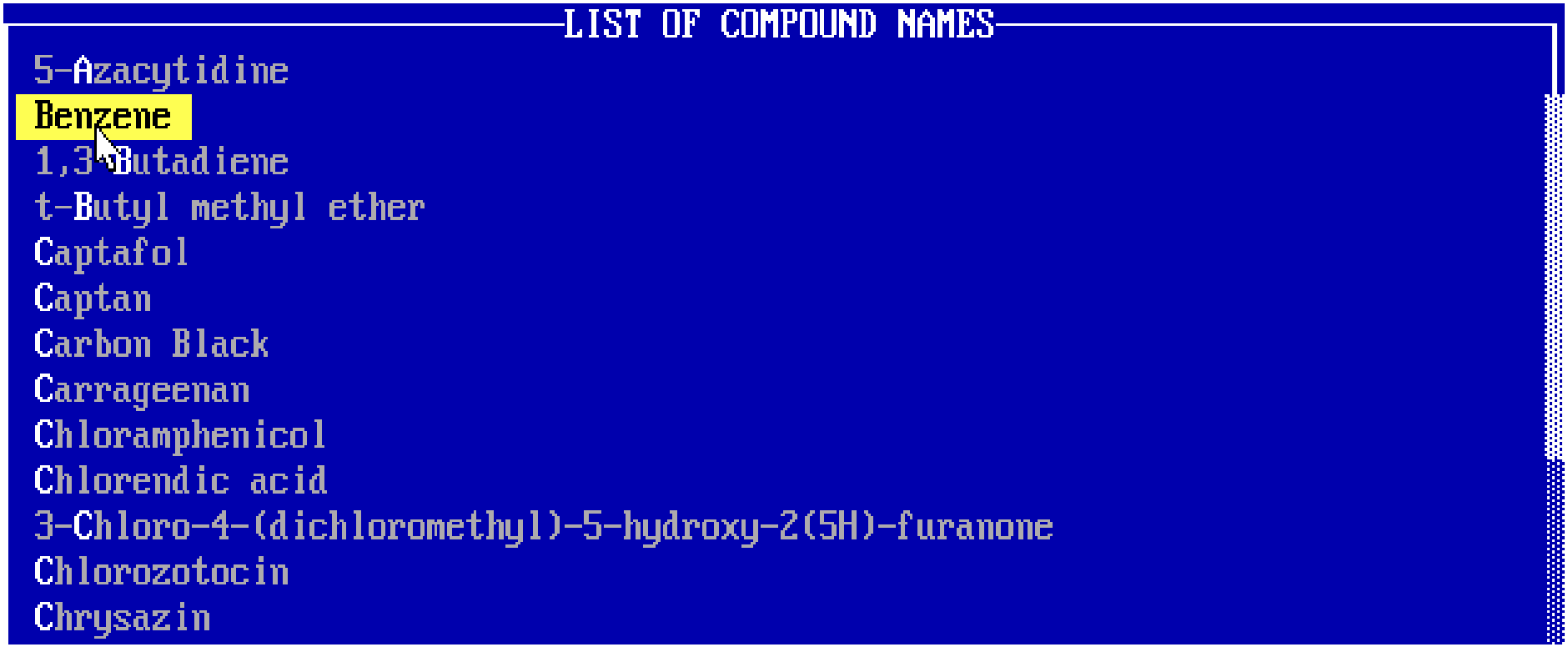
Other Chemicals

- **In addition to SAR analysis, OncoLogic includes evaluations of approximately 90 specific chemicals that do not fit into any OncoLogic class**



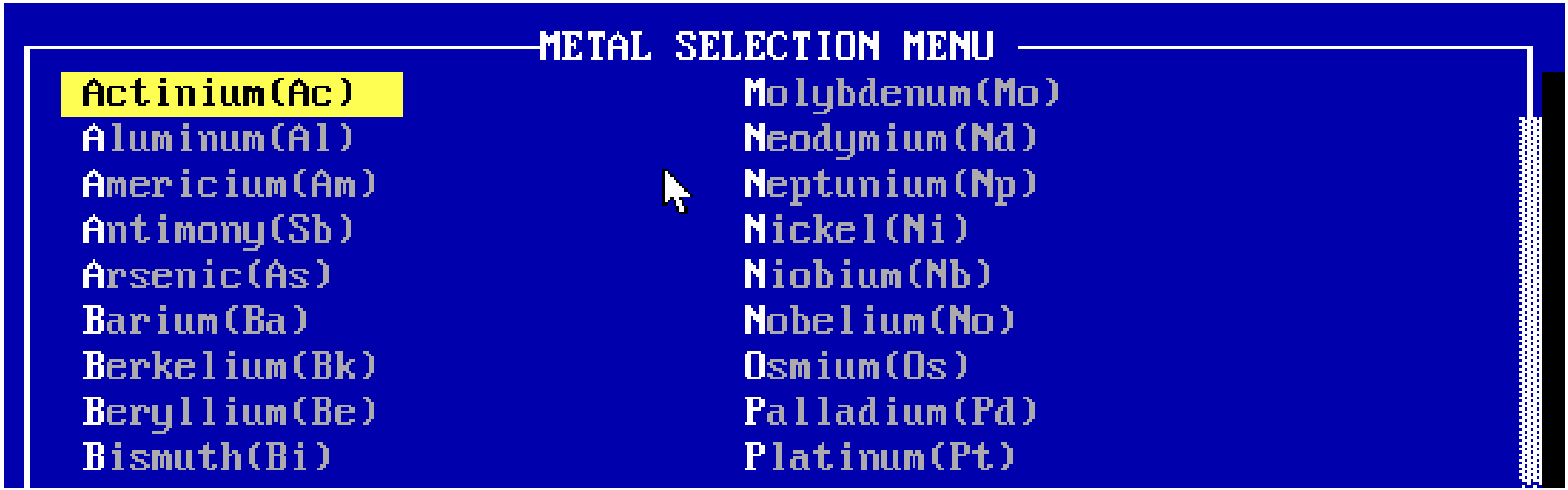
Other Chemicals (Cont.)

- **Locate chemical by CAS number or by name**



Running OncoLogic™
Metals Module

- Similar to running the organics module
- Pick the metal to be evaluated
  - OncoLogic™ will then either ask a series of questions needed to evaluate the chemical or provide a database of related compounds



Information Needed to Run the Metals Module

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

Running OncoLogic™
Polymers Module

- **Polymer must consist of covalently linked repeating units and have a number average molecular weight >1000**
- **OncoLogic™ asks a series of questions designed to aid in evaluation of carcinogenicity of the polymer**

Information Needed to Run the Polymers Module

- Percentage of polymer with MW <500 and <1000
- Percent of residual monomer
- Identification of Reactive Functional Group(s)
- Solubility
- Special features
  - Polysulfation, "water-swellability"
- Exposure route
- Breakdown products (e.g., hydrolysis)

Fibers Module

Evaluations are based on physical dimensions and physicochemical properties

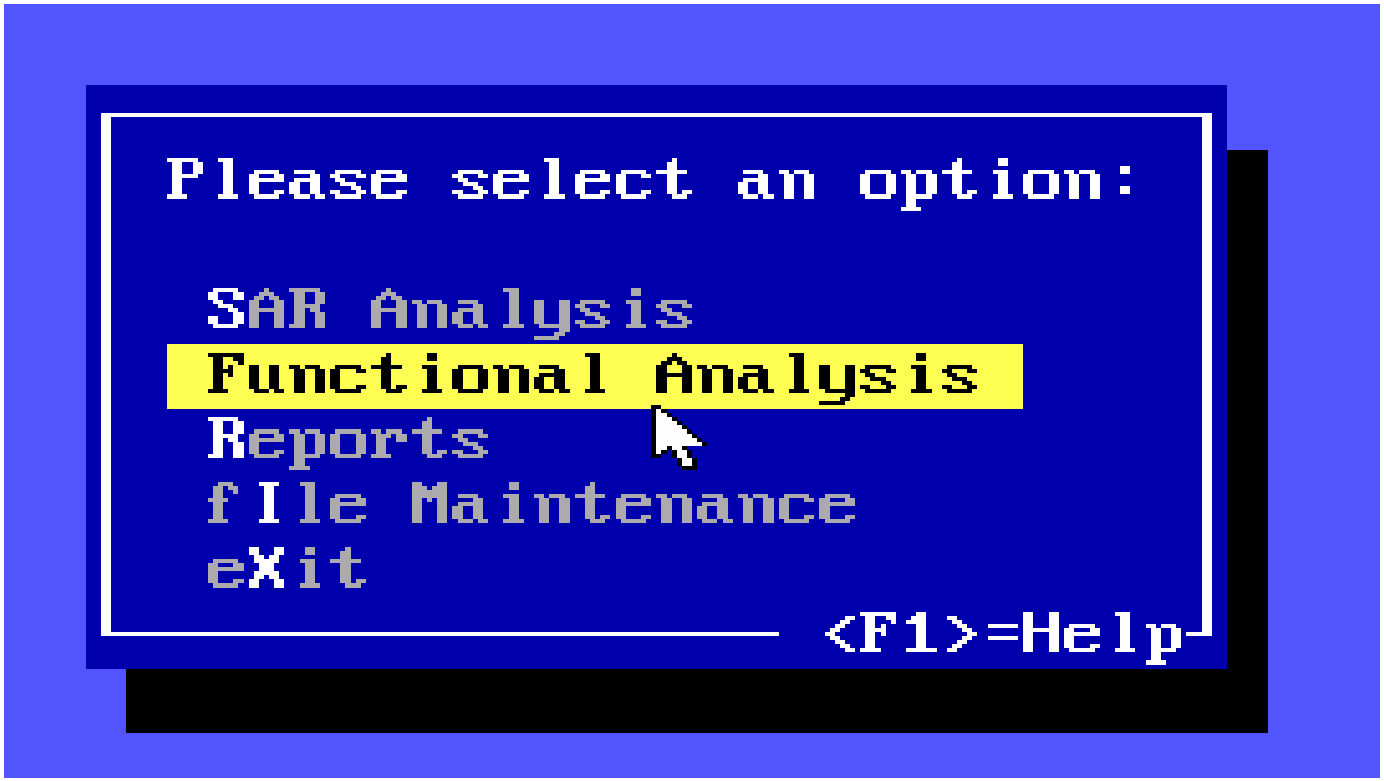
- **Physical dimensions**
  - **Diameter, length, aspect ratio**
- **Physicochemical properties**
  - **High density charge, flexibility, durability, biodegradability, smooth and defect-free surface, longitudinal splitting potential**
  - **Presence of high MW polymer, low MW organic moiety, metals/metalloids**

Fibers Module (Cont.)

Relevant manufacturing / processing / use information

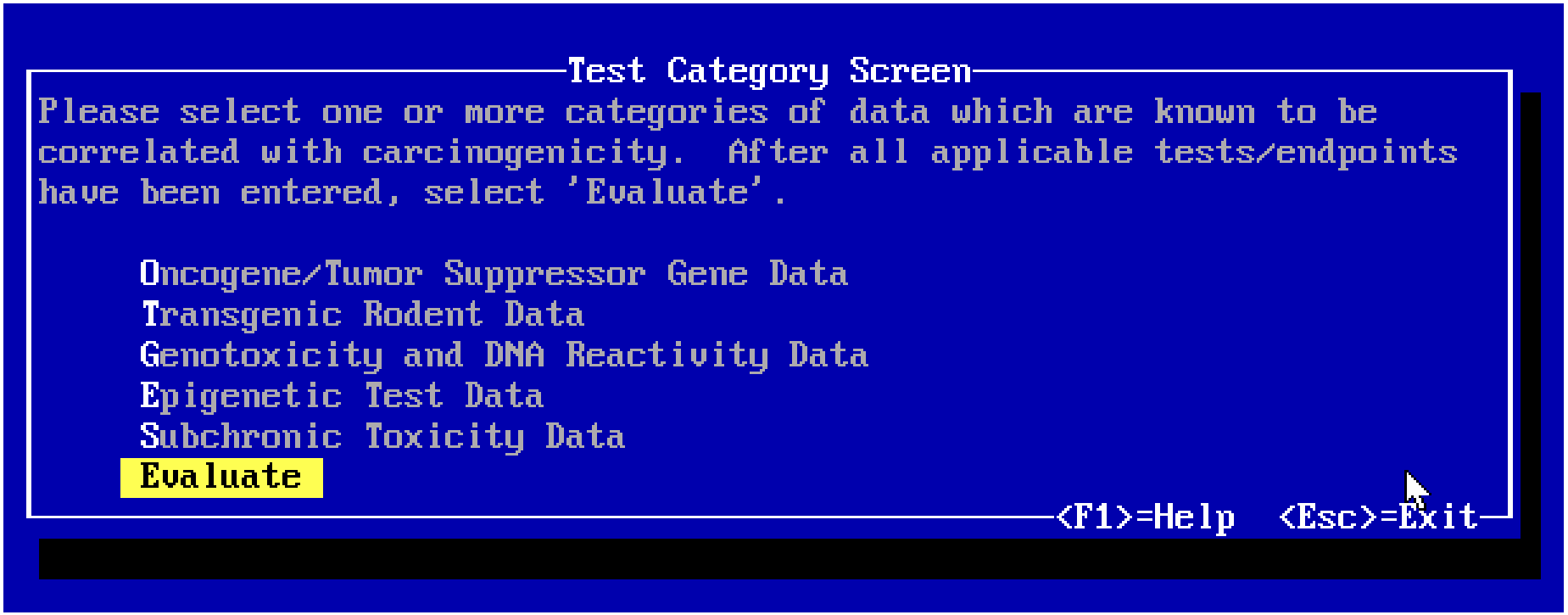
- **Crystallization, thermal extrusion, naturally occurring, unknown method**

The Functional Arm of OncoLogic™



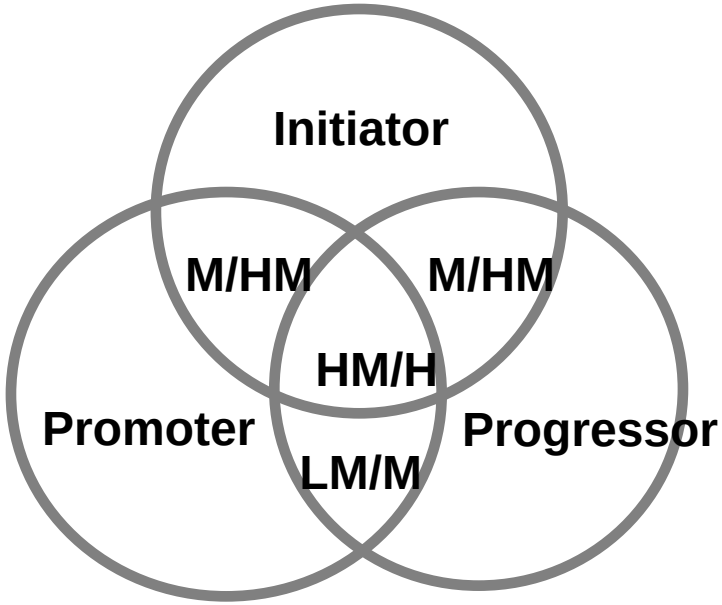
Functional Arm (Cont.)

- **OncoLogic™ can use results from some shorter-term tests to support a cancer concern.**
- **Results indicate whether chemical may be an initiator, promoter, or progressor**



Use of Non-Cancer Data: Functional Arm (Cont.)

- **Functional Arm predicts whether the chemical is likely to be a tumor initiator, promoter, and/or progressor**
  - **Possible relevance or contribution to the carcinogenesis process is indicated in the figure below**



OncoLogic™ Interpreting Results

OncoLogic Concern	SF Concern	Definition	Proceed to Risk Screen?
Low	Low	Unlikely to be carcinogenic	No
Marginal	Further Research Needed	Likely to have equivocal carcinogenic activity	Additional information is needed
Low – Moderate	Moderate	Likely to be weakly carcinogenic	Yes
Moderate		Likely to be a moderately active carcinogen	Yes
Moderate – High	High	Highly likely to be a moderately active carcinogen	Yes
High		Highly likely to be a potent carcinogen	Yes

Major References on OncoLogic™

Woo, Y.-T., Lai, D.Y., Argus, M.F. and Arcos, J.C. Development of Structure Activity Relationship Rules for Predicting Carcinogenic Potential of Chemicals. Toxico. Lett.79: 219-228, 1995.

Woo, Y.-T., Lai, D.Y., Argus, M.F. and Arcos, J.C. Carcinogenicity of Organophosphorous Pesticides/Compounds: An analysis of their Structure Activity Relationships. Environ. Carcino. & Ecotox. Revs. C14(1), 1-42, 1996.

Lai, D.Y., Woo, Y,-T., Argus, M.F. and Arcos, J.C.: Cancer Risk Reduction Through Mechanism-based Molecular Design of Chemicals. In:"Designing Safer Chemicals" (S. DeVito and R. Garrett, eds.), American Chemical Society Symposium series No. 640, Am. Chem. Soc. Washington, DC. Chp 3, pp.62-73, 1996.

Woo, Y.-T. et al.: Mechanism-Based Structure-Activity Relationship Analysis of Carcinogenic Potential of 30 NTP Test Chemicals. Environ. Carcino. & Ecotox. Revs. C15(2), 139-160, 1997.

Major References (Cont.)

Woo, Y., Lai, D., Argus, M.F., and Arcos, J.C.: An Integrative Approach of Combining Mechanistically Complementary Short-term Predictive Tests as a Basis for Assessing the Carcinogenic Potential of Chemicals. Environ. Carcino. & Ecotoxicol. Revs. C16(2), 101-122, 1998.

Woo, Y.-T., and Lai, D.Y. : Mechanism of Action of Chemical Carcinogens and their Role in Structure Activity Relationships (SAR) Analysis and Risk Assessment. In: *Quantitative Structure-Activity Relationship (QSAR) Models of Mutagens and Carcinogens.* R. Benigni, ed., CRC Press, Boca Raton, FL., pp. 41-80, 2003

Benigni, R., and Zito, R.: The second NTP comparative exercise on the prediction of rodent carcinogenicity: definitive results. Mutatation Research 566, 49-63, 2004