

OncoLogic - A Computer System to Evaluate the Carcinogenic Potential of Chemicals

Abstract

Since the inception of section 5 (Premanufacturing/Premarketing Notification, PMN) of the Toxic Substances Control Act (TSCA), structure-activity relationship (SAR) analysis has been effectively used in assessing the carcinogenic potential of chemicals for which test data are not available. To capture the expertise of the Structure Activity Team, the Agency started a collaborative project with LogiChem, Inc. to develop a knowledge rule-based expert system, the OncoLogic system, to predict the carcinogenic potential of chemicals. The unique features and the overall structure of the OncoLogic system and its predictive capabilities and usefulness in molecular design of safer chemicals are described. The utility of the system as a predictive tool in other programs will also be discussed.

[The views expressed in this paper are solely those of the authors and do not necessarily reflect those of the Agency. Mention of trade-names, commercial products or organization does not imply endorsement by the U.S. Government.]

**“Onco-Logic”
A Computer System to Evaluate the
Carcinogenic Potential of Chemicals**

A Cooperative Project Between:

U.S. EPA

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and

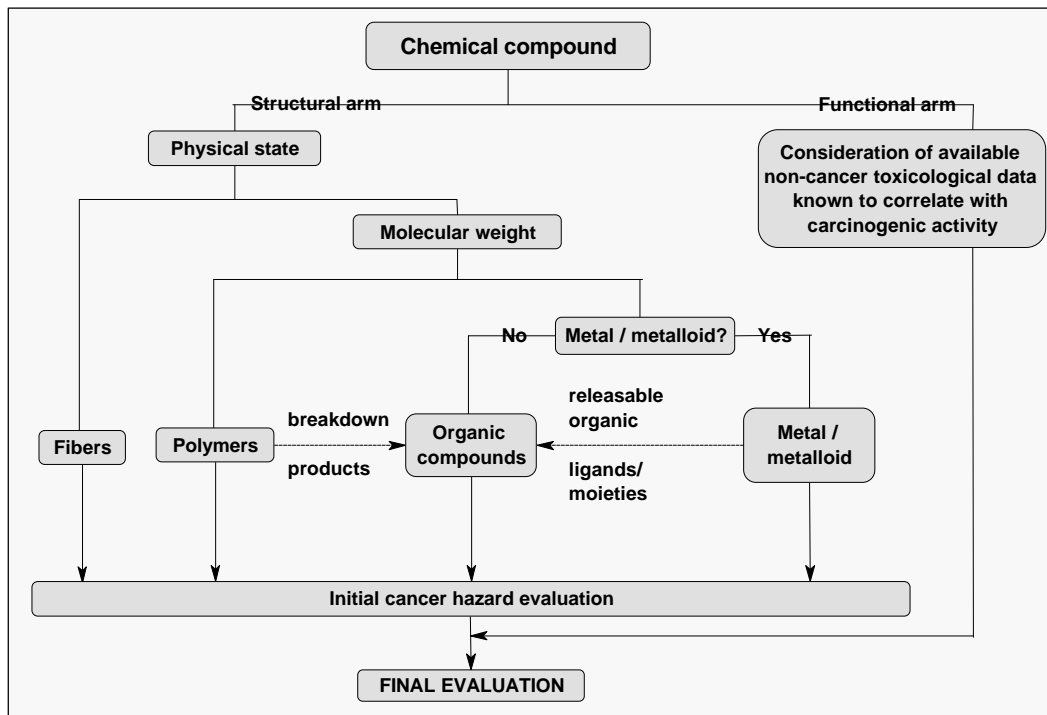
LogiChem, Inc.

Dr. Marilyn Arnott et al.

Some Unique Features of OncoLogic® System

- ✓ Developed using state-of-the-art expert system technology based on "knowledge rules" which represent formalized/codified and organized knowledge of structure-activity relationships of chemical carcinogens.
- ✓ Flexible infrastructure to allow inclusion of virtually all types (e.g., fibers, polymer) of chemical compounds and substances. Methods of evaluation are structural class-specific to maximize accuracy.
- ✓ Input includes consideration of all aspects critical to evaluation of carcinogenic potential including information not provided or not readily obvious from the chemical structure alone (e.g, physicochemical properties, route of exposure, chemical stability, etc.).
- ✓ Output includes prediction/evaluation of concern levels of carcinogenic potential along with underlying scientific rationale. Six concern levels are used: Low (L), Marginal (mar), Low-Moderate (LM), Moderate (M), High-Moderate (HM), High (H).

Overall Structure of OncoLogic Computer System



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
E = Equivocal 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

Molecular Design of Aromatic Amine Dyes with Lower Carcinogenic Potential

	Approach	Rationale
1	Introduce bulky substituent(s) <u>ortho</u> to amino / amine-generating group(s).	Provide steric hinderance to inhibit bioactivation.
2	Introduce bulky N-substituent(s) to amino / amine-generating group(s).	Make it a poor substrate for the bioactivation enzymes.
3	Introduce bulky groups <u>ortho</u> to intercylic linkages.	Distort the planarity of the molecule making it less accessible and a poorer substrate for the bioactivation enzymes.
4	Alter position of amino / amine-generating group(s) in the aromatic ring(s).	<ul style="list-style-type: none"> a. Distort the planarity of the molecule making it less accessible and a poorer substrate for the bioactivation enzymes. b. Reduce length of conjugation path and thus the force of conjugation, which facilitates departure of acyloxy anion. c. Non-linear conjugation path; less resonance stabilization of electrophilic nitrenium ion.
5	Replace electron-conducting intercylic linkages by electron-insulating intercylic linkages.	<ul style="list-style-type: none"> a. Reduce length of conjugation path and thus the force of conjugation, which facilitates departure of acyloxy anion. b. Less resonance stabilization of electrophilic nitrenium ion.
6	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.

Major References on OncoLogic®

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