OncoLogic to Estimate Potential Carcinogenicity

What Does the OncoLogic Model Do?

OncoLogic estimates the potential for a chemical to cause cancer in humans using the known carcinogenicity of chemicals with similar chemical structures, information on mechanisms of action, short-term predictive tests, epidemiological studies, and expert judgment. OncoLogic can tell the risk assessor the potential for the chemical to cause cancer in humans (carcinogenicity) and help the assessor determine if further testing of the chemical (bioassays) may be advisable**.**

How are the model predictions useful in risk assessment?

An understanding of the potential for the chemical to cause cancer helps the risk assessor estimate the impact of the release of that chemical on the surrounding human population.

Inputs

- Class of chemical (fiber, polymer, metal, or organic compound)
- Chemical structure
- Functional groups present
- Additional properties listed in Flow Diagrams for each module.

Outputs

- Summary of predicted concern level (high to low)
- Line of reasoning for estimation

Important Notes

OncoLogic users need: Good understanding of organic chemistry; Chemical class of the compound; Certain physical and chemical properties of the compound

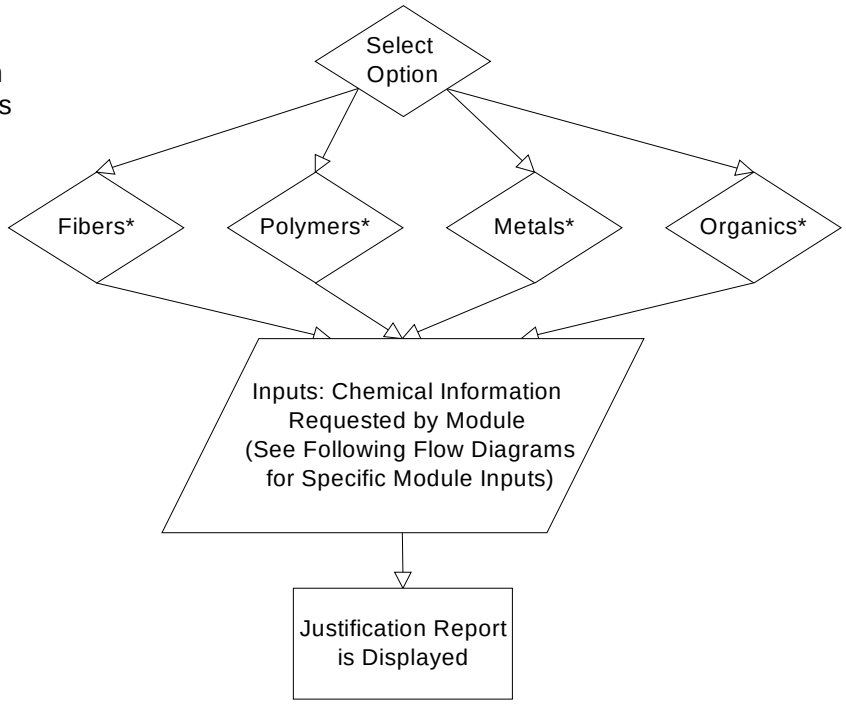
OncoLogic has modules to estimate carcinogenicity of 4 types of compounds: (1) Fibers, (2) Metals, (3) Polymers, and (4) Organics

Where Can I Get OncoLogic?

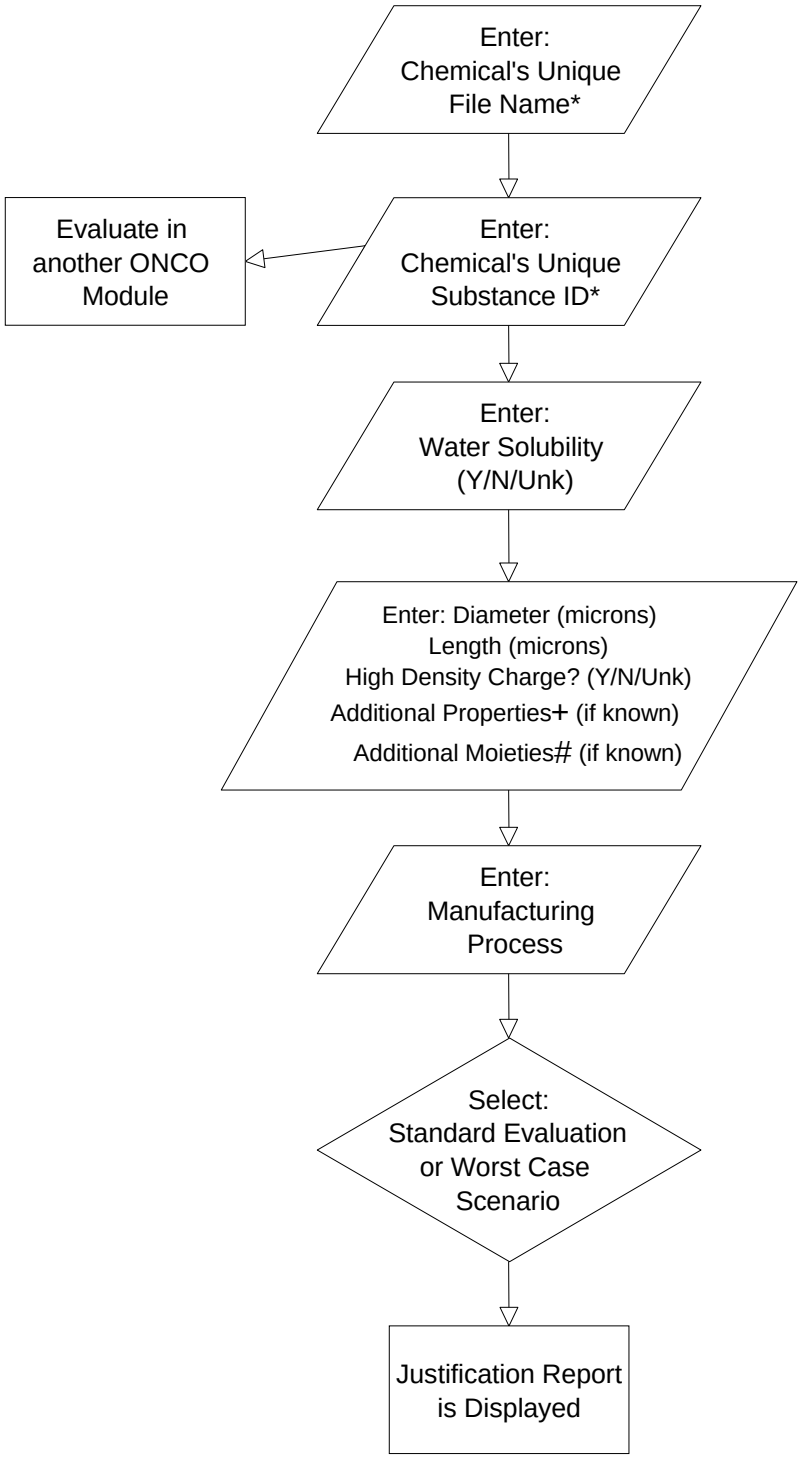
OncoLogic is being made publicly available by the Agency, and it will be downloadable from the Sustainable Futures web site.

Using OncoLogic

Shown on the right is a Flow Diagram for OncoLogic. Each of the 4 modules shown has a detailed flow diagram which is presented on the following pages.



OncoLogic Model Flow Diagram - Fibers



Inputs Needed for Fibers Evaluation:

Water solubility (yes/no)

Diameter (microns)

Length (microns)

Additional Inputs Needed for Refining the Evaluation Are:

Presence of electrical charge

Properties

- Flexibility
- Durability
- In vivo biodegradability
- Surface characteristics
- Splitting properties

Moieties

- High molecular weight polymer
- Low molecular weight organic moiety
- Metals or metalloids

Manufacturing process

Use scenario

*NOTE: The chemical's file name and substance ID are unique names that the user enters. The chemical's file name is limited to 8 characters. The program will take up to 240 characters for the chemical's substance ID.

Sample Output from OncoLogic Fibers Justification Report

INPUTS:

Chemical file name	=	Fiber1	High density charge	=	Unk
Substance Id	=	Fiber1			
Additional properties:					
Water soluble	=	No	Durability		√
Diameter	=	0.1 - 0.5 microns			
Moieties	=	none	Median(s)	=	0
Manufacturing process	=	Crystallization	Length	=	1 - 3 microns
Scenario evaluation	=	Standard	Aspect ratio	=	0

Justification Report is saved in ONCO dir. as ASCII file as "Chemical file name.JST"

RESULTS:

SUMMARY:

Code Number: Fiber1

Substance Id: Fiber1

The final level of this fiber-type substance is HIGH.

JUSTIFICATION:

STANDARD EVALUATION

The unifying concept of fiber carcinogenisis 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.

The STANDARD evaluation is the accepted method for determining the *carcinogenic* potential of a fiber. It is based on the median diameter and length. The distribution of dimensions is assumed to be uniform. When a range is entered, the program calculates the median as the average of the high and low values.

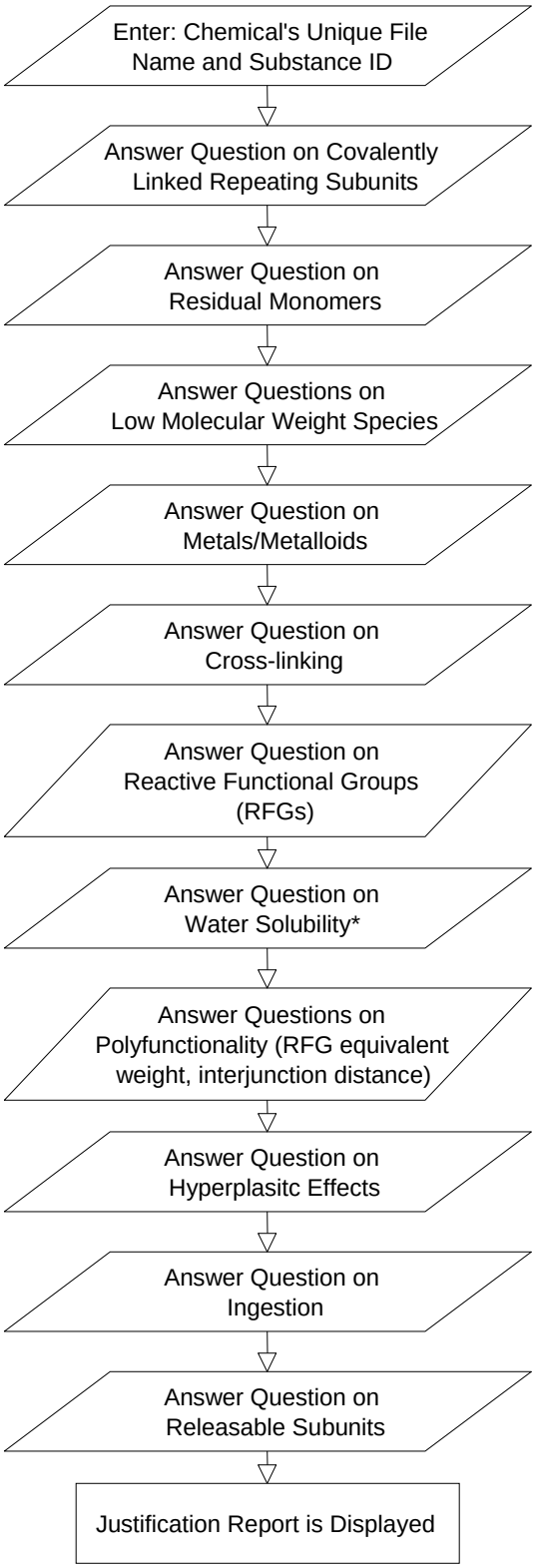
Since the diameter of the fiber is equal to or greater than 0.25 microns and less than 1.5 microns, and its aspect ratio is greater than 5 and not more than 32, the initial level of concern for *carcinogenic* potential of this fiber is MODERATE.

Naturally occurring fibers and synthetic fibers that are manufactured through a crystallization process are assumed to have strong electron donor/basic sites on their surface, since these conditions provide time for orderly build-up of surface structure. This increases the level of concern to HIGH-MODERATE.

The fiber exhibits the following property or properties: durability. 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 final level of concern is increased by only one step to HIGH.

The final concern for this fiber-type substance is HIGH.

OncoLogic Model Flow Diagram - Polymers



Inputs Needed for Polymers Evaluation:

Molecular weight

Water solubility and behavior in water

Polyfunctional behavior

Hyperplastic effects

Possible Ingestion

Information on chemical structure/properties, including presence of:

- Covalently-linked units
- Residual monomer
- Residual functional groups
- Low molecular weight species
- Metals or metalloids
- Cross-linkages
- Reactive functional groups
- Internal releasable subunits
- Terminal/pendant releasable subunits

***If water solubility is in ppm, convert to percent by dividing the number by 10,000. If water solubility is unknown, enter 0.

Sample Output from OncoLogic Polymers Justification Report

INPUTS:

Chemical file name	=	Polymer1
Substance Id	=	Polymer substance A
Molecular weight	=	1,100
Covalently linked units	=	Yes
Residual monomers >2%	=	No
Low MW species (<500) present	=	Yes
Polymer reactive functional groups (RFGs)	=	Yes
RFGs present	=	Oxygen
Oxygen RFG	=	Epoxide (unsubstituted)
Additional RFGs present	=	No
Metals/Metalloids present	=	No
Crosslinkages present	=	No
Polymer RFGs present	=	Yes
Identify Polymer RFG	=	Oxygen
Oxygen RFG	=	Epoxide (unsubstituted)
Additional RFGs present	=	No
Water solubility as percent weight	=	0.2
Polyfunctional	=	Yes
Functional groups equivalent. wt.	=	550
Interjunction distance	=	Yes
Hyperplastic effects	=	No
Absorption into soft tissue	=	Unknown
Ingestion possible	=	Yes
Internal release subunits	=	No
Terminal pendant subunits	=	No

Justification Report is saved in ONCO directory as ASCII file as “Chemical file name.JST”

RESULTS:

SUMMARY:

CODE NUMBER: 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 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.

Continued on next page

Sample Output from OncoLogic Polymers Justification Report

Continued from previous page

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.

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).

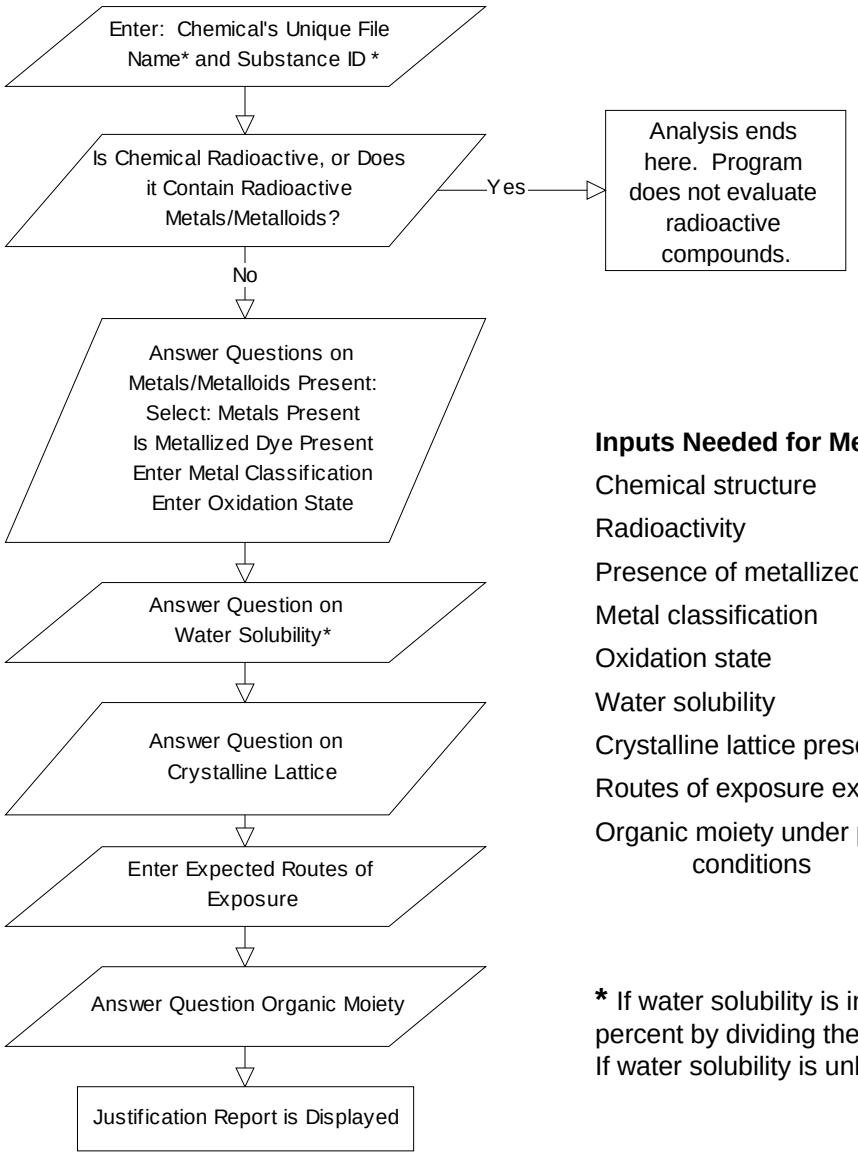
Since this polymer has been demonstrated not to cause (or is not known to have caused) inflammatory and/or hyperplastic changes, *carcinogenicity* concerns arising from these pathophysiological changes can be eliminated.

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 5,000. 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.

OncoLogic Model Flow Diagram - Metals



Inputs Needed for Metals Evaluation:

Chemical structure

Radioactivity

Presence of metallized dye or pigment

Metal classification

Oxidation state

Water solubility

Crystalline lattice present?

Routes of exposure expected

Organic moiety under physiological conditions

***** If water solubility is in ppm, convert to percent by dividing the number by 10,000 If water solubility is unknown, enter 0.

Sample Output from OncoLogic Metals Justification Report

INPUTS:

Chemical file name	=	Crystal	Oxidation state	=	Hexavalent
Substance Id	=	Crystal	Water solubility	=	Sparingly soluble
Radioactivity	=	No	Crystalline lattice	=	Yes
Metals present	=	Cr and Zr	Route of exposure	=	Inhalation
Metallized dye or pigment	=	No	Organic *moiety*	=	No
Metal classification	=	Inorganic or other comp.			

Justification Report is saved in ONCO directory as ASCII file as “Chemical file name.JST”

RESULTS:

Code Number: crystal
Substance Id: crystal

SUMMARY:

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.

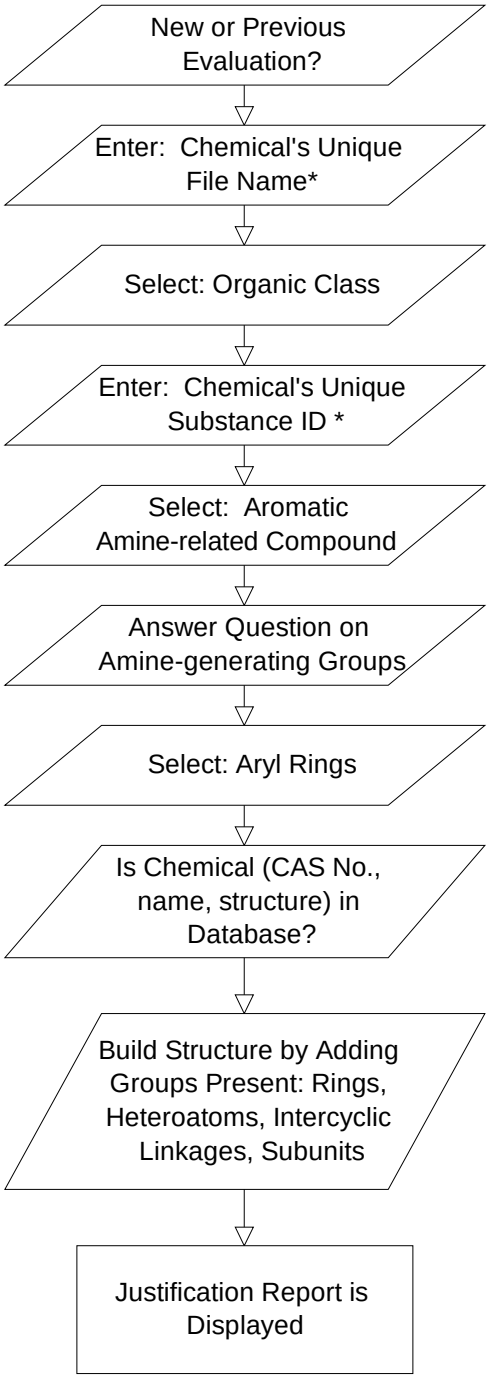
In general, virtually all Cr-containing compounds are of some *carcinogenicity* concern unless they can be clearly shown to be not bioavailable. Exposure to these compounds by inhalation or injection is of greater concern than exposure by the oral or dermal route.

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.

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.

OncoLogic Model Flow Diagram - Organics



Inputs Needed for Organics Evaluation:

Organic chemical class

CAS number/Chemical name (if listed)

Molecular structure, including presence of:

- Rings
- Functional groups
- Linkages
- Substituents

NOTE:
*The chemical's file name and substance ID are unique names that the user enters. The chemical's file name is limited to 8 characters. The program will take up to 240 characters for the chemical's substance ID.

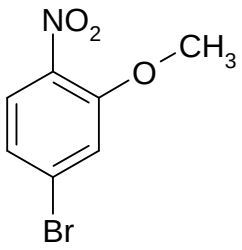
Sample Output from OncoLogic Organics Justification Report

INPUTS:

Chemical file name = Amine1
Organic class = Aromatic amine
Substance Id = Aromatic amine#1
Aromatic-related compound class = None
Amine-generating group = Yes
Aryl rings selected:
  6-member rings = 1
  Heteroatoms = No
Answers are correct

Structure building:
Select:
- Build
- Add
- Substituents
- Alkoxy (-OCH_3)
- Amine-generating group (NO_3)
- Other (Br)

RESULTS:



Justification Report is saved in ONCO directory as ASCII file as “Chemical file name.JST”

SUMMARY

Code Number: Amine1 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 is determined by considering the number or 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.