OncoLogic 9.0

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OncoLogic 9 User Manual

1. OncoLogic 8.0 Recollection

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, 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

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2. OncoLogic 9.0 standalone application

The migration of OncoLogic 8.0 to OncoLogic 9.0 is initiated as part of the Framework contract concerning the development of the OECD QSAR Toolbox.

OncoLogic 9.0 is a standalone system based on the current version of OncoLogic 8.0. The application is written in C# language for .NET platform. The migration of the knowledge from Oncologic 8.0 to Oncologic 9.0 included transfer of thousands of lines of source code and developing of a new software platform.
The new system allows user to define the target chemical by: CAS number; Chemical name; SMILES or by drawing the chemical structure in 2D editor. The system identifies the chemical classes to which target chemical belongs and then applies the respective oncologic decision tree logic to produce results for each of the identified classes.

The main steps of the migration of the knowledge from Oncologic 8.0 to Oncologic 9.0 are:

- Building of a new software platform (Oncologic 9.0) with all functionalities that are needed for the final prediction;
- Migration of 33 chemical classes from (see section 3. Target chemical classes).

Note: Oncologic 9.0 is foreseen to be implemented in OECD QSAR Toolbox as a part of the future developments of the system. The knowledge and rules of Oncologic 9.0 could be used as a profiling tool, as a categorization tool for finding analogues and as a SAR model for prediction purposes.

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3. Target chemical classes

3.1 Acylating agents

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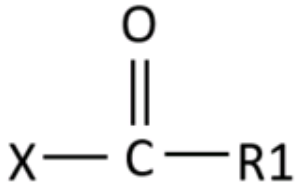
3.1.1 Acyl and Benzoyl Halides

Introduction

Acyl or benzoyl halides are reactive chemicals which may acylate critical macromolecules to exert carcinogenic action. Very few acylating agents have been adequately tested for carcinogenic activity. The most notable carcinogenic acylating agent is N,N-dimethylcarbamyl chloride. In view of the high tendency of acylating agents to be hydrolyzed, their potential activity is expected to be limited to the immediate vicinity of the point of contact. In general, low molecular weight, volatile acylating agents are of higher concern, particularly if the expected route of exposure is by inhalation.

Skeleton templates



R1: Alkyl (Cn), aryl (phenyl, benzyl, phenylethyl).

X: Halogens: F, Cl, Br, I.

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.

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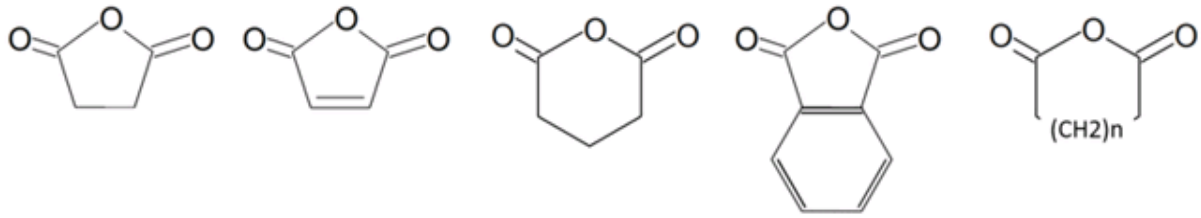
3.1.2 Anhydrides

Introduction

Anhydrides are reactive chemicals which may acylate critical macromolecules to exert carcinogenic action. Very few acylating agents have been adequately tested for carcinogenic activity. The most notable carcinogenic acylating agent is N,N-dimethylcarbamyl chloride. In view of the high tendency of acylating agents to be hydrolyzed, their potential activity is expected to be limited to the immediate vicinity of the point of contact. In general, low molecular weight, volitile acylating agents are of higher concern, particularly if the expected route of exposure is inhalation.

Skeleton templates



Ring substituents:

Ring substituents that may be added to the ring carbons:

- alkyl groups (Cn)
- halogens (Cl, Br, I, F)
- hydroxyl (OH)
- carboxylic acid (COOH)
- sulfonic acid (SO3H).

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

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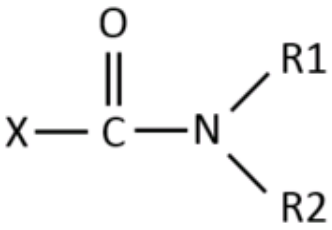
3.1.3 Carbamyl Halides

Introduction

Carbamyl halides are reactive chemicals which may acylate critical macromolecules to exert carcinogenic action. Very few acylating agents have been adequately tested for carcinogenic activity.The most notable carcinogenic acylating agent is N,N-dimethylcarbamyl chloride. In view of the high tendency of acylating agents to be hydrolyzed, their potential activity is expected to be limited to the immediate vicinity of the point of contact. In general, low molecular weight, volatile acylating agents are of higher concern, particularly if the expected route of exposure is by inhalation.

Skeleton templates



R1, R2: Alkyl (Cn), aryl (phenyl, benzyl, phenyl-ethyl), hydrogen atom, other.

X: Halogens: F, Cl, Br, I.

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.

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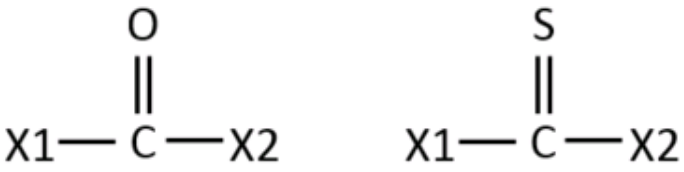
3.1.4 Phosgene-type Compounds

Introduction

Phosgene and related compounds are direct-acting acylating agents that do not require metabolic transformation to exert their carcinogenic action.

Skeleton templates



X1, X2: Halogens: F, Cl, Br, I.

Substituents: None.

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

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3.2 Aromatic amines

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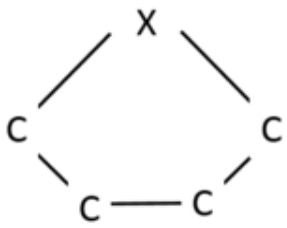
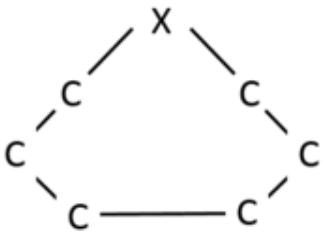
3.2.1 5-membered or 7-membered heterocyclic rings

Introduction

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

Skeleton templates





Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

Heteroatoms:

The heteroatom can be one of the following atoms:

- N or N-R;
- O;
- S;
- P or P-R;
- As or As-R;
- Se;
- Si;
- Z;
- non of the above, but with free orbital electrons so as to be able to contribute to aromaticity.

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.

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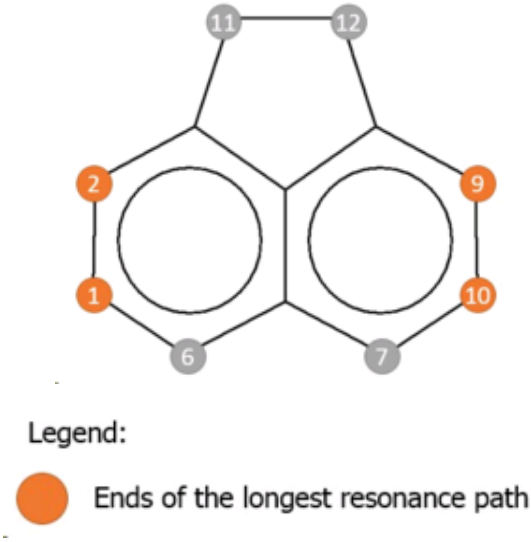
3.2.2 Acenaphthene-type compounds

Introduction

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

Skeleton templates



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- N=C=O
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- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: -C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

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3.2.3 Anthracene-type compounds

Introduction

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

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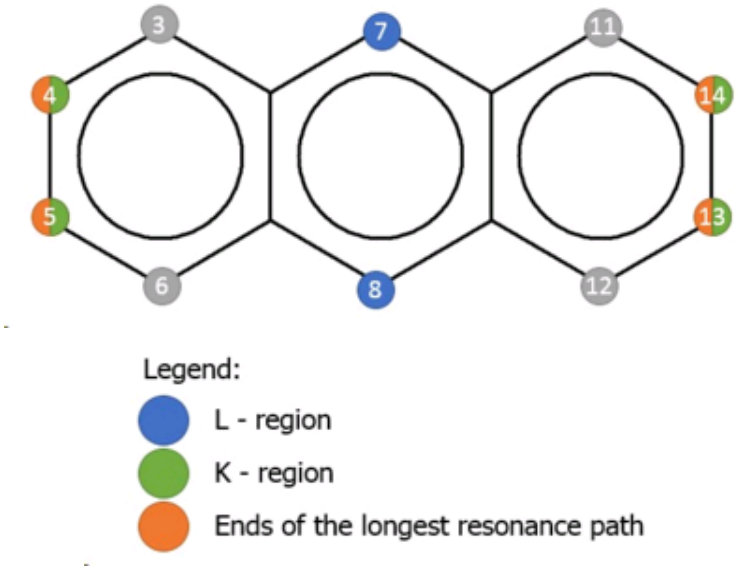

Amino and Amine generating groups:

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- NO2
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- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

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3.2.4 Fluorene-type compounds

Introduction

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

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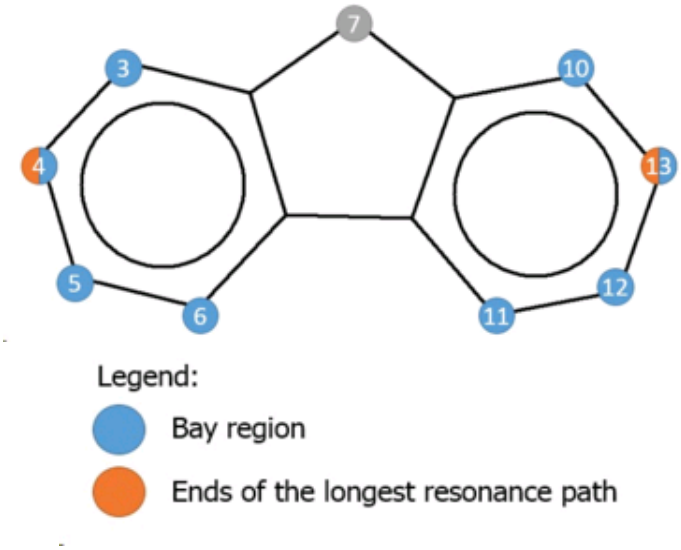

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- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3

(n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.

- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

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3.2.5 Four, five and six membered non-linear fused aromatic systems (-type compound)

Introduction

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

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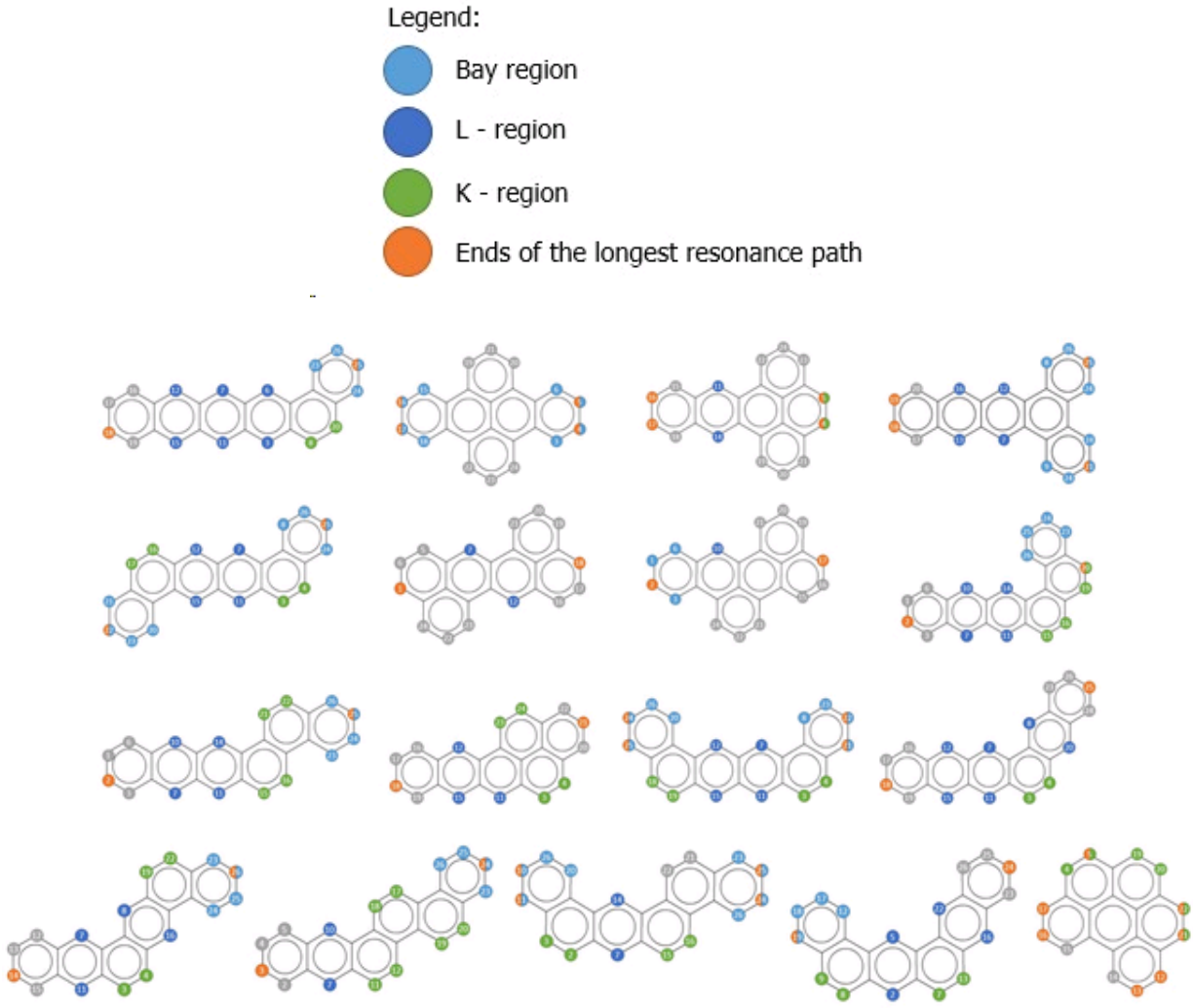

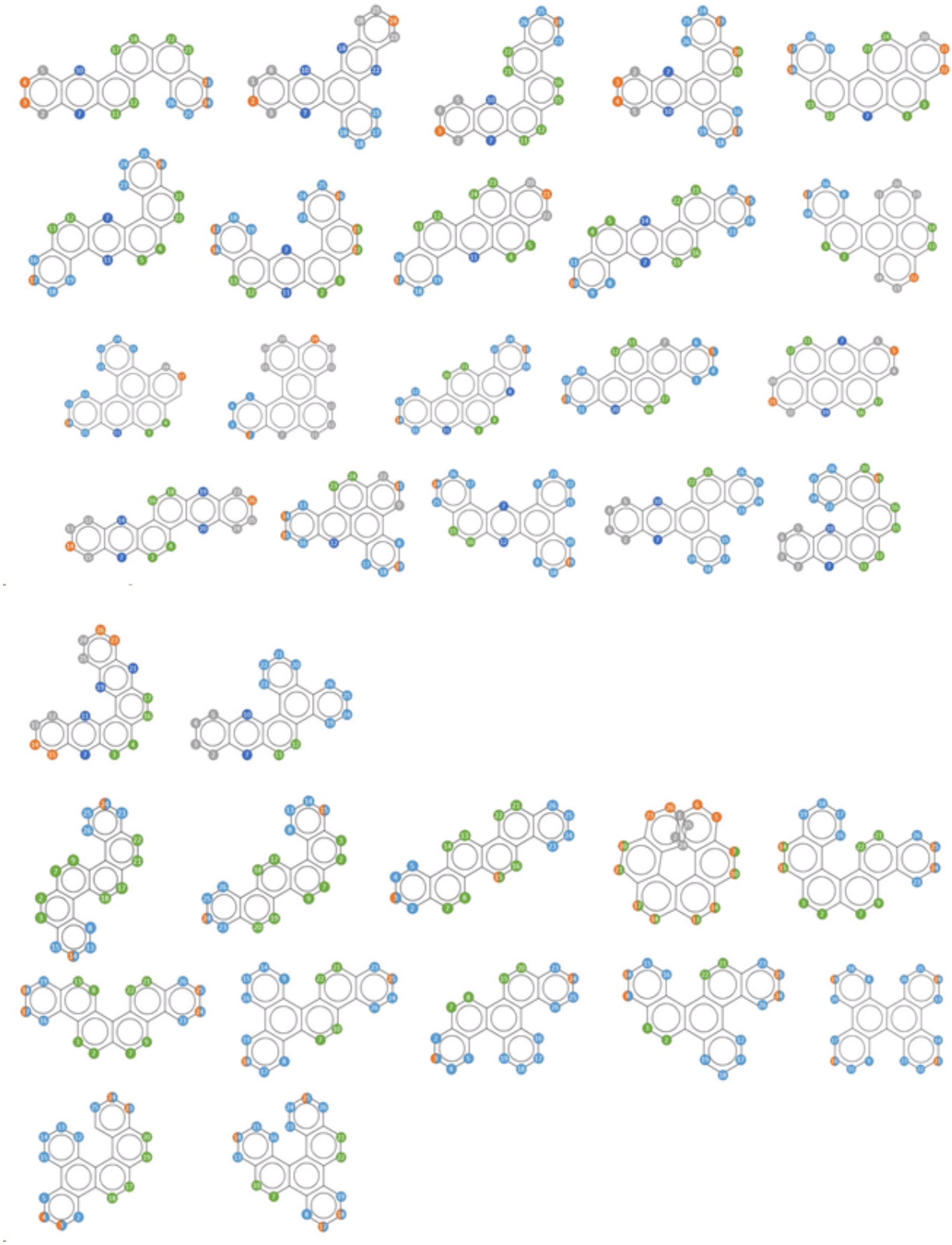

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- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

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3.2.6 Naphthacene-, pentacene- and hexacene-type compounds

Introduction

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

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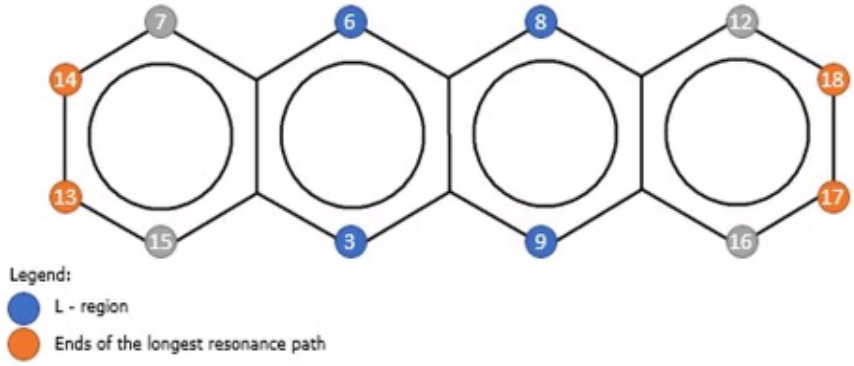

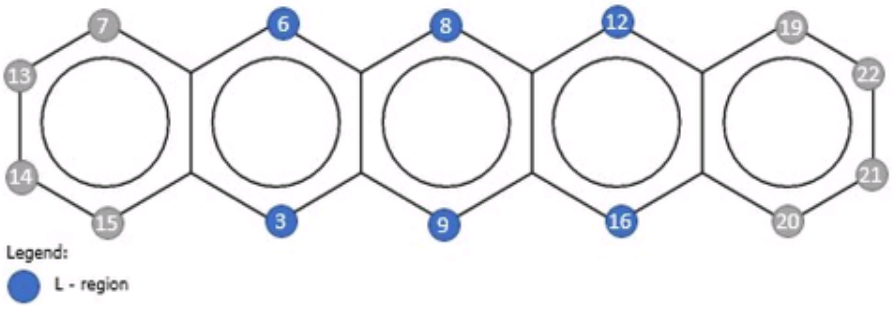

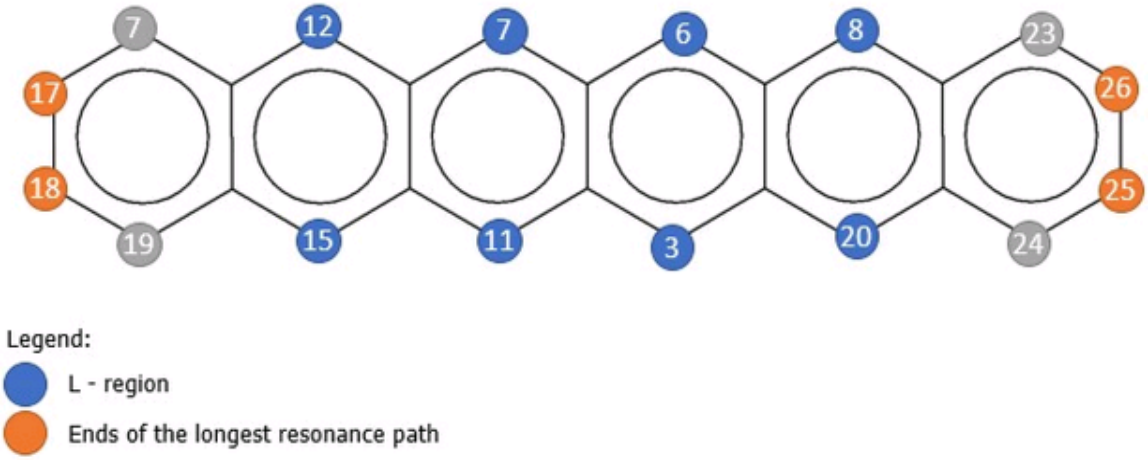

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Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO

- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

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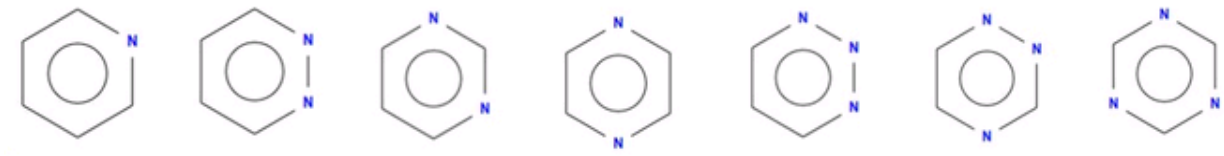
3.2.7 One 6-membered ring with 1 to 3 nitrogen heteroatoms

Introduction

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

Skeleton templates



Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

-o-

3.2.8 One benzene ring and one amino group

Introduction

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

Skeleton templates

Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: -

C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).

- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

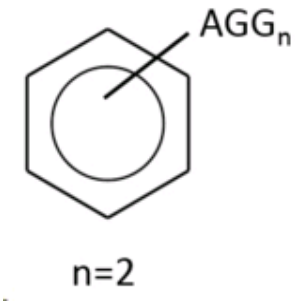
-o-

3.2.9 One benzene ring and two amino groups

Introduction

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

Skeleton templates



Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).

- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

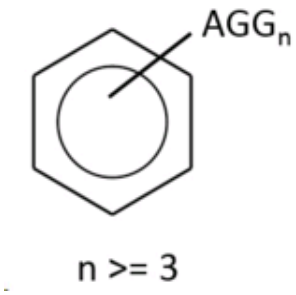
-o-

3.2.10 One benzene ring with more than two amino groups

Introduction

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

Skeleton templates



Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).

- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

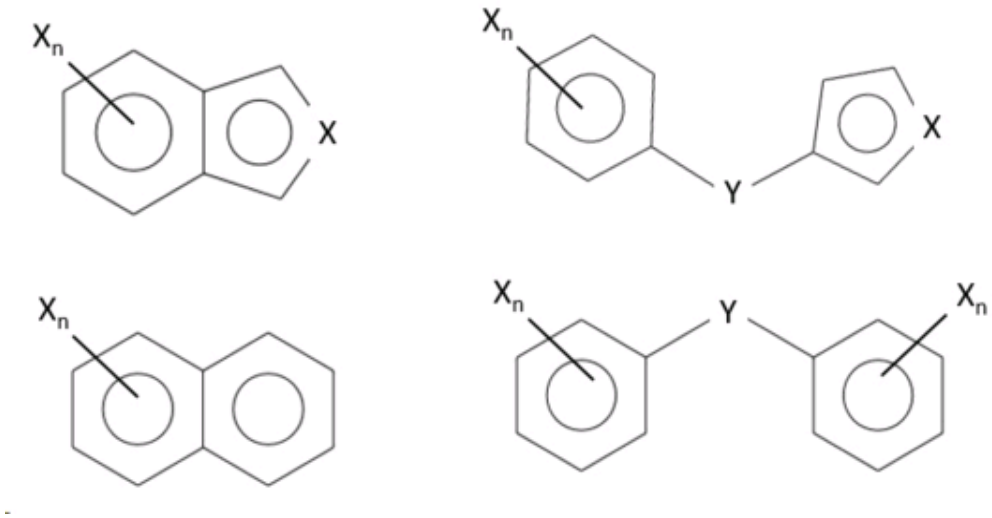
-o-

3.2.11 Pair of fused or linked 6 and(or) 5-membered heterocyclics

Introduction

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

Skeleton templates



Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O

- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

Linkages

The linkage, designed by “Y” may be defined with one of the following linkages:

- direct link;
- Oxygen (O);
- Sulphur (S);
- NH;
- CH2;

- N=CH;
- N=N;
- =N;
- =CH;
- (C C)n;
- (C=C)n;
- (CH2)n;
- C(=O);
- S(=O);
- S=O(=O);
- NHC(=O)NH;
- C(=O)NH;
- C(=O)CH=CH;
- C(CH3)CH3.

Heteratoms

The heteroatom atom can be one of the following atoms:

- N-H;
- O;
- S;
- N.

There may be more than one nitrogen atom placed within the 6-memmeberd ring. The number and position of the heteroatoms vary but are limited to maintain the aromaticity of the structure.

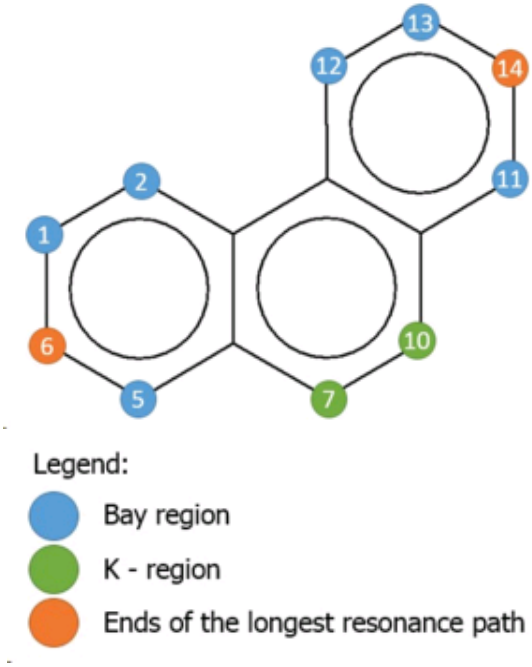
-o-

3.2.12 Phenanthrene-type compounds

Introduction

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

Skeleton templates



Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C

- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

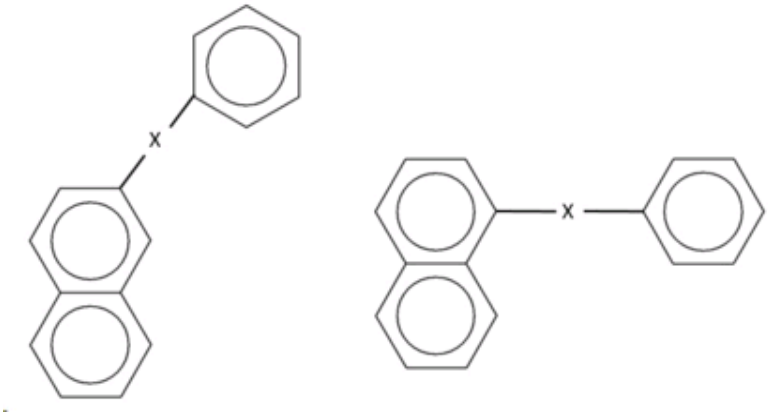
-o-

3.2.13 Phenyl-naphthyl-type

Introduction

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

Skeleton templates



Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on

the R groups.

- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: -C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

Linkages

The linkage, designed by “Y” may be defined with one of the following linkages:

- direct link;
- Oxygen (O);
- Sulphur (S);
- NH;
- CH2;
- N=CH;

- N=N;
- =N;
- =CH;
- (C C)n;
- (C=C)n;
- (CH2)n;
- C(=O);
- S(=O);
- S=O(=O);
- NHC(=O)NH;
- C(=O)NH;
- C(=O)CH=CH;
- C(CH3)CH3.

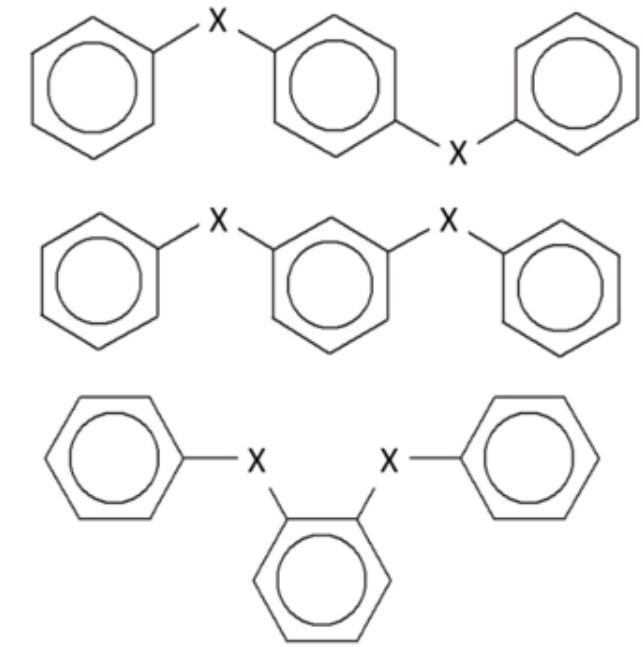
-o-

3.2.14 Terphenyl-type compounds

Introduction

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

Skeleton templates



Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C

- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

Linkages

The linkage, designed by “Y” may be defined with one of the following linkages:

- direct link;
- Oxygen (O);
- Sulphur (S);

- NH;
- CH2;
- N=CH;
- N=N;
- =N;
- =CH;
- (C C)n;
- (C=C)n;
- (CH2)n;
- C(=O);
- S(=O);
- S=O(=O);
- NHC(=O)NH;
- C(=O)NH;
- C(=O)CH=CH;
- C(CH3)CH3.

Heteratoms

The heteroatom atom can be one of the following atoms:

- N-H;
- O;
- S;
- N.

There may be more than one nitrogen atom placed within the 6-memmeberd ring. The number and position of the heteroatoms vary but are limited to maintain the aromaticity of the structure.

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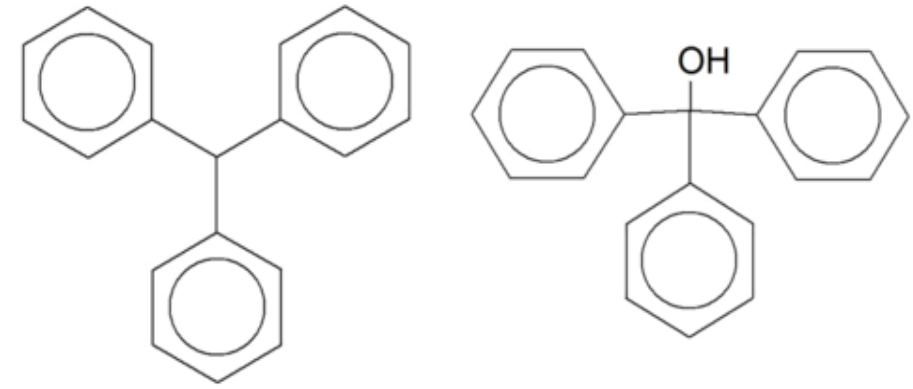
3.2.15 Triphenylmethane-type compounds

Introduction

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

Skeleton templates



Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on

the R groups.

- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: -C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).
- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

-o-

3.2.16 Two 6-membered fused or linked homocyclic rings

Introduction

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

Skeleton templates

Amino and Amine generating groups:

Amino and Amine generating groups (AGG):

- NH2
- NO2
- NO
- NHOH
- N=C
- N=CHR
- N=C=O
- NR1(OR2), where R1: -H; -CH3; -C2H5; Cn (n > 3); - C(=O)(CH2)nCH3 (n >= 0). R2: -SO3H; - C(=O)(CH2)nCH3 (n >= 0). No substituents on the R groups.
- NR1COR2, where R1: -H; -CH3; -C2H5; Cn (n > 3); R2: - C(=O)(CH2)nCH3; - C(=O)(CH2)nAr (n >= 0).

- NR1R2, where R1/ R2: -H; -CH3; -C2H5; Cn (n > 3); -CN; -CH2CH2CN; -COOH; -SO3H; -(CH2)nAr (n >= 1); -CH=(CH2)nH; -C (CH2)nH.

At least one AGG must be placed on the ring system.

Substituents:

The substituents may include:

- carboxylic acid (COOH)
- sulfonic acid (SO3H)
- halogens (Cl, Br, I, F)
- cyano (CN)
- hydroxyl (OH)
- aldehyde (CHO)
- carbamoyl (C(O)NR2)
- carboxymethyl (COOCH3)
- alkyl
- hydroxyalkyl
- alkoxy
- other

Linkages

The linkage, designed by “Y” may be defined with one of the following linkages:

- direct link;
- Oxygen (O);
- Sulphur (S);
- NH;
- CH2;
- N=CH;
- N=N;
- =N;
- =CH;

- (C C)n;
- (C=C)n;
- (CH2)n;
- C(=O);
- S(=O);
- S=O(=O);
- NHC(=O)NH;
- C(=O)NH;
- C(=O)CH=CH;
- C(CH3)CH3.

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3.3 Carbamates and thiocarbamates

-o-

3.3.1 Carbamates

Introduction

Carbamates represent an important class of chemical carcinogens.

From studies on urethan (ethyl carbamate) and its analogs, some structural features that favor carcinogenicity of carbamates can be discerned. They are:

(a) a small alkyl group at the carboxy end;

(b) a 1,1-diaryl-2-acetylenic moiety at the carboxy end; the aryl and acetylenic moieties are probably involved in stabilizing the carbonium ion which would arise after departure of the carbamoyloxy moiety;

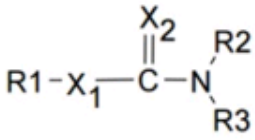
(c) N-substitution with a good leaving group such as an acyloxy group.

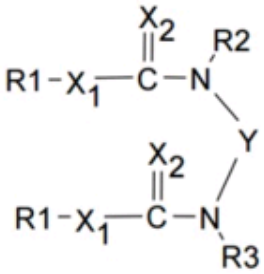
In contrast,N,N-Disubstitution or substitution with bulky groups generally decreases carcinogenicity. Thus, the three potential electrophilic sites in carbamates - the alkyl group at the carboxy end, the carbamoyl group, and the amino group - are among the major factors considered in the evaluation of the carcinogenic potential of carbamates.

Substitution of one or both oxygen atoms of carbamates with sulfur gives rise to thiocarbamates or dithiocarbamates, which in general are of somewhat lesser concern than the corresponding carbamates based on structure-activity relationships (SAR) analysis. For dithiocarbamates, some of their biological activities may be due to the release of carbon disulfide, which is a suspect carcinogen.

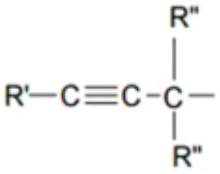
Skeleton templates

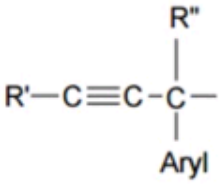
Two basic skeletons:

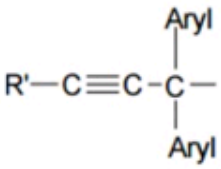


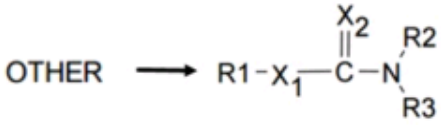


Acetylenic R1 skeletons:









R1: The acetylenic R group (R1) may contain one of the acetylenic R1 skeletons.

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

X1, X2: Oxygen or Sulfur atoms.

Substituents: The substituents may include:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- sulfonate (SO3),
- acyloxy (O(O)CCn).

Y: To define the linkage for dicarbamates, one of the following four groups

could be used:

- -CH2-
- -CHCH3
- -(CH2)2-
- Other.

-o-

3.3.2 Thiocarbamates

Introduction

Carbamates represent an important class of chemical carcinogens.

From studies on urethan (ethyl carbamate) and its analogs, some structural features that favor carcinogenicity of carbamates can be discerned. They are:

(a) a small alkyl group at the carboxy end;

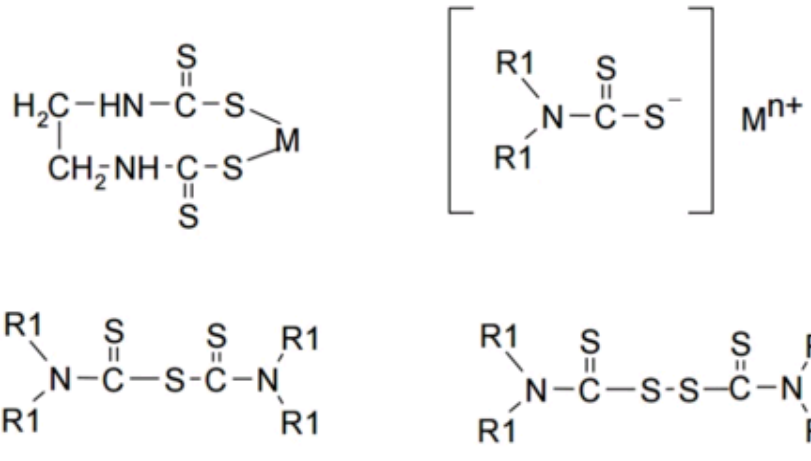
(b) a 1,1-diaryl-2-acetylenic moiety at the carboxy end; the aryl and acetylenic moieties are probably involved in stabilizing the carbonium ion which would arise after departure of the carbamoyloxy moiety;

(c) N-substitution with a good leaving group such as an acyloxy group.

In contrast,N,N-Disubstitution or substitution with bulky groups generally decreases carcinogenicity. Thus, the three potential electrophilic sites in carbamates - the alkyl group at the carboxy end, the carbamoyl group, and the amino group - are among the major factors considered in the evaluation of the carcinogenic potential of carbamates.

Substitution of one or both oxygen atoms of carbamates with sulfur gives rise to thiocarbamates or dithiocarbamates, which in general are of somewhat lesser concern than the corresponding carbamates based on structure-activity relationships (SAR) analysis. For dithiocarbamates, some of their biological activities may be due to the release of carbon disulfide, which is a suspect carcinogen.

Skeleton templates



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

acetylenic R1 group..

M: Indicates a metal (such as As, Be, Cd, Cr, Ni, Sb or other).

Substituents: The substituents may include:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- sulfonate (SO3),
- acyloxy (O(O)CCn).

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3.4 Coumarins and Furocoumarins

-o-

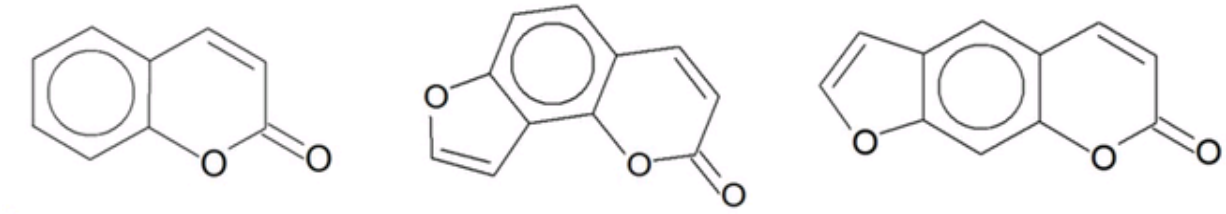
3.4.1 Coumarins and Furocoumarins

Introduction

Coumarin is the basic structure of a variety of naturally occurring substances of plant and microorganism origins. Naturally occurring coumarins possess diverse physiological activities and chemical structures which vary from simple coumarins containing alkyl, alkoxyl, hydroxyl, or other aliphatic side chains to complex coumarins with furanoyl, benzoyl, pyranyl and other substituents.

There is some evidence that coumarin itself is carcinogenic in rats and mice. Limited bioassays have also shown that several simple coumarin derivatives are moderately to weakly carcinogenic in experimental animals. The mechanism(s) of carcinogenic activity of coumarins is not well understood. Some genotoxic activities have been reported for coumarin (including gene mutations in the Ames test, and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells). Based on results from metabolism studies of coumarin, it has been postulated that coumarin epoxide intermediates may be formed and be responsible for its carcinogenic and mutagenic activities.

Skeleton templates



Substituents: The substituents may include:

- alkyl groups (Cn, OCn),
- hydroxyalkyl (CnOH),
- carbamoyl (C(O)NR2),
- cyano (CN),
- acyl halide (Cn(O)X),
- aldehyde (C(O)H),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- halogens (F, Ci, Br, I),

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

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3.5 Diazene and Triazene Compounds

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3.5.1 Aliphatic Azo and Azoxy Compounds

Introduction

Aliphatic azo and azoxy compounds are, in many respects, quite similar to 1,2-dialkyl hydrazines in terms of carcinogenic activity and metabolic activation. Most of the aliphatic azo and azoxy compounds that have been tested are carcinogenic. Factors that are known to iminish or abolish the carcinogenic activity of aliphatic azo and azoxy compounds include:

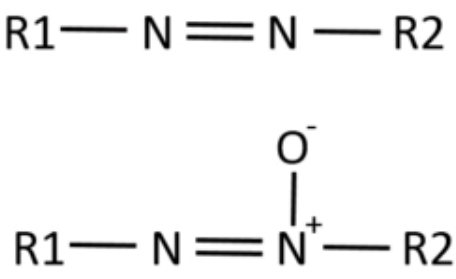
(i) bulky substituents,

(ii) highly hydrophilic substituents, and

(iii) steric hindrance at the alpha-carbon.

Both the nature and the position of the substituent(s) are considered in the overall assessment of the carcinogenic potential of aliphatic azo and azoxy compounds.

Skeleton templates



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

Substituents: The substituents may include:

- 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 (Cn) on alkyl groups.

Comments: Other than a vinyl or an allyl R groups, other unsaturated aliphatic chain can not be drawn..

-o-

3.5.2 Triazenes

Introduction

Aliphatic azo and azoxy compounds are, in many respects, quite similar to 1,2-dialkyl hydrazines in terms of carcinogenic activity and metabolic activation. Most of the aliphatic azo and azoxy compounds that have been tested are carcinogenic. Factors that are known to iminish or abolish the carcinogenic activity of aliphatic azo and azoxy compounds include:

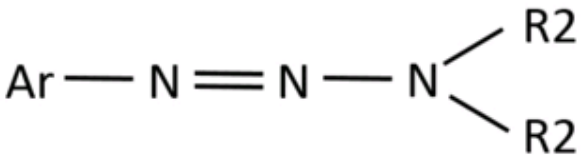
(i) bulky substituents,

(ii) highly hydrophilic substituents, and

(iii) steric hindrance at the alpha-carbon.

Both the nature and the position of the substituent(s) are considered in the overall assessment of the carcinogenic potential of aliphatic azo and azoxy compounds.

Skeleton templates



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

Ar: Ar is an aryl ring, one or two fused. Triazenes with aryl ring systems consisting of more than 2 aromatic rings should be evaluated as PAH chemical class.

Substituents: The substituents may include:

- 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 (Cn) on alkyl groups.

Comments: Other than a vinyl or an allyl R groups, other unsaturated aliphatic chain can not be drawn..

-o-

3.6 Direct-Acting Alkylating Agents

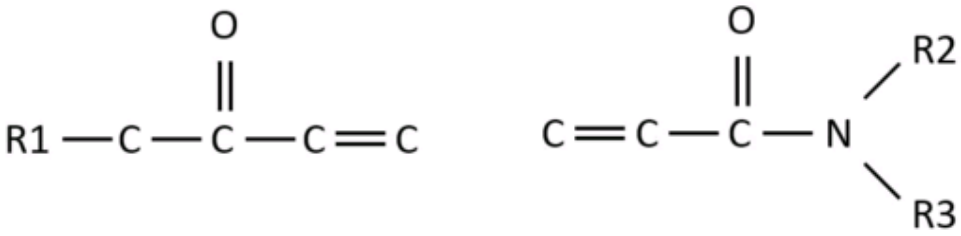
-o-

3.6.1 Acrylates, acrylamides and related compounds

Introduction

The acrylates and the acrylamides are potential alkylating agents which may bind, via Michael addition, to key macromolecules to initiate/exert carcinogenic action. The alkylating activity of acrylates and/ or acrylamides can be substantially inhibited by substitution at the double bond, particularly by bulky or hydrophilic groups. The nature and molecular size/shape of the molecule to which the acrylate (acrylamides) is attached may also play a role in affecting the overall activity of the compound.

Skeleton templates



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

Substituents: The substituents may include:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H).

In addition to these, aryl R group my have vinyl and allyl groups as well as alkyl (Cn) on aromatic rings. The ethylene moiety (C=C) may be substituted with the following:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- cyano (CN),
- Other.

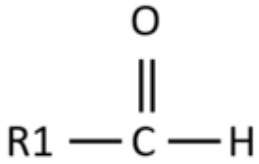
-o-

3.6.2 Aldehydes

Introduction

Aldehydes are reactive electrophilic chemicals which may react with macromolecules or cause crosslinking to initiate carcinogenesis. However, being soft electrophiles, aldehydes tend to react preferentially with cellular nucleophiles such as glutathione before attacking macromolecules. Furthermore, aldehydes can be readily oxidized to acids which are not electrophilic and can be readily excreted. Therefore, the carcinogenic action of aldehydes tends to require relatively high doses and to confine close to the site of administration. In general, the carcinogenic activity of aldehydes decreases with increase in molecular size. Introduction of hydrophilic group(s) is also inhibitory. alpha,beta-Unsaturation generally increases the carcinogenic potential provided that the beta-position is not sterically hindered. Halogenation of the alpha-carbon also increases the carcinogenic potential.

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

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- other.

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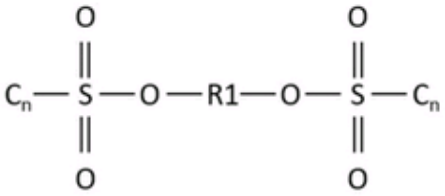
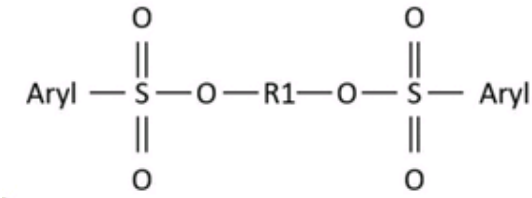
3.6.3 Alkanesulfonoxy Esters

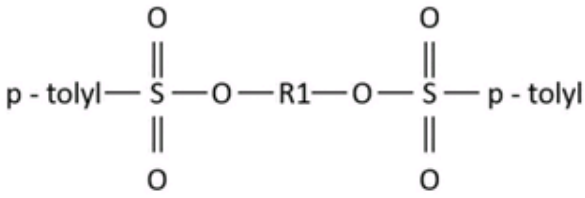
Introduction

Bifunctional alkanesulfonoxy esters, consisting of an alkyl chain capped by two alkanesulfonoxy or arylsulfonoxy groups at both ends, are potential crosslinking agents which may initiate/exert carcinogenic action by causing DNA-DNA or DNA-protein crosslinks. The crosslinking activity is dependent on the nature of the reactive alkane-aryl-sulfonoxy groups and the distance between the two reactive functional groups. In general, p-toluenesulfonoxy and methanesulfonoxy groups are good leaving groups whereas unmethylated arylsulfonoxy groups are poorer leaving groups. An intergroup distance of 2 to 6 atoms appears to be the most favorable range for carcinogenic activity, while the distances outside this range are less favorable, or may even reduce the level of concern.

Skeleton templates







R1: Alyphatic alkyl chain.

Substituents: The following substituents may be placed on R1 groups:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- other.

Comments: The substituents can only be placed on the R1 between the

sulfonoxy 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.

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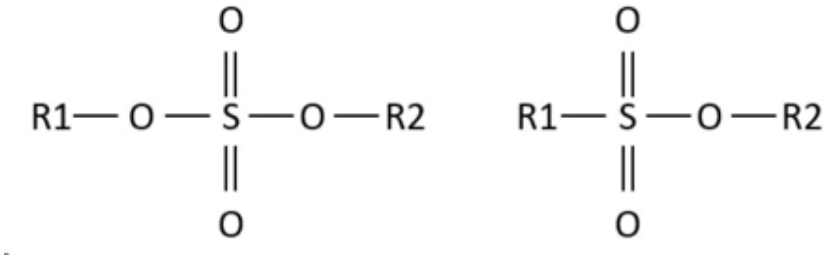
3.6.4 Alkyl Sulfates and Alkyl Alkanesulfonates

Introduction

Dialkyl sulfates or alkyl alkanesulfonates with small alkyl groups (C<5 and benzyl) are good to moderately active direct-acting alkylating agents. They may exert carcinogenic action by alkylating cellular macromolecules, especially when administered by a route that may provide direct access to target tissues, such as inhalation or injection. The alkylating activity, however, decreases with increasing size of the alkyl group.

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.

Comments: 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.

-o-

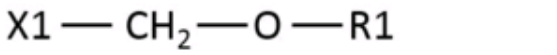
3.6.5 alpha(beta)-Haloethers

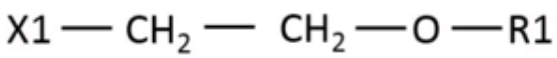
Introduction

An alpha-haloether is a potential alkylating agent. The departure of the halogen can generate a carbonium ion which can bind to key macromolecules to initiate/exert carcinogenic action. Owing to the lack of a favorable stabilization mechanism, the carbonium ion thus formed tends to be short-lived. Therefore, the concern for these compounds tends to be higher for exposure scenarios (e.g. inhalation and injection) with easy access to target tissue.

A beta-haloether is a potential alkylating agent. It may be weakly direct-acting or may require metabolic activation to yield reactive intermediates to bind to key macromolecules to initiate/exert carcinogenic action.

Skeleton templates





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

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

Substituents: The following substituents may be placed on alkyl R groups :

- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- halogens (Cl, Br, I, F),

In addition to these, aryl R group my have: vinyl and allyl groups as well as alkyl (Cn) on the aromatic rings.

The methylene/ethylene moiety (C-X/C-C-X) may be substituted with the

following: OH, COOH, SO3H, Cl, Br, I, F, Cn, and Other.

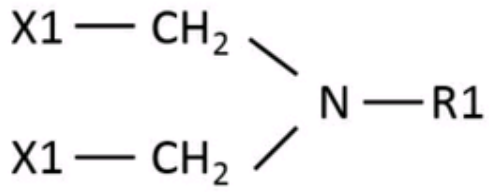
-o-

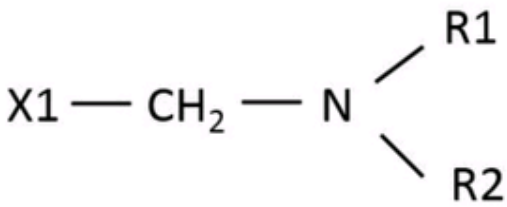
3.6.6 alpha-Haloalkylamines

Introduction

An alpha-haloalkylamine is a potential alkylating agent. The departure of the halogen can generate a carbonium ion which can bind to key macromolecules to initiate/exert carcinogenic action. Owing to the lack of a favorable stabilization mechanism, the carbonium ion thus formed tends to be short-lived. Therefore, the concern for these compounds tends to be higher for exposure scenarios (e.g. inhalation and injection) with easy access to target tissue.

Skeleton templates





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

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

Substituents: The following substituents may be placed on alkyl R groups :

- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- halogens (Cl, Br, I, F),

In addition to these, aryl R group my have: vinyl and allyl groups as well as alkyl (Cn) on the aromatic rings.

The methylene moiety (C-X) may be substituted with the following: OH, COOH, SO3H, Cl, Br, I, F, Cn, and Other.

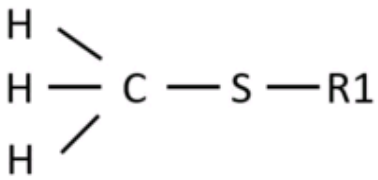
-o-

3.6.7 alpha-Halothioethers

Introduction

An alpha-halothioether is a potential alkylating agent. The departure of the halogen can generate a carbonium ion which can bind to key macromolecules to initiate/exert carcinogenic action. Owing to the lack of a favorable stabilization mechanism, the carbonium ion thus formed tends to be short-lived. Therefore, the concern for these compounds tends to be higher for exposure scenarios (e.g. inhalation and injection) with easy access to target tissue.

Skeleton templates



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

In addition to these, aryl R group my have vinyl and allyl groups as well as alkyl (Cn) on aromatic rings.

The methylene moiety (S-C) may be substituted with the following: OH, COOH, SO3H, Cl, Br, I, F, Cn, and Other.

At least one halogen must be placed on the methylene moiety.

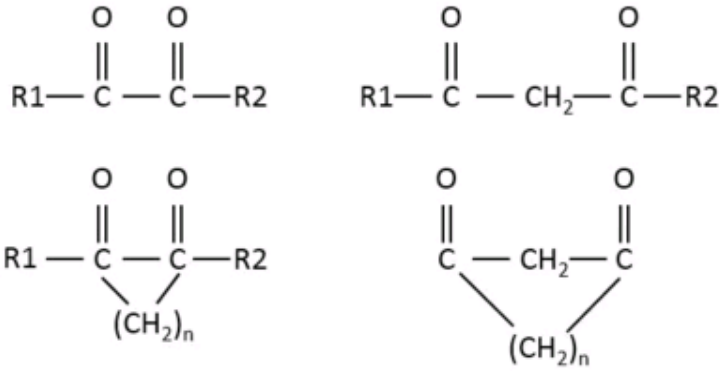
-o-

3.6.8 Dicarbonyls

Introduction

Dicarbonyls are direct-acting agents that do not require metabolic transformation to exert their carcinogenic action. A number of 1,2-dicarbonyls have been shown to be mutagenic. Very little information is available on 1,3-dicarbonyls, other than that 2,4-pentanedione is a moderately active mutagen in several test systems.

Skeleton templates



R1: aliphatic and alicyclic alkyl groups (alkyl chain), phenyl, 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),
- other.

In addition to these, "n" must be greater than 3.

Ring substituents include halogens, alkyl chains, sulfonic and carboxylic acids, hydroxyl.

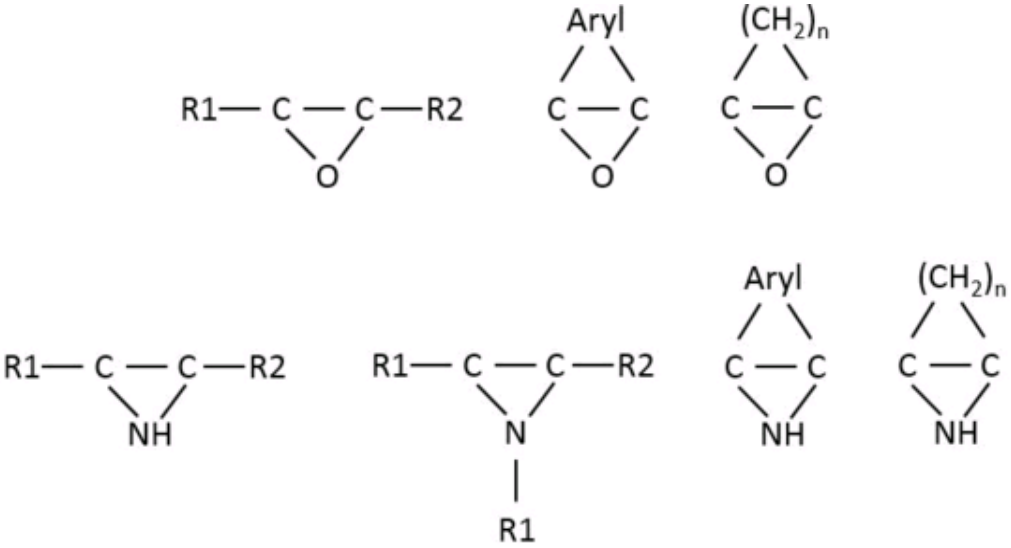
-o-

3.6.9 Epoxides and Ethyleneimines

Introduction

Epoxides and ethyleneimines are potential alkylating agent. The strained ring system facilitates the opening of the ring to generate a carbonium ion which can alkylate key macromolecules to initiate/exert carcinogenic action. The alkylating activity of epoxides and ethyleneimines can be substantially inhibited by ring substitution, particularly by bulky or hydrophilic groups. In general, epoxides or ethyleneimines at terminal end(s) of an aliphatic chain are of much greater concern than those embedded inside an aliphatic chain or those embedded in a rigid cycloaliphatic ring. The nature and molecular size/shape of the molecule to which the epoxide or ethyleneimines is attached may also play a role by serving as a carrier molecule to facilitate uptake/transport or as an intercalating agent.

Skeleton templates



R1, R2: aliphatic (alkyl chain), alicyclic (cycloaliphatic), aromatic (aromatic ring system 1-4 rings), normal body constituent (amino acids, 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.

Substituents: The following substituents may be placed on R groups :

- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- halogens (Cl, Br, I, F),
- other.

In addition to these, aryl R group may have vinyl or allyl groups as well as alkyl chain on the aromatic rings.

The epoxide or ethyleneimine carbons my be substituted with the following: OH, COOH, SO3H, Cl, Br, I, F, alkyl (Cn), alkoxy (OCn) and acyloxy (O(O)Cn)

-o-

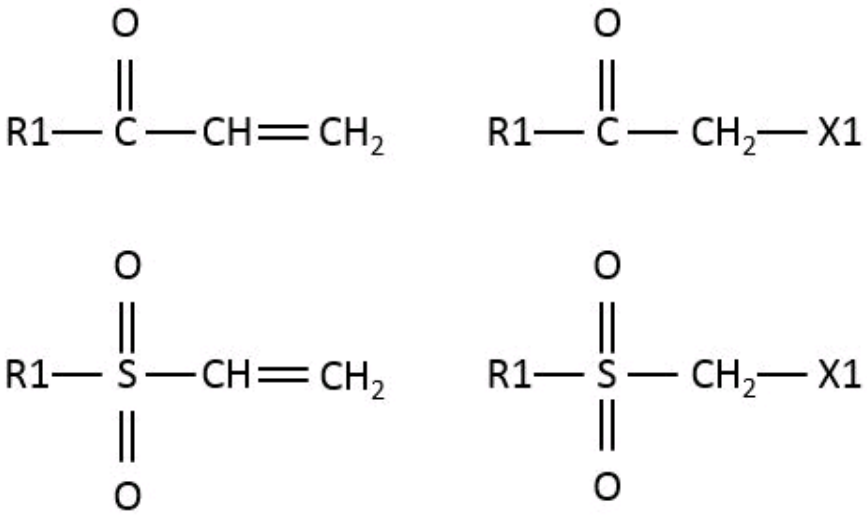
3.6.10 Ketones and Sulfones

Introduction

An alpha,beta-unsaturated ketone or sulfone is a potential alkylating agents which may bind, via Michael addition, to key macromolecules to initiate/exert carcinogenic action. The alkylating activity of alpha,beta-unsaturated ketones can be substantially inhibited by substitution at the double bond, particularly by bulky or hydrophilic groups. The nature and molecular size/shape of the molecule to which the alpha,beta-unsaturated ketone is attached may also play a role in affecting the overall activity of the compound.

An alpha-halo ketone or sulfone is a potential alkylating agent. The departure of the halogen can generate a carbonium ion which can bind to key macromolecules to initiate/exert carcinogenic action. Owing to the lack of a favorable stabilization mechanism, the carbonium ion thus formed tends to be short-lived. Therefore, the concern for these compounds tends to be higher for exposure scenarios (e.g. inhalation and injection) with easy access to target tissue.

Skeleton templates



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

types (H, benzyl, phenylethyl).

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

Substituents: The following substituents may be placed on R groups :

- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- halogens (Cl, Br, I, F),
- other.

In addition to these, aryl R group may have vinyl or allyl groups as well as alkyl chain on the aromatic rings.

The methylene/ ethylene moiety (C-X/ C=C) my be substituted with the following: OH, COOH, SO3H, Cl, Br, I, F, alkyl (Cn), other.

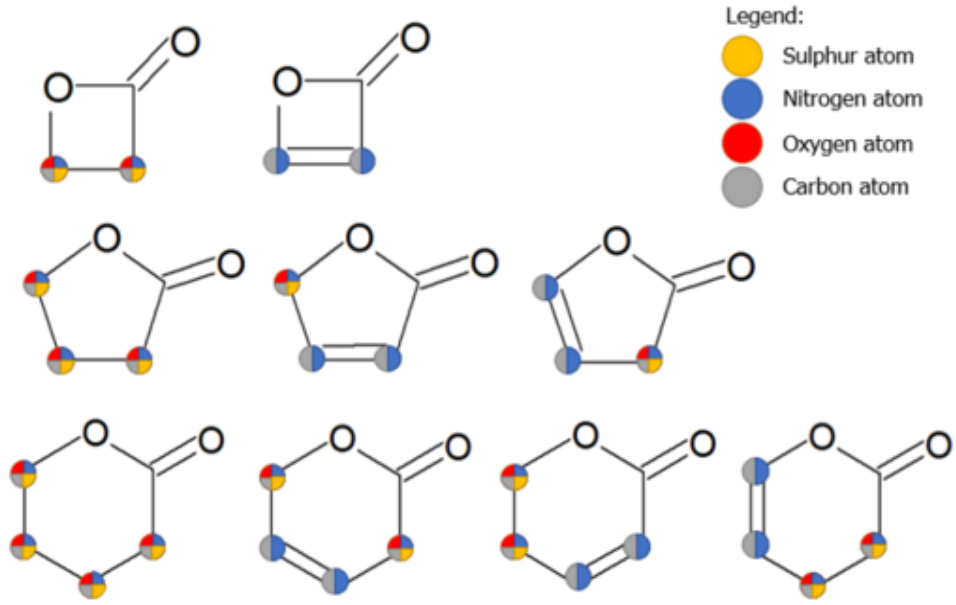
-o-

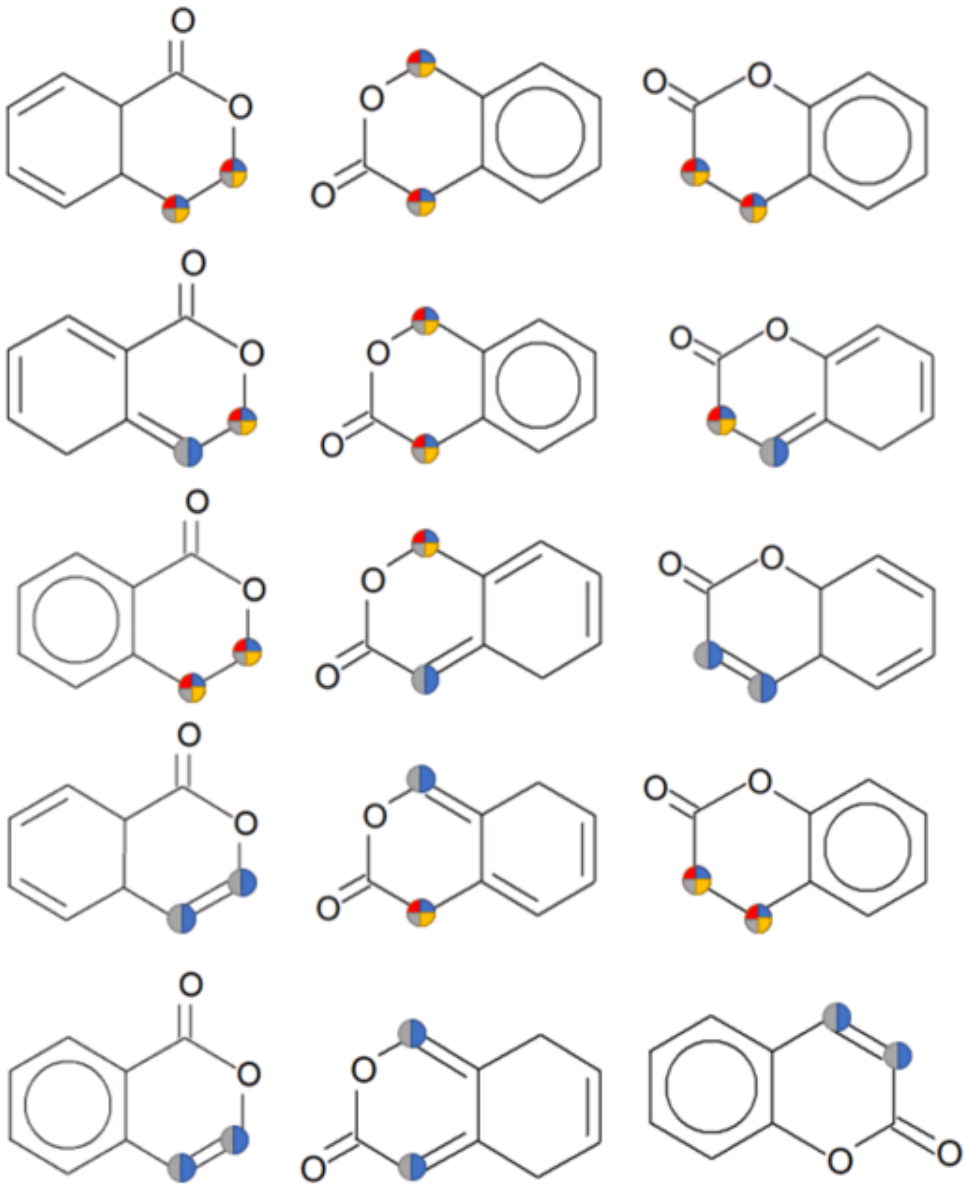
3.6.11 Lactones and Sultones

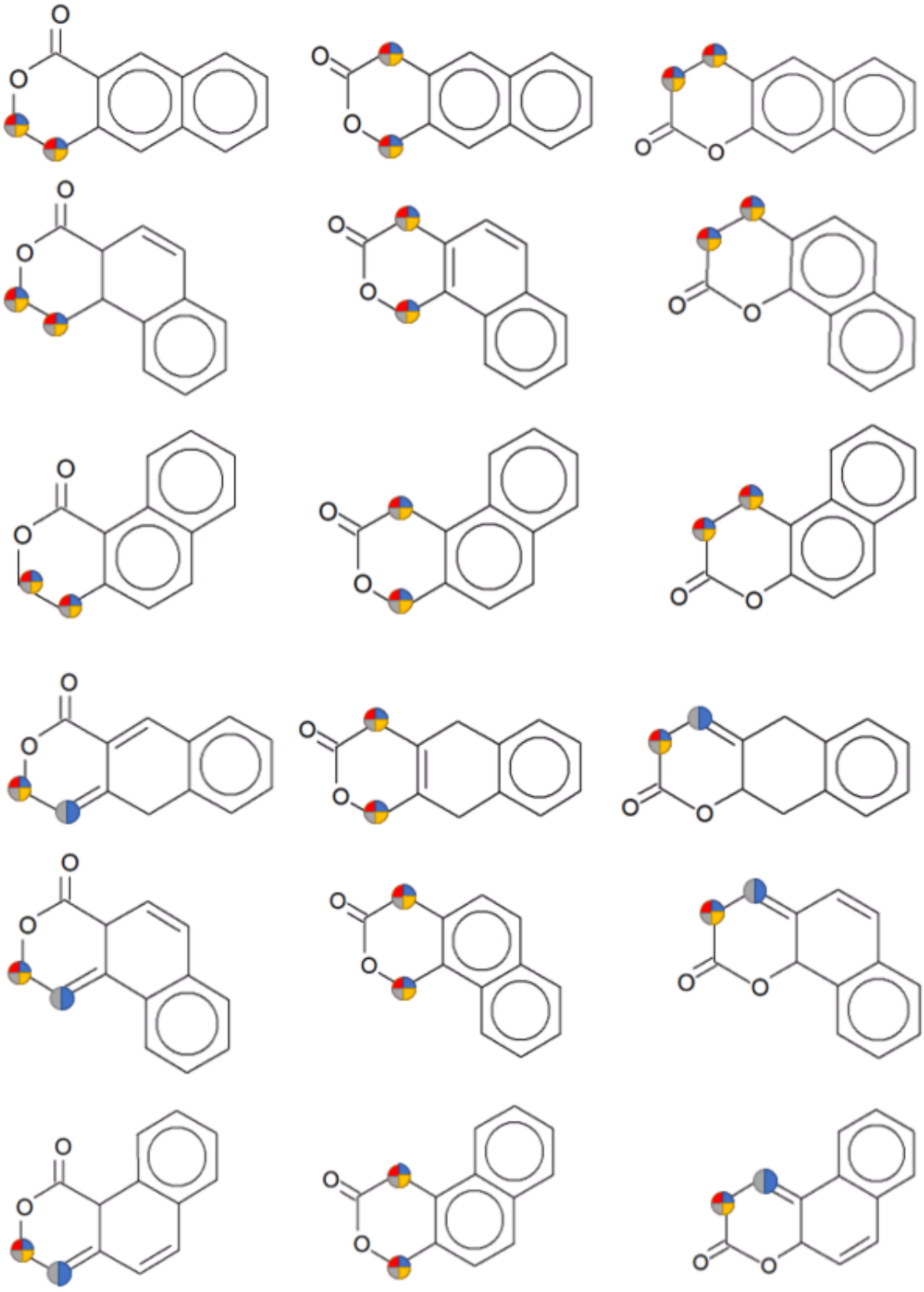
Introduction

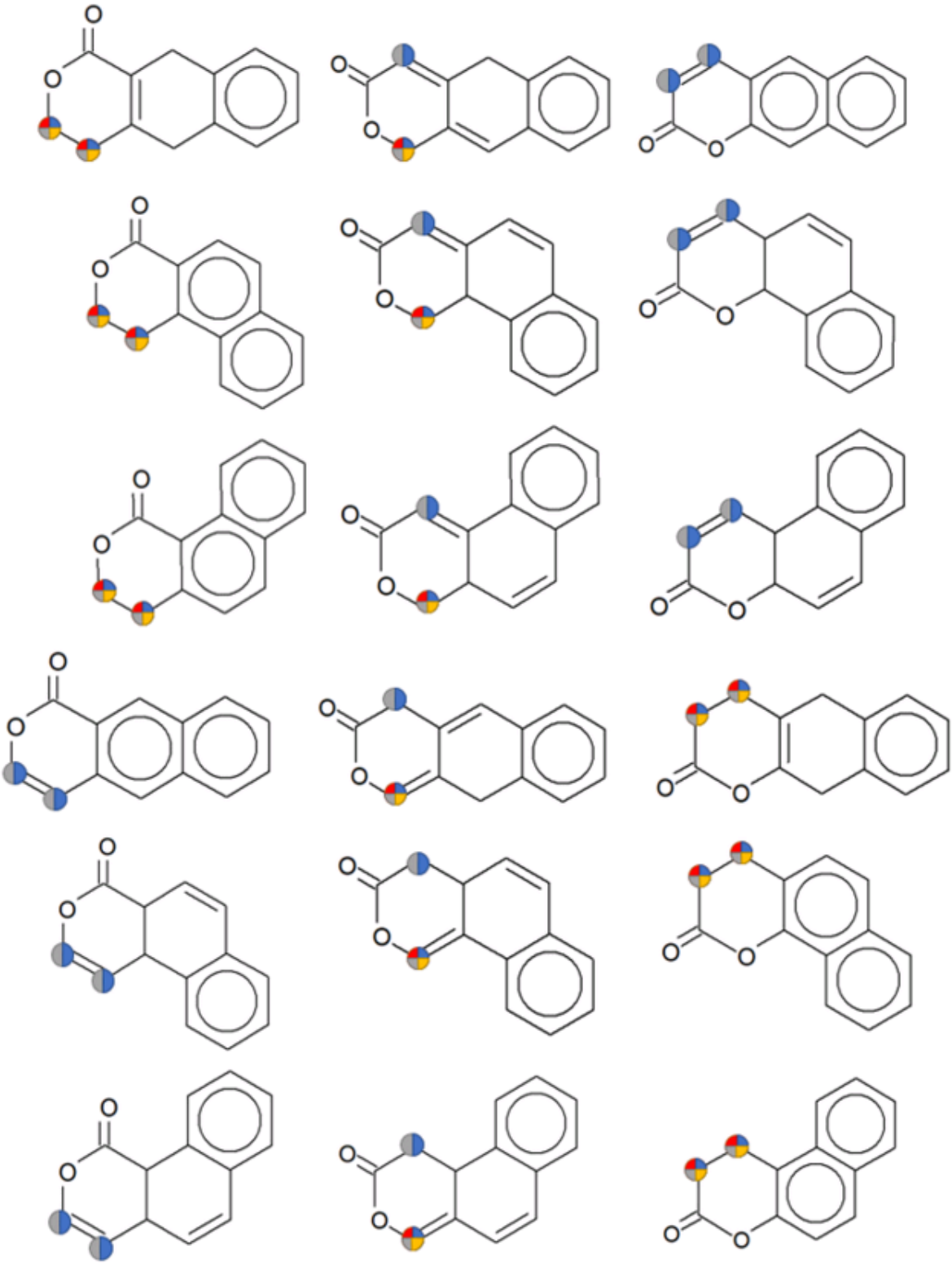
Lactones and sultones are direct-acting alkylating or acylating agents which may bind to key macromolecules to initiate/exert carcinogenic action. The alkylating/acylating activity of lactones is dependent upon the ring strain in the order: 4-membered (beta-lactone) > 6-membered (delta-lactone) >= 5-membered (gamma-lactone) >> rings with more than 6 atoms. For sultones, the activity follows the order: 5-membered (gamma-sultone) > 6-membered (delta-sultone) >> rings with more than 6 atoms. In general, ring substitution with a double bond alpha, beta to the carbonyl/sulfonyl group tends to increase the activity with the exception that for beta-lactones such substitution is expected to make the compound too unstable. Ring substitution with bulky or hydrophilic groups tends to decrease the activity.

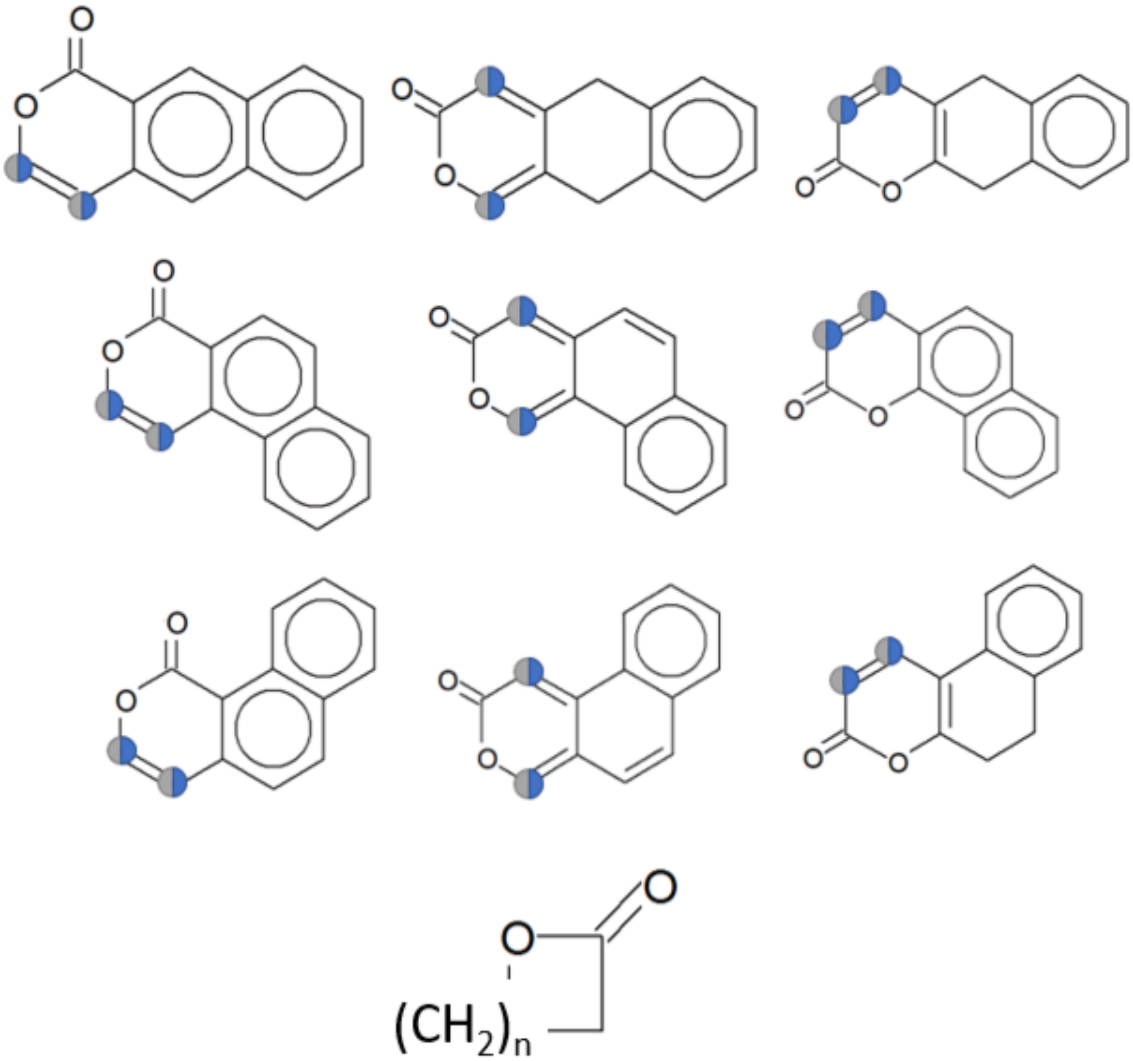
Skeleton templates

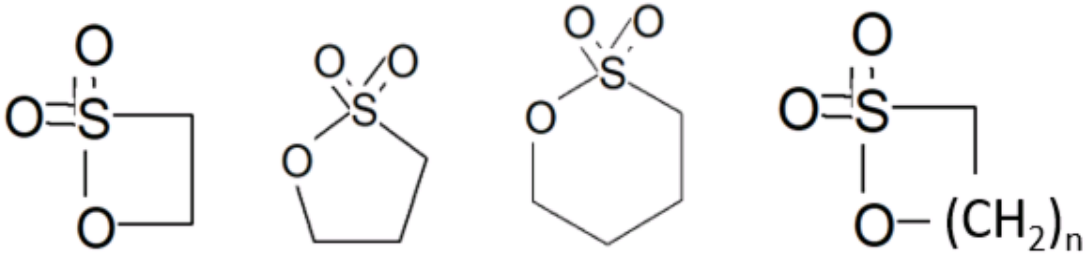












Heteroatoms:

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

Substituents:

Halogens (Cl, Br, I, F), sulfonic acid (SO_3H), carboxylic acid (COOH), and alkyl chains (Cn) may be placed on the lactone ring. Alkyl ring substituents may also contain substituents may also contain the above substituents including hydroxyl (OH).

In addition to these, aryl R group may have vinyl or allyl groups as well as alkyl chain on the aromatic rings.

The methylene/ ethylene moiety (C-X/ C=C) my be substituted with the following: OH, COOH, SO3H, Cl, Br, I, F, alkyl (Cn), other.

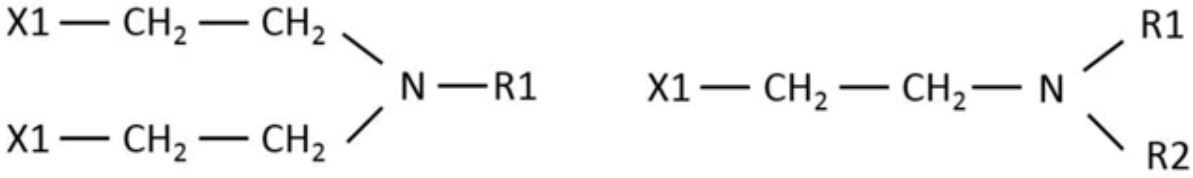
-o-

3.6.12 Nitrogen Mustards

Introduction

A nitrogen mustard is a potential alkylating agent. The departure of the halogen can generate a carbonium ion which can be partially stabilized by cyclization to an episulfonium ion and bind to key macromolecules to initiate/exert carcinogenic action. In general, full mustards are of much greater concern than half mustards. The nature and molecular size/shape of the molecule to which the nitrogen mustard functional group is attached may play an important role by serving as a carrier molecule to facilitate uptake/transport or as an intercalating agent.

Skeleton templates



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

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

Substituents: The following substituents may be placed on R groups :

- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- halogens (Cl, Br, I, F),
- other.

In addition to these, aryl R group may have vinyl or allyl groups as well as alkyl chain on the aromatic rings.

The ethyl moiety (C-C-X) my be substituted with the following: OH, COOH, SO3H, Cl, Br, I, F, alkyl (Cn), other.

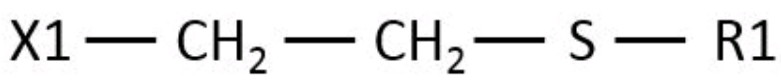
-o-

3.6.13 Sulfur Mustards

Introduction

A sulfur mustard is a potential alkylating agent. The departure of the halogen can generate a carbonium ion which can be partially stabilized by cyclization to an episulfonium ion and bind to key macromolecules to initiate/exert carcinogenic action. In general, full mustards are of much greater concern than half mustards. The nature and molecular size/shape of the molecule to which the nitrogen mustard functional group is attached may play an important role by serving as a carrier molecule to facilitate uptake/transport or as an intercalating agent.

Skeleton templates



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

X1: At least one halogen must be placed on the beta position of the ethylene moiety (F, Cl, Br, I).

Substituents: The following substituents may be placed on R groups :

- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- halogens (Cl, Br, I, F),
- other.

In addition to these, aryl R group may have vinyl or allyl groups as well as alkyl chain on the aromatic rings.

The ethyl moiety (C-C-X) my be substituted with the following: OH, COOH, SO3H, Cl, Br, I, F, alkyl (Cn), other.

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3.7 Direct-Acting arylating Agents

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3.7.1 Aryldiazonium Salts, O-Halogenated Heterocyclics and Halogenated Nitroaromatics

Introduction - Aryldiazonium compounds

Aryldiazonium compounds are potential arylating agents. The departure of nitrogen can leave behind a positively charged ring which may arylate key macromolecules to exert carcinogenic action.

Skeleton templates

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

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.

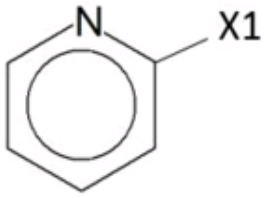
At least one N+=N ring substituent must be placed on the skeleton.

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.

Introduction - O-Halogenated Heterocyclics

Ortho-halogenated heterocyclic compounds, characterized by the presence of a halogen at a ring carbon atom ortho to a ring nitrogen, are potential arylating agents. This arrangement of the ring substituents facilitates the departure of the halogen leaving behind a positively charged ring which may arylate key macromolecules to exert carcinogenic action.

Skeleton templates



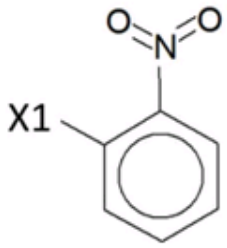
Heteroatom: Nitrogen (N) - the ring must contain at least one nitrogen atom and a halogen ortho to the nitrogen atom.

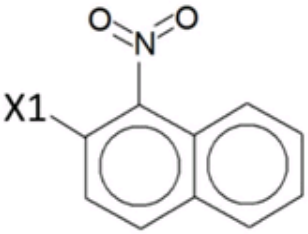
Ring Substituents: alkyl groups (Cn), halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), and sulfonic acid (SO3H) may be added to the ring carbons.

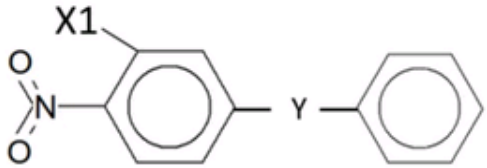
Introduction - Halogenated Nitroaromatics

Halogenated nitroaromatic compounds, which contain a halogen ortho or para to one or more nitro group(s), are potential arylating agents. This arrangement of the ring substituents facilitates the departure of the halogen leaving behind a positively charged ring which may arylate key macromolecules to exert carcinogenic action.

Skeleton templates







Heteroatom: Nitrogen (N).

Ring Substituents: alkyl chains, halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), and sulfonic acid (SO3H).

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

Linkages

The linkage, designed by “Y” may be defined with one of the following linkages:

- direct link;
- Oxygen (O);
- Sulphur (S);
- NH;
- CH2;

- N=CH;
- N=N;
- =N;
- =CH;
- (C C)n;
- (C=C)n;
- (CH2)n;
- C(=O);
- S(=O);
- S=O(=O);
- NHC(=O)NH;
- C(=O)NH;
- C(=O)CH=CH;
- C(CH3)CH3.

-o-

3.8 Halogenated Aromatic Hydrocarbons

-o-

3.8.1 Halogenated benzenes

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.

Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.

Other halogenated biphenyls, naphthalenes and benzenes, which induce the cytochrome P-450 2B family, on the other hand, have been postulated to act via inhibition of "intercellular communication" (also called "metabolic cooperation"). Other epigenetic mechanisms that have been linked to carcinogenesis of halogenated aromatics include (i) hormone imbalance (e.g. estrogen mimics), (ii) immunosuppresion, and (iii) cytotoxicity.

Halogenation of the aromatics renders them more lipid-soluble, more slowly metabolized, and therefore more persistent in animal tissues. In general, the rate of oxidative metabolism decreases as the degree of halogenation increases because of steric hindrance by the halogen atoms. Moreover, the position of halogenation plays an important role in determining the rate of oxidative metabolism. For instance, it has been shown that chlorinated and brominated benzenes having two adjacent unsubstituted carbon atoms are more rapidly metabolized than those without adjacent unsubstituted carbon atoms, despite a similar degree of halogenation. Hence, in addition to the type of halogens, the degree and position of halogenation are important factors inevaluating the carcinogenicity potential of halogenated aromatics. The carcinogenicity concern levels of these compounds are determined based on structure-activity relationship analysis as well as metabolism and mechanism

considerations.

Skeleton templates

Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

-o-

3.8.2 Halogenated biphenyls

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.

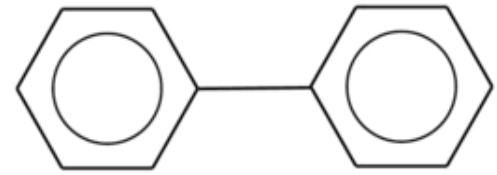
Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.

Other halogenated biphenyls, naphthalenes and benzenes, which induce the cytochrome P-450 2B family, on the other hand, have been postulated to act via inhibition of "intercellular communication" (also called "metabolic cooperation"). Other epigenetic mechanisms that have been linked to carcinogenesis of halogenated aromatics include (i) hormone imbalance (e.g. estrogen mimics), (ii) immunosuppresion, and (iii) cytotoxicity.

Halogenation of the aromatics renders them more lipid-soluble, more slowly metabolized, and therefore more persistent in animal tissues. In general, the rate of oxidative metabolism decreases as the degree of halogenation increases because of steric hindrance by the halogen atoms. Moreover, the position of halogenation plays an important role in determining the rate of oxidative metabolism. For instance, it has been shown that chlorinated and brominated benzenes having two adjacent unsubstituted carbon atoms are more rapidly metabolized than those without adjacent unsubstituted carbon atoms, despite a similar degree of halogenation. Hence, in addition to the type of halogens, the degree and position of halogenation are important factors inevaluating the carcinogenicity potential of halogenated aromatics. The carcinogenicity concern levels of these compounds are determined based on structure-activity relationship analysis as well as metabolism and mechanism

considerations.

Skeleton templates



Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

-o-

3.8.3 Halogenated Dibenzofurans and Dibenzothiophenes

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.

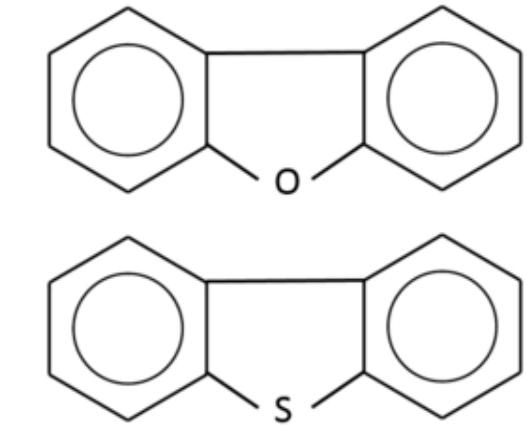
Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.

Other halogenated biphenyls, naphthalenes and benzenes, which induce the cytochrome P-450 2B family, on the other hand, have been postulated to act via inhibition of "intercellular communication" (also called "metabolic cooperation"). Other epigenetic mechanisms that have been linked to carcinogenesis of halogenated aromatics include (i) hormone imbalance (e.g. estrogen mimics), (ii) immunosuppresion, and (iii) cytotoxicity.

Halogenation of the aromatics renders them more lipid-soluble, more slowly metabolized, and therefore more persistent in animal tissues. In general, the rate of oxidative metabolism decreases as the degree of halogenation increases because of steric hindrance by the halogen atoms. Moreover, the position of halogenation plays an important role in determining the rate of oxidative metabolism. For instance, it has been shown that chlorinated and brominated benzenes having two adjacent unsubstituted carbon atoms are more rapidly metabolized than those without adjacent unsubstituted carbon atoms, despite a similar degree of halogenation. Hence, in addition to the type of halogens, the degree and position of halogenation are important factors inevaluating the carcinogenicity potential of halogenated aromatics. The carcinogenicity concern levels of these compounds are determined based on structure-activity relationship analysis as well as metabolism and mechanism

considerations.

Skeleton templates



Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

-o-

3.8.4 Halogenated Dibenzo-p-Dioxins

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.

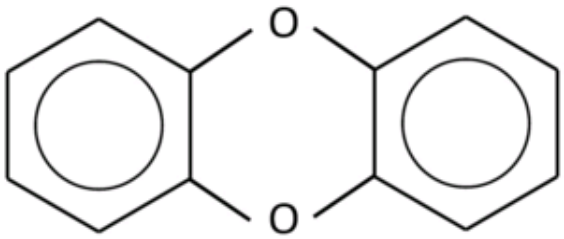
Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.

Other halogenated biphenyls, naphthalenes and benzenes, which induce the cytochrome P-450 2B family, on the other hand, have been postulated to act via inhibition of "intercellular communication" (also called "metabolic cooperation"). Other epigenetic mechanisms that have been linked to carcinogenesis of halogenated aromatics include (i) hormone imbalance (e.g. estrogen mimics), (ii) immunosuppresion, and (iii) cytotoxicity.

Halogenation of the aromatics renders them more lipid-soluble, more slowly metabolized, and therefore more persistent in animal tissues. In general, the rate of oxidative metabolism decreases as the degree of halogenation increases because of steric hindrance by the halogen atoms. Moreover, the position of halogenation plays an important role in determining the rate of oxidative metabolism. For instance, it has been shown that chlorinated and brominated benzenes having two adjacent unsubstituted carbon atoms are more rapidly metabolized than those without adjacent unsubstituted carbon atoms, despite a similar degree of halogenation. Hence, in addition to the type of halogens, the degree and position of halogenation are important factors inevaluating the carcinogenicity potential of halogenated aromatics. The carcinogenicity concern levels of these compounds are determined based on structure-activity relationship analysis as well as metabolism and mechanism

considerations.

Skeleton templates



Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

-o-

3.8.5 Halogenated Diphenyl Compounds

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.

Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.

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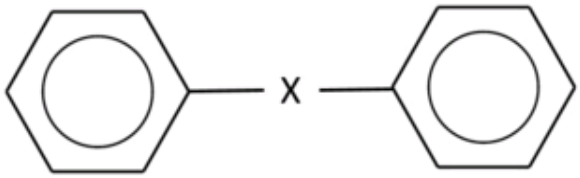
considerations.

Skeleton templates



Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

Diphenyl Linked Skeleton

Diphenyl Linked Skeleton: The linkage, designed by “X” may be defined with one of the following 12 linkages:

- CHCH2Cl;
- Oxygen (O);
- Sulphur (S);
- C=CH2;
- C=O;
- CH(OH);

- C=CHCl;
- CHC(Cl3);
- CH2;
- C(OH)C(Cl3);
- C=CCl2.

-o-

3.8.6 Halogenated m-terphenyls

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.

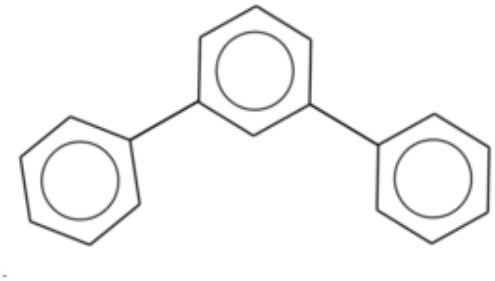
Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.

Other halogenated biphenyls, naphthalenes and benzenes, which induce the cytochrome P-450 2B family, on the other hand, have been postulated to act via inhibition of "intercellular communication" (also called "metabolic cooperation"). Other epigenetic mechanisms that have been linked to carcinogenesis of halogenated aromatics include (i) hormone imbalance (e.g. estrogen mimics), (ii) immunosuppresion, and (iii) cytotoxicity.

Halogenation of the aromatics renders them more lipid-soluble, more slowly metabolized, and therefore more persistent in animal tissues. In general, the rate of oxidative metabolism decreases as the degree of halogenation increases because of steric hindrance by the halogen atoms. Moreover, the position of halogenation plays an important role in determining the rate of oxidative metabolism. For instance, it has been shown that chlorinated and brominated benzenes having two adjacent unsubstituted carbon atoms are more rapidly metabolized than those without adjacent unsubstituted carbon atoms, despite a similar degree of halogenation. Hence, in addition to the type of halogens, the degree and position of halogenation are important factors inevaluating the carcinogenicity potential of halogenated aromatics. The carcinogenicity concern levels of these compounds are determined based on structure-activity relationship analysis as well as metabolism and mechanism

considerations.

Skeleton templates



Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

-o-

3.8.7 Halogenated naphthalenes

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.

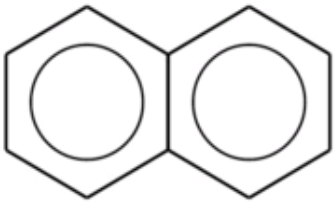
Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.

Other halogenated biphenyls, naphthalenes and benzenes, which induce the cytochrome P-450 2B family, on the other hand, have been postulated to act via inhibition of "intercellular communication" (also called "metabolic cooperation"). Other epigenetic mechanisms that have been linked to carcinogenesis of halogenated aromatics include (i) hormone imbalance (e.g. estrogen mimics), (ii) immunosuppresion, and (iii) cytotoxicity.

Halogenation of the aromatics renders them more lipid-soluble, more slowly metabolized, and therefore more persistent in animal tissues. In general, the rate of oxidative metabolism decreases as the degree of halogenation increases because of steric hindrance by the halogen atoms. Moreover, the position of halogenation plays an important role in determining the rate of oxidative metabolism. For instance, it has been shown that chlorinated and brominated benzenes having two adjacent unsubstituted carbon atoms are more rapidly metabolized than those without adjacent unsubstituted carbon atoms, despite a similar degree of halogenation. Hence, in addition to the type of halogens, the degree and position of halogenation are important factors inevaluating the carcinogenicity potential of halogenated aromatics. The carcinogenicity concern levels of these compounds are determined based on structure-activity relationship analysis as well as metabolism and mechanism

considerations.

Skeleton templates



Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

-o-

3.8.9 Halogenated o-terphenyls

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

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Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.

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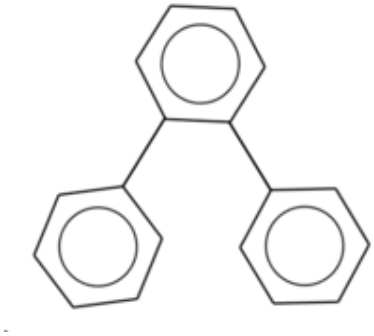
considerations.

Skeleton templates



Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

-o-

3.8.10 Halogenated p-terphenyls

Introduction

Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.

However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.

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Other halogenated biphenyls, naphthalenes and benzenes, which induce the cytochrome P-450 2B family, on the other hand, have been postulated to act via inhibition of "intercellular communication" (also called "metabolic cooperation"). Other epigenetic mechanisms that have been linked to carcinogenesis of halogenated aromatics include (i) hormone imbalance (e.g. estrogen mimics), (ii) immunosuppresion, and (iii) cytotoxicity.

Halogenation of the aromatics renders them more lipid-soluble, more slowly metabolized, and therefore more persistent in animal tissues. In general, the rate of oxidative metabolism decreases as the degree of halogenation increases because of steric hindrance by the halogen atoms. Moreover, the position of halogenation plays an important role in determining the rate of oxidative metabolism. For instance, it has been shown that chlorinated and brominated benzenes having two adjacent unsubstituted carbon atoms are more rapidly metabolized than those without adjacent unsubstituted carbon atoms, despite a similar degree of halogenation. Hence, in addition to the type of halogens, the degree and position of halogenation are important factors inevaluating the carcinogenicity potential of halogenated aromatics. The carcinogenicity concern levels of these compounds are determined based on structure-activity relationship analysis as well as metabolism and mechanism

considerations.

Skeleton templates

Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);
- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

Substituents:

Ring substituents include:

- Halogens (Cl, Br, I, F);
- alkyl chains (Cn);
- hydroxyl (-OH);
- carboxylic acid (COOH);
- sulfonic acid (SO3H);
- cyano (CN);

- aldehyde (C(O)H);
- alkoxy (OCn);
- other.

By definition of halogenated aromatic, at least one halogen must be placed on the structure.

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3.9 Halogenated Cycloalkanes and Cycloalkenes

-o-

3.9.1 Halogenated bicycloheptanes

Introduction

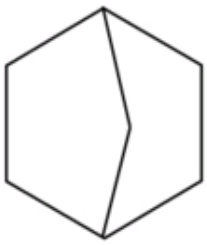
Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

On the other hand, some of these compounds and/or their metabolites possess latent alkylating properties, which may play a role in their biological/carcinogenic activity. For example, epoxidation of the double bond(s) in halogenated cycloalkenes may yield electrophilic intermediates that can bind to DNA. Cl, Br, or I on an allylic carbon (alpha to a double bond in halogenated cycloalkenes) are reactive. Vicinally halogenated non-vinylic carbons of cycloalkanes and cycloalkenes may be activated by the glutathione conjugation pathway. However, large substitutions (e.g. by I) at a vinylic carbon may provide steric hindrance for epoxidation; geminally substituted (with an additional halogen at a carbon atom) halo-compounds are less reactive in comparison with those that are monohalo-substituted.

The concern levels of these compounds are determined based on structure-activity relationship analysis as well as mechanistic considerations. It should be noted that different steroisomers exist for some halogenated cycloalkanes and cycloalkenes, and different steroisomers may differ in their biological activities. Since commercially available products (technical grade) usually occur as mixtures of different steroisomers, the concern levels herein express the potential carcinogenicity of the mixtures rather than individual isomers.

Skeleton templates



Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

3.9.2 Halogenated bicycloheptenes and bicycloheptadienes

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

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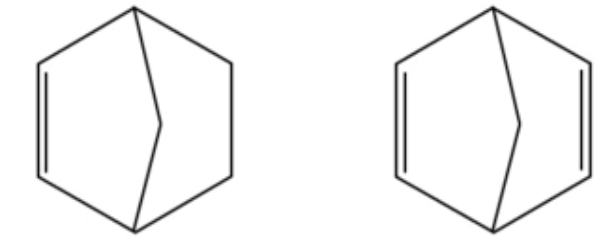
Skeleton templates



Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

3.9.3 Halogenated bicyclo-terpenes

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

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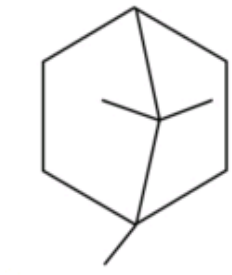
The concern levels of these compounds are determined based on structure-activity relationship analysis as well as mechanistic considerations. It should be noted that different steroisomers exist for some halogenated cycloalkanes and cycloalkenes, and different steroisomers may differ in their biological activities. Since commercially available products (technical grade) usually occur as mixtures of different steroisomers, the concern levels herein express the potential carcinogenicity of the mixtures rather than individual isomers.

Skeleton templates



Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.9.4 Halogenated cyclohexadienes

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

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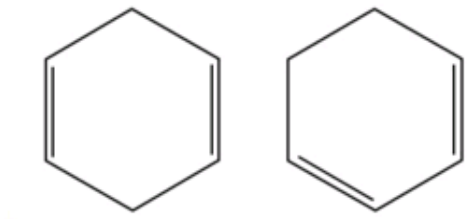
The concern levels of these compounds are determined based on structure-activity relationship analysis as well as mechanistic considerations. It should be noted that different steroisomers exist for some halogenated cycloalkanes and cycloalkenes, and different steroisomers may differ in their biological activities. Since commercially available products (technical grade) usually occur as mixtures of different steroisomers, the concern levels herein express the potential carcinogenicity of the mixtures rather than individual isomers.

Skeleton templates



Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.9.5 Halogenated cyclohexanes

Introduction

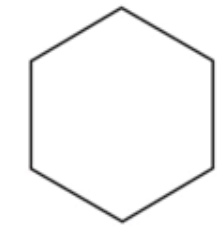
Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

On the other hand, some of these compounds and/or their metabolites possess latent alkylating properties, which may play a role in their biological/carcinogenic activity. For example, epoxidation of the double bond(s) in halogenated cycloalkenes may yield electrophilic intermediates that can bind to DNA. Cl, Br, or I on an allylic carbon (alpha to a double bond in halogenated cycloalkenes) are reactive. Vicinally halogenated non-vinylic carbons of cycloalkanes and cycloalkenes may be activated by the glutathione conjugation pathway. However, large substitutions (e.g. by I) at a vinylic carbon may provide steric hindrance for epoxidation; geminally substituted (with an additional halogen at a carbon atom) halo-compounds are less reactive in comparison with those that are monohalo-substituted.

The concern levels of these compounds are determined based on structure-activity relationship analysis as well as mechanistic considerations. It should be noted that different steroisomers exist for some halogenated cycloalkanes and cycloalkenes, and different steroisomers may differ in their biological activities. Since commercially available products (technical grade) usually occur as mixtures of different steroisomers, the concern levels herein express the potential carcinogenicity of the mixtures rather than individual isomers.

Skeleton templates



Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

3.9.6 Halogenated cyclohexenes

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

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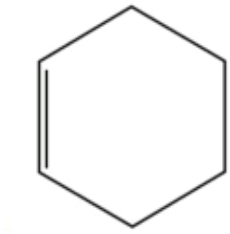
Skeleton templates



Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.9.7 Halogenated cyclopentadienes

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

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Skeleton templates

Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.9.8 Halogenated cyclopentanes

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

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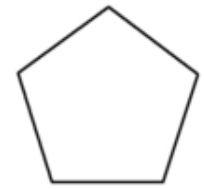

Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.9.9 Halogenated cyclopentenes

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

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The concern levels of these compounds are determined based on structure-activity relationship analysis as well as mechanistic considerations. It should be noted that different steroisomers exist for some halogenated cycloalkanes and cycloalkenes, and different steroisomers may differ in their biological activities. Since commercially available products (technical grade) usually occur as mixtures of different steroisomers, the concern levels herein express the potential carcinogenicity of the mixtures rather than individual isomers.

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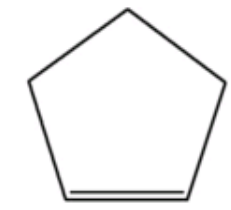

Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.9.10 Other halogenated cyclocompounds (subset A)

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

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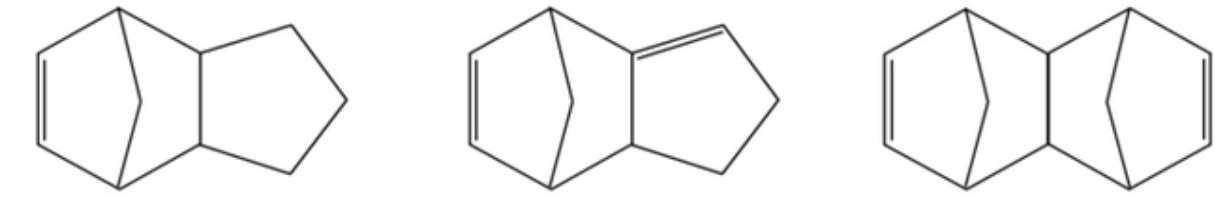
The concern levels of these compounds are determined based on structure-activity relationship analysis as well as mechanistic considerations. It should be noted that different steroisomers exist for some halogenated cycloalkanes and cycloalkenes, and different steroisomers may differ in their biological activities. Since commercially available products (technical grade) usually occur as mixtures of different steroisomers, the concern levels herein express the potential carcinogenicity of the mixtures rather than individual isomers.

Skeleton templates



Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.9.11 Other halogenated cyclocompounds (subset B)

Introduction

Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.

Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include: (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.

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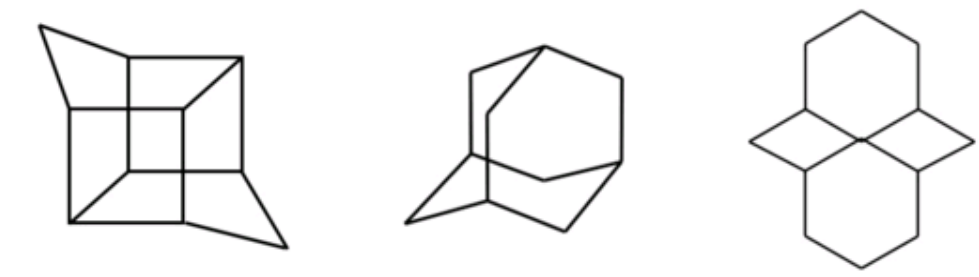
The concern levels of these compounds are determined based on structure-activity relationship analysis as well as mechanistic considerations. It should be noted that different steroisomers exist for some halogenated cycloalkanes and cycloalkenes, and different steroisomers may differ in their biological activities. Since commercially available products (technical grade) usually occur as mixtures of different steroisomers, the concern levels herein express the potential carcinogenicity of the mixtures rather than individual isomers.

Skeleton templates



Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10 Halogenated Linear Aliphatics

-o-

3.10.1 Haloacetylenes

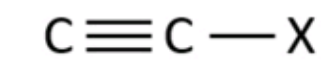
Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

The chemical reactivity of direct-acting haloalkanes and haloalkenes is dependent on the nature, the number, and the position of the halogen substituents. As the size of the halogen atom increases (in the order: F<Cl<Br<I), the bond length increases and the bond energy decreases, thus weakening the C-X (X = halogen) bond and facilitating the leaving of the halogen atom in nucleophilic reactions. In general, the chemical reactivity of direct-acting haloalkanes/haloalkenes follows the order: I>Br>Cl>F. However, chemical reactivity decreases with the increase in the degree of halogenation; geminally substituted (with an additional halogen at a carbon atom) halo-compounds are generally less reactive in comparison with those that are monohalo-/vicinally substituted.

The potential of haloalkanes and haloalkenes to alkylate cellular nucleophiles is the basis of concern for their carcinogenicity. However, a number of haloalkanes and haloalkenes appear to be non-genotoxic; their carcinogenic activity is believed to be related to cytotoxicity and various epigenetic mechanisms. The concern level of the compound is determined based on structure-activity relationship analysis as well as mechanistic considerations.

Skeleton templates



Substituents: X = Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.2 Haloalkanes with 4 to 6 carbons

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

The chemical reactivity of direct-acting haloalkanes and haloalkenes is dependent on the nature, the number, and the position of the halogen substituents. As the size of the halogen atom increases (in the order: F<Cl<Br<I), the bond length increases and the bond energy decreases, thus weakening the C-X (X = halogen) bond and facilitating the leaving of the halogen atom in nucleophilic reactions. In general, the chemical reactivity of direct-acting haloalkanes/haloalkenes follows the order: I>Br>Cl>F. However, chemical reactivity decreases with the increase in the degree of halogenation; geminally substituted (with an additional halogen at a carbon atom) halo-compounds are generally less reactive in comparison with those that are monohalo-/vicinally substituted.

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Skeleton templates

$$C_n — X$$

$$4 \leq n \leq 6$$

Substituents: X = Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.3 Haloalkanes with 7 to 15 carbons

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

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Skeleton templates

$$C_n — X$$

$$7 \leq n \leq 15$$

Substituents: X = Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.4 Haloalkanes with more than 15 carbons

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

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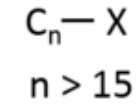
Skeleton templates



Substituents: X = Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.5 Haloalkenes with 5 to 10 carbons

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

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The potential of haloalkanes and haloalkenes to alkylate cellular nucleophiles is the basis of concern for their carcinogenicity. However, a number of haloalkanes and haloalkenes appear to be non-genotoxic; their carcinogenic activity is believed to be related to cytotoxicity and various epigenetic mechanisms. The concern level of the compound is determined based on structure-activity relationship analysis as well as mechanistic considerations.

Skeleton templates

$$R_n — X$$

$$5 \leq n \leq 10$$

Substituents:

X = Halogens (Cl, Br, I, F) - at least one must be placed.

R = alkene

-o-

3.10.6 Haloalkenes with more than 10 carbons

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

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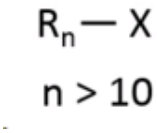
Skeleton templates



Substituents:

X = Halogens (Cl, Br, I, F) - at least one must be placed.

R = alkene

3.10.7 Haloalkynes with more than 4 carbons

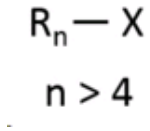
Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

The chemical reactivity of direct-acting haloalkanes and haloalkenes is dependent on the nature, the number, and the position of the halogen substituents. As the size of the halogen atom increases (in the order: F<Cl<Br<I), the bond length increases and the bond energy decreases, thus weakening the C-X (X = halogen) bond and facilitating the leaving of the halogen atom in nucleophilic reactions. In general, the chemical reactivity of direct-acting haloalkanes/haloalkenes follows the order: I>Br>Cl>F. However, chemical reactivity decreases with the increase in the degree of halogenation; geminally substituted (with an additional halogen at a carbon atom) halo-compounds are generally less reactive in comparison with those that are monohalo-/vicinally substituted.

The potential of haloalkanes and haloalkenes to alkylate cellular nucleophiles is the basis of concern for their carcinogenicity. However, a number of haloalkanes and haloalkenes appear to be non-genotoxic; their carcinogenic activity is believed to be related to cytotoxicity and various epigenetic mechanisms. The concern level of the compound is determined based on structure-activity relationship analysis as well as mechanistic considerations.

Skeleton templates



Substituents:

X = Halogens (Cl, Br, I, F) - at least one must be placed.

R = alkyne

3.10.8 Halobutenes

Introduction

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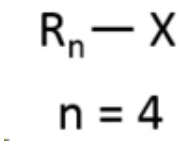
Skeleton templates



Substituents:

X = Halogens (Cl, Br, I, F) - at least one must be placed.

R = alkene

-o-

3.10.9 Halobutynes

Introduction

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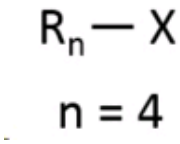
Skeleton templates



Substituents:

X = Halogens (Cl, Br, I, F) - at least one must be placed.

R = alkyne

-o-

3.10.10 Haloethanes

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

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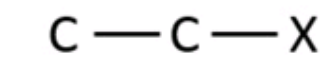

Substituents: X = Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.11 Haloethylenes

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

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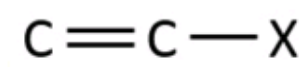

Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.12 Halomethanes

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

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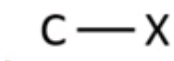

Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.13 Halopropanes

Introduction

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

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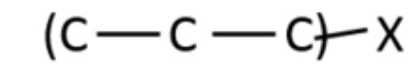

Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.14 Halopropylenes

Introduction

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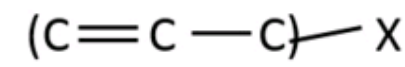

Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.10.15 Halopropynes

Introduction

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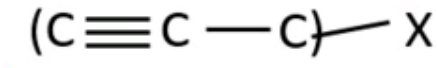


Substituents: Halogens (Cl, Br, I, F) - at least one must be placed.

-o-

3.11 Hydrazo Compounds

-o-

3.11.1 Hydrazines, hydrazides and hydrazones

Introduction

Hydrazo compounds (hydrazines and hydrazides) represent a well established class of chemical carcinogens. Most of the hydrazo compounds that have been tested are carcinogenic. In general, hydrazines are more carcinogenic then hydrazides. Among the hydrazines, 1,2-disubstituted hydrazines are the most active. Factors that are known to diminish or abolish carcinogenic activity of hydrazo compounds include:

(i) bulky substituents,

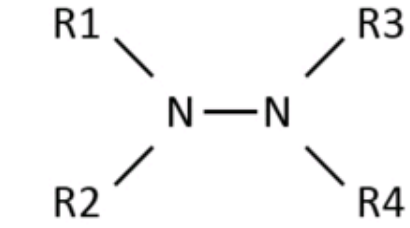
(ii) highly hydrophilic substituents, and

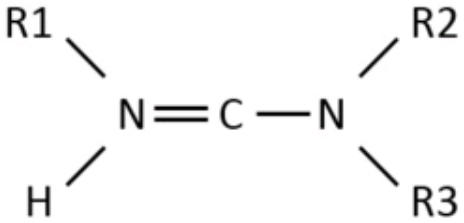
(iii) steric hindrance at the alpha-carbon.

Both the nature and the position of the substituent(s) are considered in the overall assessment of the carcinogenic potential of hydrazo compounds.

Hydrazone compounds are expected to be hydrolyzed in the acidic environment of the stomach to an aldehyde (R1CHO) and a 1,1-disubstituted hydrazo compound. The evaluation will proceed on the 1,1-disubstituted hydrazo compound. The Aldehyde product should be evaluated in the Aldehyde component and then compared to the level of concern generated by the Hydrazo component. The higher level of concern should be used.

Skeleton templates





R1, R2, R3, R4:

- aliphatic (alkyl chain, cycloC6, vinyl, allyl)
- aromatic types (phenyl, benzyl, phenylethyl,)
- acyl type (carbamyl, arylsulfonyl, pyridyl, acyl)
- hydrogen

Substituents:

The substituents may include:

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

-o-

3.12 Nitroso Compounds

-o-

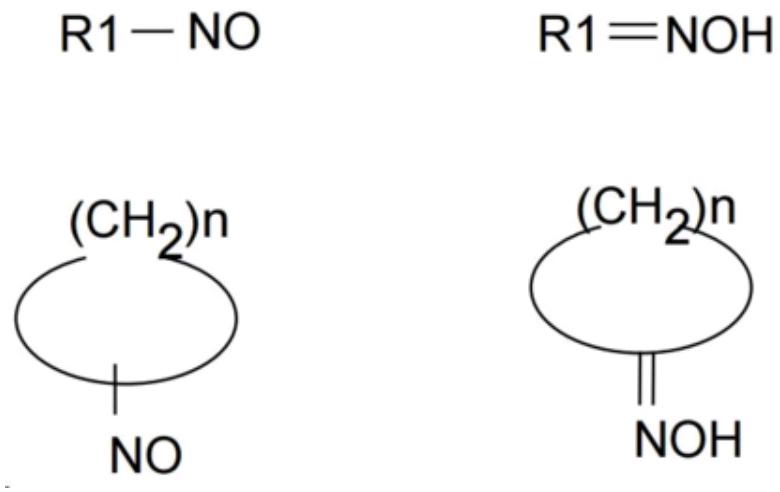
3.12.1 C-Nitroso Compounds and Oximes

Introduction

Since C-Nitroso compounds can tautomerize to oximes and the carcinogenic action of alkyl ketoximes appears to be due to oxidation to nitroalkanes, aliphatic C-Nitroso compounds and oximes are evaluated assuming their conversion to nitroalkanes and are, here after, referred to as Nitroalkane/Nitroalkene.

Evidence from carcinogenicity studies in animals, short-term mutagenicity tests and studies on DNA damage in vivo has suggested that secondary nitroalkanes are much more biologically active than primary nitroalkanes. Tertiary nitroalkanes are generally inactive, probably due to the lack of any alpha hydrogen required for the formation of their nitronic acid forms (aci forms), which have been suggested to be involved in their biological activities. Thus, the formation and stability of the electrophilic aci forms are, among other factors, considered in the evaluation of the carcinogenic potential of nitroalkanes.

Skeleton templates



Substituents:

Substituents, that the user could add 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)
- alkoxy groups (OR)
- nitroso (NO)
- nitro(NO2)
- oxime (NOH).

Comments:

“n" is representing the number of atoms in the ring. “n" must be greater than 2.

Aromatic compounds with nitroso or oxime are evaluated as aromatic amines.

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.

-o-

-o-

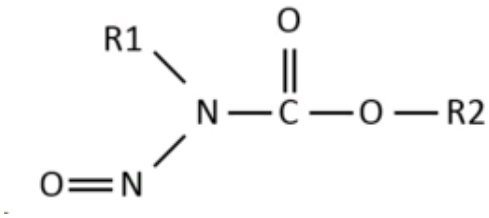
3.13.1 N-nitrosocarbamate

Introduction

N-Nitrosamide compounds represent a well established class of chemical carcinogens. Most of the N-Nitrosamide compounds that have been tested are carcinogenic. Most N-Nitrosamides are activated by simple alkali- or sulfhydryl-catalyzed hydrolysis whereas some may need esterase-catalyzed hydrolysis. Factors that are known to diminish or abolish the carcinogenic activity of N-Nitroso compounds include:

- lack of alpha-hydrogen
- steric hindrance particularly at the alpha-carbon
- bulky substituent
- highly hydrophilic substituentsBoth the nature and the position of the substituents are considered in the overall assessment of carcinogenic potential of N-Nitrosamide compounds.

Skeleton templates



R1, R2:

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

Substituents:

The substituents may include:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- alkoxy (OR),

- phenoxy(OC6H5).

-o-

3.13.2 N-nitrosocarboxylamide

Introduction

N-Nitrosamide compounds represent a well established class of chemical carcinogens. Most of the N-Nitrosamide compounds that have been tested are carcinogenic. Most N-Nitrosamides are activated by simple alkali- or sulfhydryl-catalyzed hydrolysis whereas some may need esterase-catalyzed hydrolysis. Factors that are known to diminish or abolish the carcinogenic activity of N-Nitroso compounds include:

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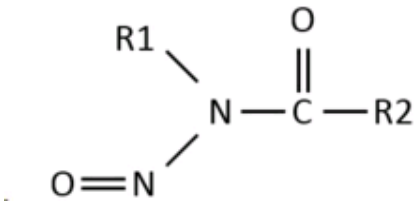


R1, R2:

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

Substituents:

The substituents may include:

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

-o-

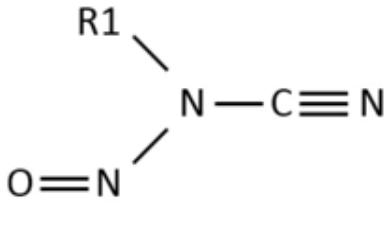
3.13.3 N-nitrosocyanamide

Introduction

N-Nitrosamide compounds represent a well established class of chemical carcinogens. Most of the N-Nitrosamide compounds that have been tested are carcinogenic. Most N-Nitrosamides are activated by simple alkali- or sulfhydryl-catalyzed hydrolysis whereas some may need esterase-catalyzed hydrolysis. Factors that are known to diminish or abolish the carcinogenic activity of N-Nitroso compounds include:

- lack of alpha-hydrogen
- steric hindrance particularly at the alpha-carbon
- bulky substituent
- highly hydrophilic substituentsBoth the nature and the position of the substituents are considered in the overall assessment of carcinogenic potential of N-Nitrosamide compounds.

Skeleton templates



R1, R2:

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

Substituents:

The substituents may include:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- alkoxy (OR),

- phenoxy(OC6H5).

-o-

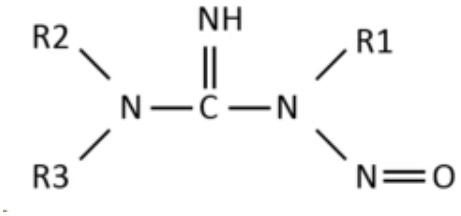
3.13.4 N-nitrosoguanidine

Introduction

N-Nitrosamide compounds represent a well established class of chemical carcinogens. Most of the N-Nitrosamide compounds that have been tested are carcinogenic. Most N-Nitrosamides are activated by simple alkali- or sulfhydryl-catalyzed hydrolysis whereas some may need esterase-catalyzed hydrolysis. Factors that are known to diminish or abolish the carcinogenic activity of N-Nitroso compounds include:

- lack of alpha-hydrogen
- steric hindrance particularly at the alpha-carbon
- bulky substituent
- highly hydrophilic substituentsBoth the nature and the position of the substituents are considered in the overall assessment of carcinogenic potential of N-Nitrosamide compounds.

Skeleton templates



R1, R2:

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

Substituents:

The substituents may include:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- alkoxy (OR),

- phenoxy(OC6H5).

-o-

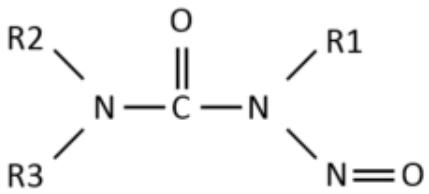
3.13.5 N-nitrosourea

Introduction

N-Nitrosamide compounds represent a well established class of chemical carcinogens. Most of the N-Nitrosamide compounds that have been tested are carcinogenic. Most N-Nitrosamides are activated by simple alkali- or sulfhydryl-catalyzed hydrolysis whereas some may need esterase-catalyzed hydrolysis. Factors that are known to diminish or abolish the carcinogenic activity of N-Nitroso compounds include:

- lack of alpha-hydrogen
- steric hindrance particularly at the alpha-carbon
- bulky substituent
- highly hydrophilic substituentsBoth the nature and the position of the substituents are considered in the overall assessment of carcinogenic potential of N-Nitrosamide compounds.

Skeleton templates



R1, R2:

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

Substituents:

The substituents may include:

- halogens (Cl, Br, I, F),
- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acid (SO3H),
- alkoxy (OR),

- phenoxy(OC6H5).

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3.14 N-nitrosamine Compounds

-o-

3.14.1 N-nitrosamine (acyclic)

Introduction

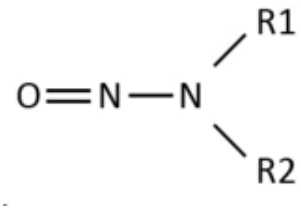
N-Nitroso compounds (N-nitrosamines and N-nitrosamides) represent a well established class of chemical carcinogens. Most of the N-nitroso compounds that have been tested are carcinogenic. Most N-nitrosamines are metabolically bioactivated by alpha-hydroxylation to yield reactive intermediates; some N-nitrosamines may be metabolically activated by alpha- or omega-oxidation.

Factors that are known to diminish or abolish the carcinogenic activity of N-nitroso compounds include:

- lack of an alpha- hydrogen,
- steric hindrance, particularly at the alpha- carbon,
- bulky substituents, and
- highly hydrophilic substituents.

Both the nature and the position of the substituents are considered in the overall assessment of carcinogenic potential of N-nitroso compounds.

Skeleton templates



R1, R2:

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

Substituents:

The substituents may include:

- 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,
- tosylate (TOS).

-o-

3.14.2 N-nitrosamine (cycloaliphatic)

Introduction

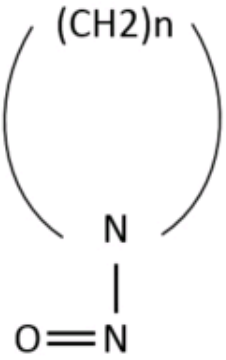
N-Nitroso compounds (N-nitrosamines and N-nitrosamides) represent a well established class of chemical carcinogens. Most of the N-nitroso compounds that have been tested are carcinogenic. Most N-nitrosamines are metabolically bioactivated by alpha-hydroxylation to yield reactive intermediates; some N-nitrosamines may be metabolically activated by alpha- or omega-oxidation.

Factors that are known to diminish or abolish the carcinogenic activity of N-nitroso compounds include:

- lack of an alpha- hydrogen,
- steric hindrance, particularly at the alpha- carbon,
- bulky substituents, and
- highly hydrophilic substituents.

Both the nature and the position of the substituents are considered in the overall assessment of carcinogenic potential of N-nitroso compounds.

Skeleton templates



R1, R2:

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

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:

The substituents may include:

- 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,
- tosylate (TOS).

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3.15 Organophosphorus Compounds

-o-

3.15.1 (Thio)phosphoramides

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

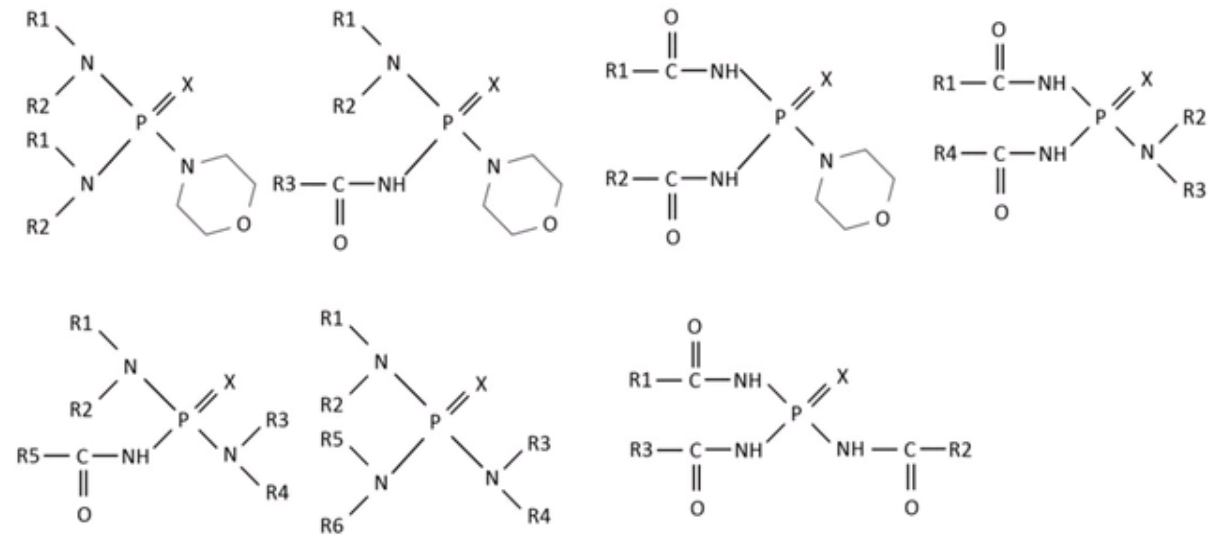
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1-6:

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

X: Heteroatom: oxygen or sulphur.

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

-o-

3.15.2 Cyclophosphamides

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

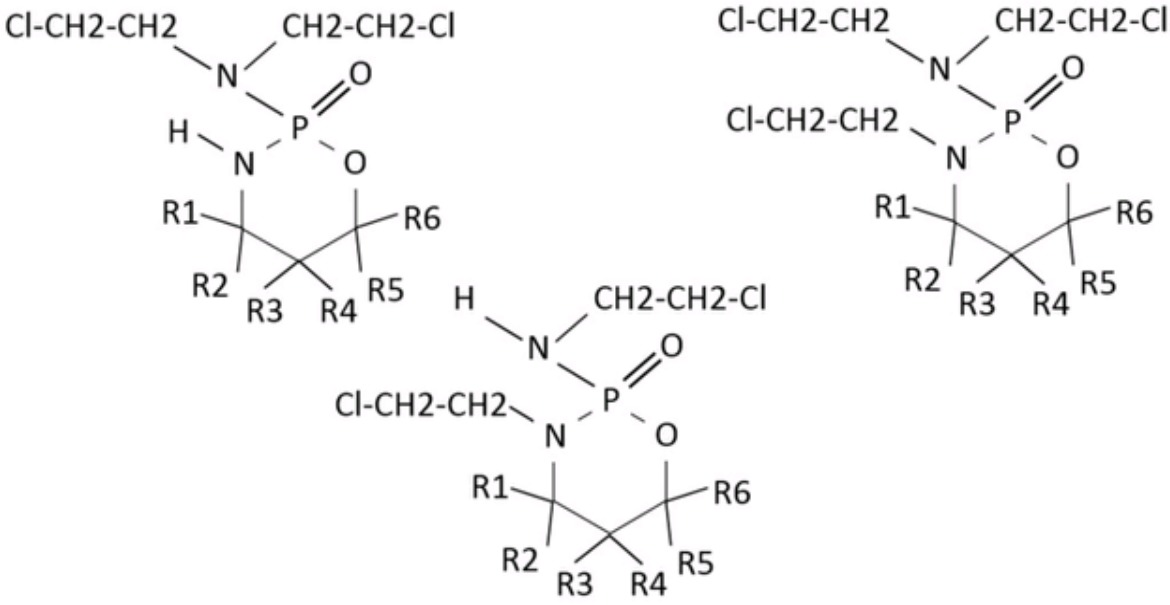
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1-6:

- aliphatic (alkyl chains, cycloC6, vinyl, allyl)
- aromatic types (phenyl, benzyl, phenylethyl, carbamyl)
- hydrogen atom, halogen atoms (Cl, Br, I or F), hydroxyl group (-OH), sulfo- or carboxyl gropus (-COOH or -SO3H)

-o-

3.15.3 Dialkyl (thio)phosphonates

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

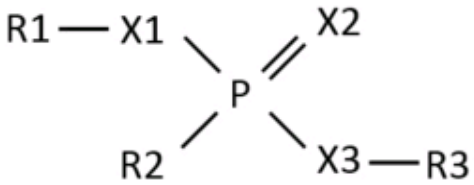
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1-3: aliphatic (alkyl chains, vinyl, allyl).

X: Heteroatom: oxygen or sulphur.

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

3.15.4 Dialkyl (thio)phosphoroamidate

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

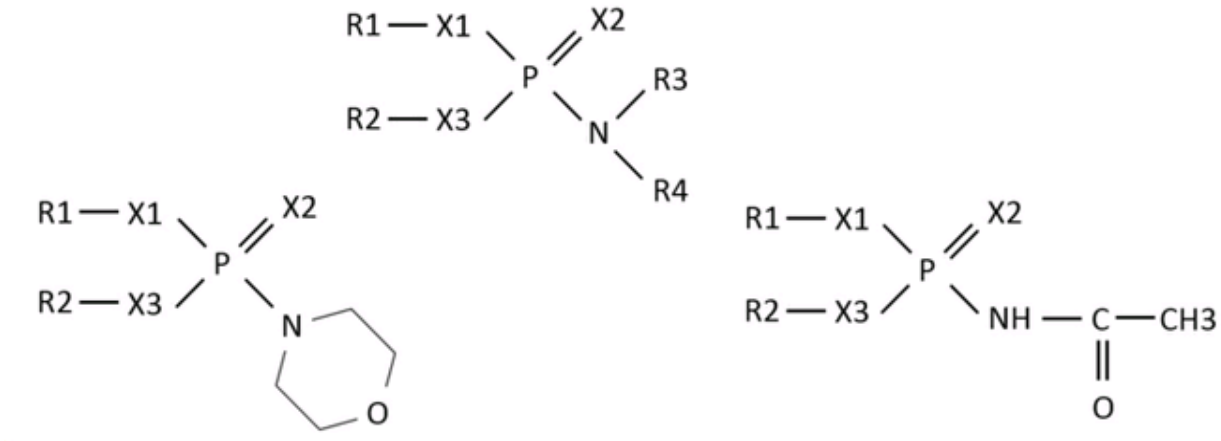
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1-4:

- aliphatic (alkyl chains, cycloC6, vinyl, allyl)

- aromatic types (phenyl, benzyl, phenylethyl, carbamyl)

X: Heteroatom: oxygen or sulphur.

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

-o-

3.15.5 Dialkylmonoaryl (thio)phosphates

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

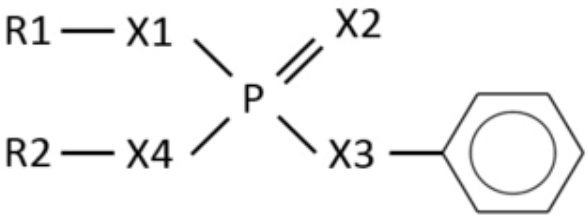
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1-2:

- aliphatic (alkyl chains, vinyl, allyl)

X: Heteroatom: oxygen or sulphur.

Substituents: Halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid

(COOH), sulfonic acid (SO3H), and additionally alkyl (Cn) on the aryl ring.

-o-

3.15.6 Diaryl (thio)phosphonates

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

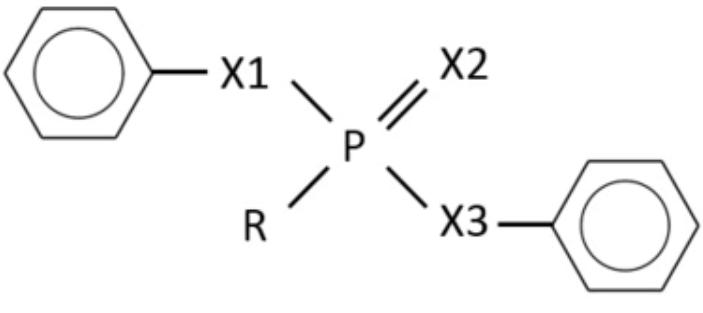
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R:

- aliphatic (alkyl chains, vinyl, allyl)

X: Heteroatom: oxygen or sulphur.

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

-o-

3.15.7 Monoalkyldiaryl and triaryl (thio)phosphates

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

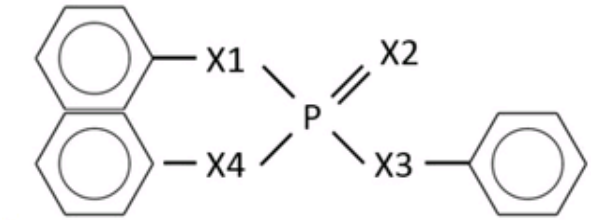
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

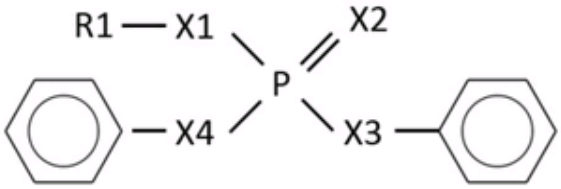
The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates





R1:

- aliphatic (alkyl chains, vinyl, allyl)

X: Heteroatom: oxygen or sulphur.

Substituents: Halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid

(COOH), sulfonic acid (SO3H), and additionally alkyl (Cn) on the aryl ring.

-o-

3.15.8 Monoalkylmonoaryl (thio)phosphonates

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

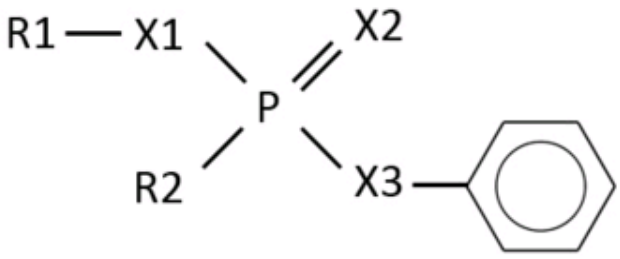
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R:

- aliphatic (alkyl chains, vinyl, allyl)

X: Heteroatom: oxygen or sulphur.

Substituents: Halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid

(COOH), sulfonic acid (SO3H), and additionally alkyl (Cn) on the aryl ring.

-o-

3.15.9 Monoalkylmonoaryl and diaryl (thio) phosphoroamidate

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

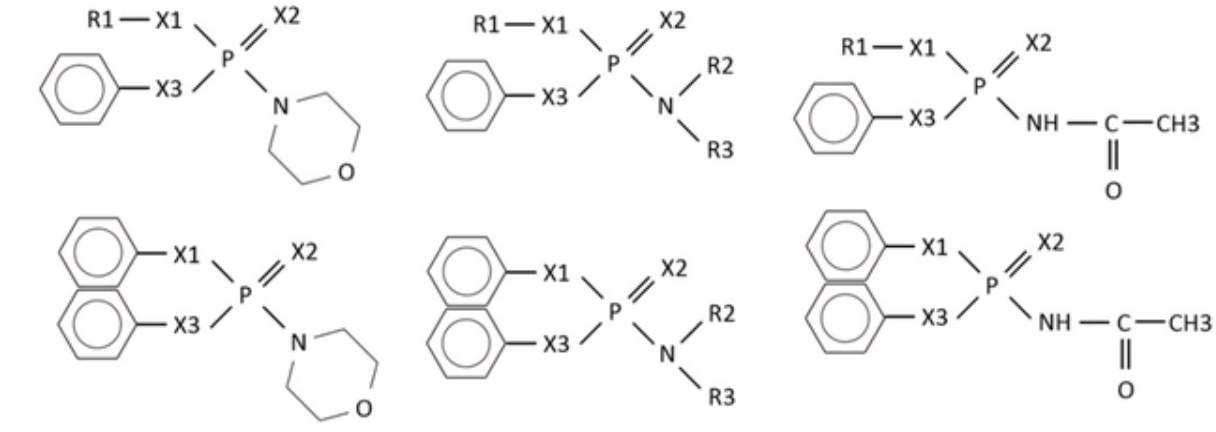
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1:

- aliphatic (alkyl chains, vinyl, allyl), hydrogen.

R2, R3:

- aliphatic (alkyl chains, vinyl, allyl), hydrogen (H),
- aryl (benzyl, phenyl), hydrogen (H).

X: Heteroatom: oxygen or sulphur.

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

-o-

3.15.10 Phosphinates and thiophosphinates

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

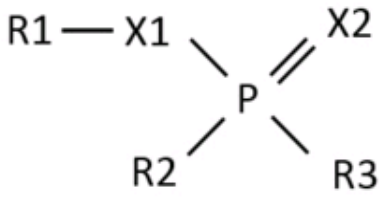
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1-3:

- aliphatic (alkyl chains, vinyl, allyl), hydrogen.
- aryl (benzyl, phenyl).

X: Heteroatom: oxygen or sulphur.

Substituents: Halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid

(COOH), sulfonic acid (SO3H), and additionally alkyl (Cn) on the aryl ring.

-o-

3.15.11 Phosphines and phosphine oxides

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

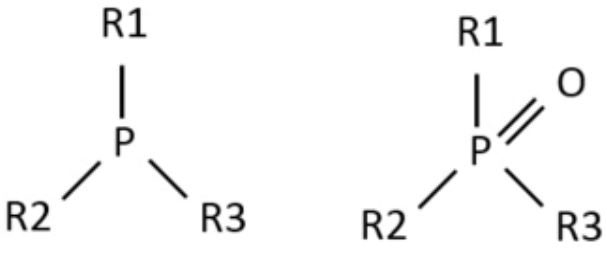
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1-3:

- aliphatic (alkyl chains, vinyl, allyl),
- aryl (phenyl).

Substituents: Halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid

(COOH), sulfonic acid (SO3H), and additionally alkyl (Cn) on the aryl ring.

-o-

3.15.12 Trialkyl (thio)phosphates

Introduction

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent. The principal carcinogenic OP compounds are:

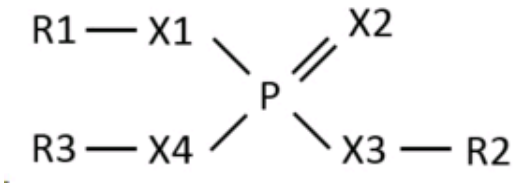
- alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates,thiophosphonates, thiophosphoroamidates.
- phosphoramides, and
- phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

- nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.
- presence or absence of electron-withdrawing group which may enhance alkylating activity.
- ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.
- potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

Skeleton templates



R1-3:

- aliphatic (alkyl chains, vinyl, allyl)

X: Heteroatom: oxygen or sulphur.

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

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3.16 PAH

-o-

3.16.1 Homocyclic Polyaromatic Hydrocarbons

Introduction

The compound that you have selected is a member of the Polycyclic Aromatic Hydrocarbon (PAH) class, a well studied class of chemical carcinogens. Most carcinogenic PAHs require metabolic activation; several activation pathways (bay region dihydrodiol epoxide formation, one-electron oxidation, biomethylation) have been identified. The critical factors that determine the carcinogenic activity of PAHs are:

- molecular size and shape,
- tendency to yield carbonium ion or free radical after metabolic activation,
- availability of resonance stabilization of the reactive intermediate.

Structural features known to be associated with carcinogenic activity of PAHs include:

- favorable molecular size, shape, and planarity,
- lack of a high degree of symmetry,
- unsubstituted 'bay' region benzo ring,
- unoccupied peri- position adjacent to the bay-region benzo ring (e.g. 5-position of benz[a]anthracene; referred to as the '-P effect' if occupied)
- substitution at the intra bay-region peri- position of the inner naphtho moiety of the bay-region with methyl or small alkyl group (e.g. 5-position of chrysene, referred to as the '+B effect'),
- substitution at the L-region with methyl group(s),
- lack of bulky or highly hydrophilic substituents.

The unsubstituted parent compound, Benzo[c]phenanthrene, has been tested for carcinogenic activity. A baseline level of concern of LOW-MODERATE has been assigned to the parent compound considering its activity in comparison to benzo[a]pyrene, which has a concern level of high.

Skeleton templates:

Aromatic structures containing 3-6 six-membered rings.

Substituents:

The following substituents may be placed on the skeletons:

- hydroxyl (OH),
- carboxylic acid (COOH),
- sulfonic acide (SO3H),
- halogens (Cl, Br, F, I),
- cyano (CN),
- alkyl (Cn),
- alkoxy (OCn),
- formyl (C(O)H).

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3.17 Thiocarbonyls

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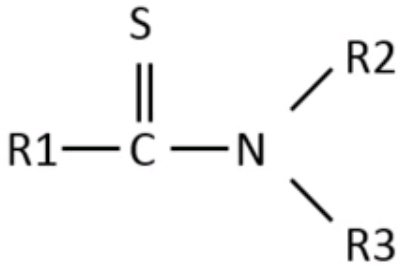
3.17.1 Thioamide

Introduction

The mechanisms of carcinogenesis by thiourea, thiouracil and their derivatives are not clearly understood.It is generally believed that the modes of carcinogenic action of these substances are identical, at least in thyroid tumorigenesis.They act indirectly by causing hormonal imbalance resulting from an altered thyroid-pituitary relationship.

Skeleton templates:



R1-3:

- aliphatic (alkyl chain, cycloC6, vinyl, allyl)
- aromatic types (phenyl, benzyl, phenylethyl carbamyl)

Substituents: No restrictions.

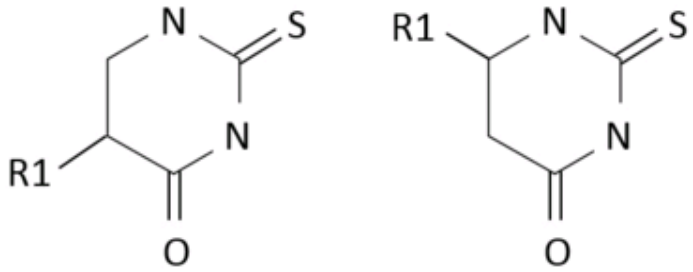
-o-

3.17.2 Thiouracil

Introduction

The mechanisms of carcinogenesis by thiourea, thiouracil and their derivatives are not clearly understood.It is generally believed that the modes of carcinogenic action of these substances are identical, at least in thyroid tumorigenesis.They act indirectly by causing hormonal imbalance resulting from an altered thyroid-pituitary relationship.

Skeleton templates:



R1:

- aliphatic (alkyl chain, cycloC6, vinyl, allyl)
- aromatic types (phenyl, benzyl, phenylethyl carbamyl)

Substituents: No restrictions.

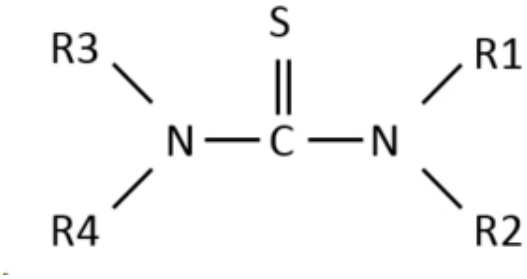
-o-

3.17.3 Thiourea (acyclic)

Introduction

The mechanisms of carcinogenesis by thiourea, thiouracil and their derivatives are not clearly understood.It is generally believed that the modes of carcinogenic action of these substances are identical, at least in thyroid tumorigenesis.They act indirectly by causing hormonal imbalance resulting from an altered thyroid-pituitary relationship.

Skeleton templates:



R1-4:

- aliphatic (alkyl chain, cycloC6, vinyl, allyl)
- aromatic types (phenyl, benzyl, phenylethyl carbamyl)

Substituents: No restrictions.

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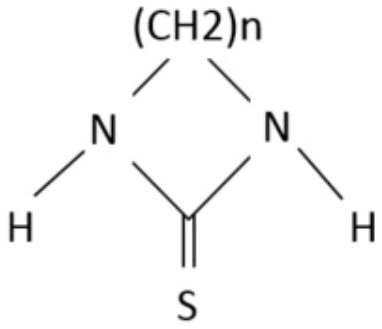
3.17.4 Thiourea (cyclic)

Introduction

The mechanisms of carcinogenesis by thiourea, thiouracil and their derivatives are not clearly understood.It is generally believed that the modes of carcinogenic action of these substances are identical, at least in thyroid tumorigenesis.They act indirectly by causing hormonal imbalance resulting from an altered thyroid-pituitary relationship.

Skeleton templates:



R:

- aliphatic (alkyl chain, cycloC6, vinyl, allyl)
- aromatic types (phenyl, benzyl, phenylethyl carbamyl)

Substituents: No restrictions.

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3.18 Urea Compounds

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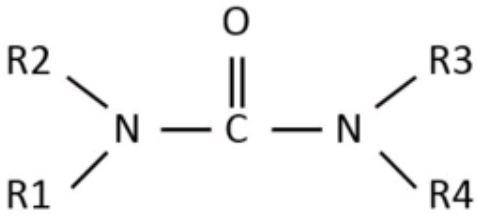
3.18.1 Urea

Introduction

The mechanisms of carcinogenesis by thiourea, thiouracil and their derivatives are not clearly understood.It is generally believed that the modes of carcinogenic action of these substances are identical, at least in thyroid tumorigenesis.They act indirectly by causing hormonal imbalance resulting from an altered thyroid-pituitary relationship.

Skeleton templates:



R1-4: alkyl chain, hydrogen, aryl (nonspecific), alkoxy.

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4. Workflow

4.1 Input a target chemical

The system allows the evaluation of a single chemical only. There are three ways to input a chemical:

- by CAS;
- by chemical name;
- by structure.

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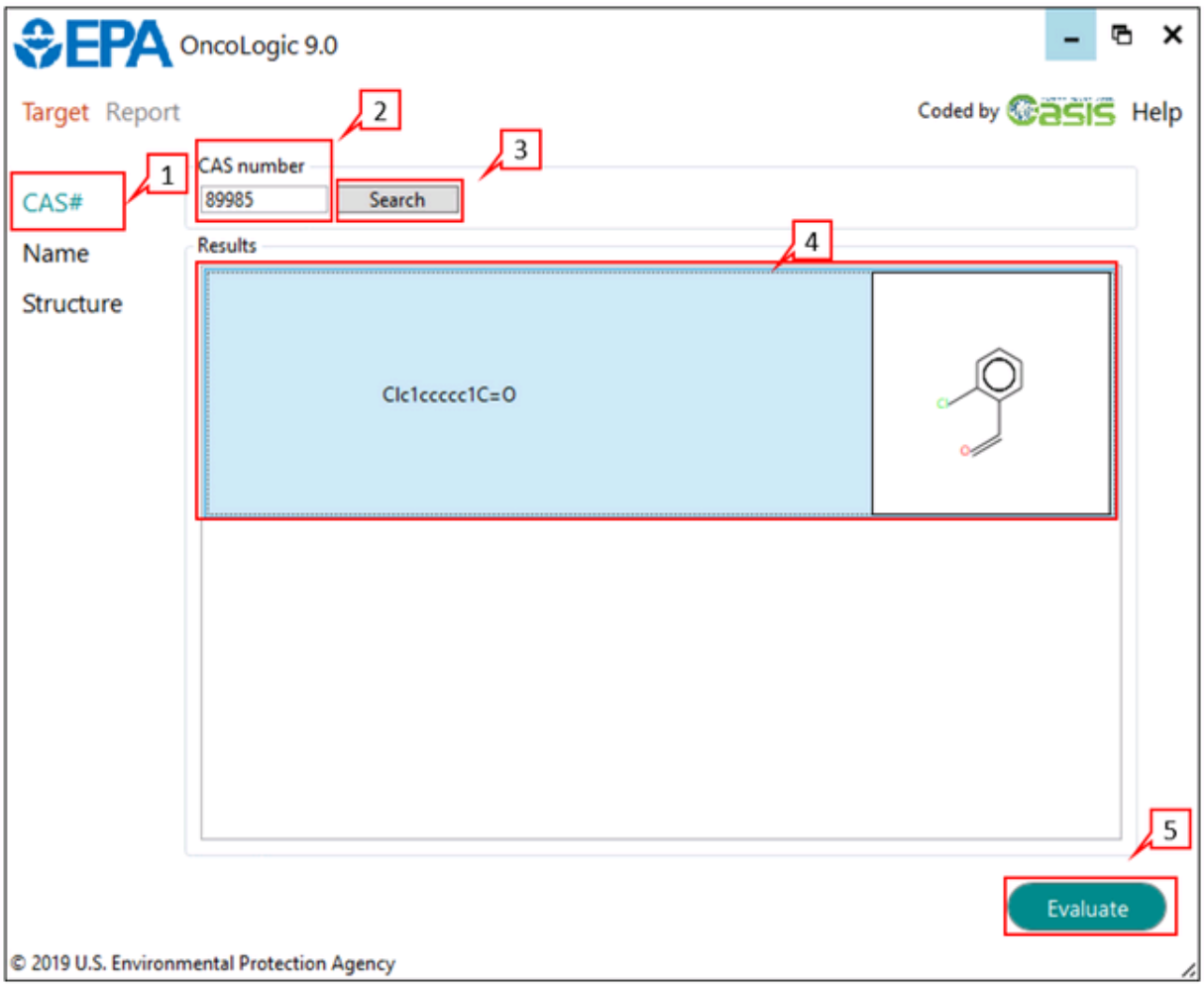
4.1.1 Enter a chemical by CAS

The input of a target chemical by CAS (Chemical Abstract Service) is only possible if the user has already installed on the same computer QSAR Toolbox 4.3 system (available at: https://qsartoolbox.org/download/).

To enter a chemical by its CAS number simply click *CAS #* (1), enter the CAS number of the chemical without hyphens (2), click the *Search* button(3) (Figure 1). In cases when the CAS # could be related to more than one substance, more than one chemical identity could be retrieved. Selecting the chemical of interest (4) colours the background in blue. The button *Evaluate* is activated and its color turns green. Click *Evaluate* (5).



Fugure 1

-o-

4.1.2 Entering a chemical by chemical name

The input of a target chemical by name is only possible if the user has already installed on the same computer QSAR Toolbox 4.3 system (available at: https://qsartoolbox.org/download/).

To enter a chemical via its name click *Name* (1), fill in the name of the target chemical (or part of it) (2), choose a search option (3) and then click *Search* (4) (Figure 1). All chemicals that match the search criteria will be listed. You should select the one of interest (5) The button *Evaluate* is activated and its color turns in green. Finally, click *Evaluate* (6).

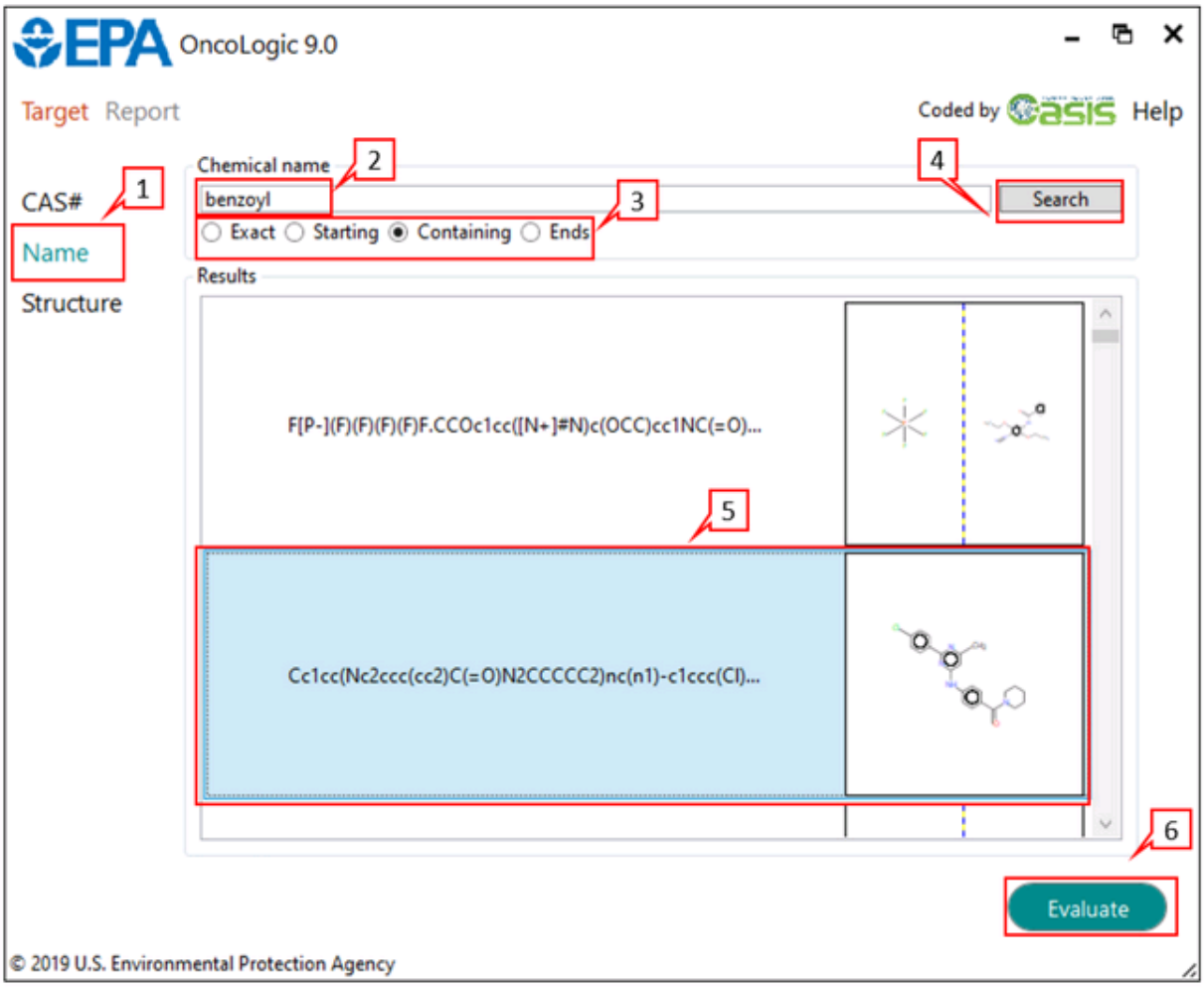


Figure 1

-o-

4.1.3 Enter a chemical by structure

Atom connectivity could be defined by drawing the chemical 2D structure. Select *Structure* (1), then press *Edit* (2), paste the SMILES (3) or draw the structure of the target chemical in the Structure Drawing window (4). Click the *Wrench* button (5) to adjust the bond lengths and angles. If the atom connectivity is coded correctly the complete drawing must be confirmed by clicking *OK* (6) (Figure 1). Finally, click *Evaluate* (7).

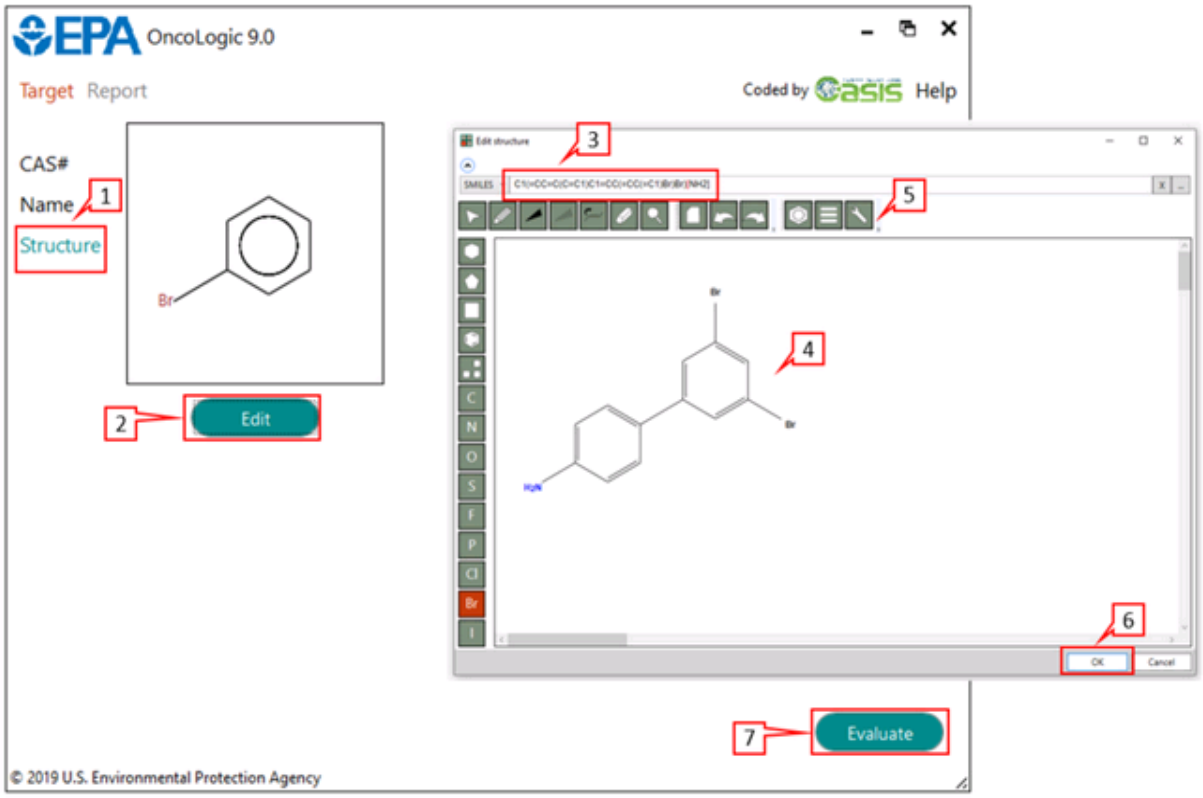


Figure 1

In case of incorrect entry code, the incorrect entry will be colored and the structure will not be displayed. Short explanation text appears under the SMILES field (Figure 2).

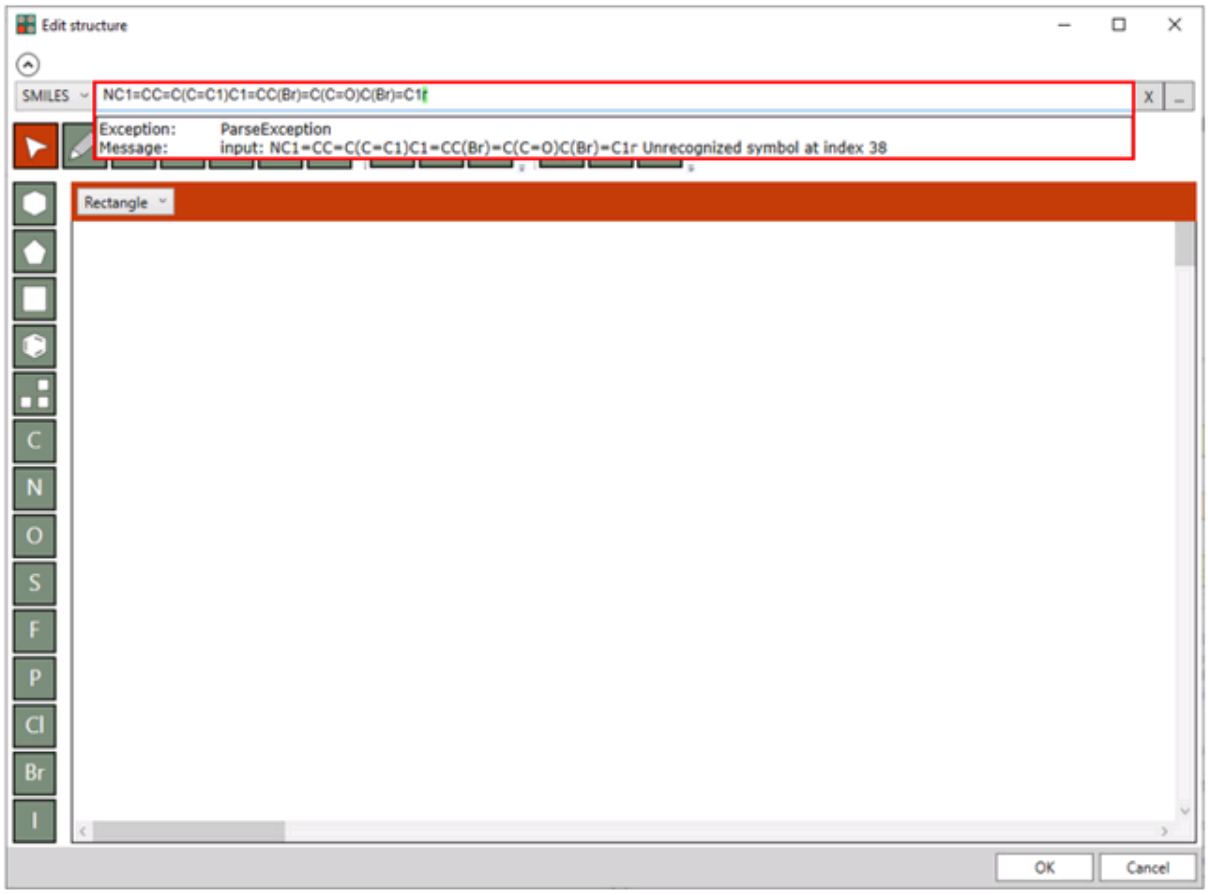

Edit structure
SMILES
NC1=CC=C(C=C1)C1=CC(Br)=C(C=O)C(Br)=C1r
X
Exception: ParseException
Message: input: NC1=CC=C(C=C1)C1=CC(Br)=C(C=O)C(Br)=C1r Unrecognized symbol at index 38
Rectangle
C
N
O
S
F
P
Cl
Br
I
OK
Cancel

Figure 2

-o-

4.2 Evaluate

-o-

4.2.1 Evaluation steps

First step - Analyzing chemical categories

The evaluation of the target chemical starts with profiling the target by the primary categorization scheme, implemented in the system. The scheme contains all 33 migrated chemical classes (see section 3. Target chemical classes). Hence, one chemical could belong to more than one chemical class and thus the user will have more than one evaluation.

The first categorization of the target takes a little time and the window displayed in Figure 1 appears.

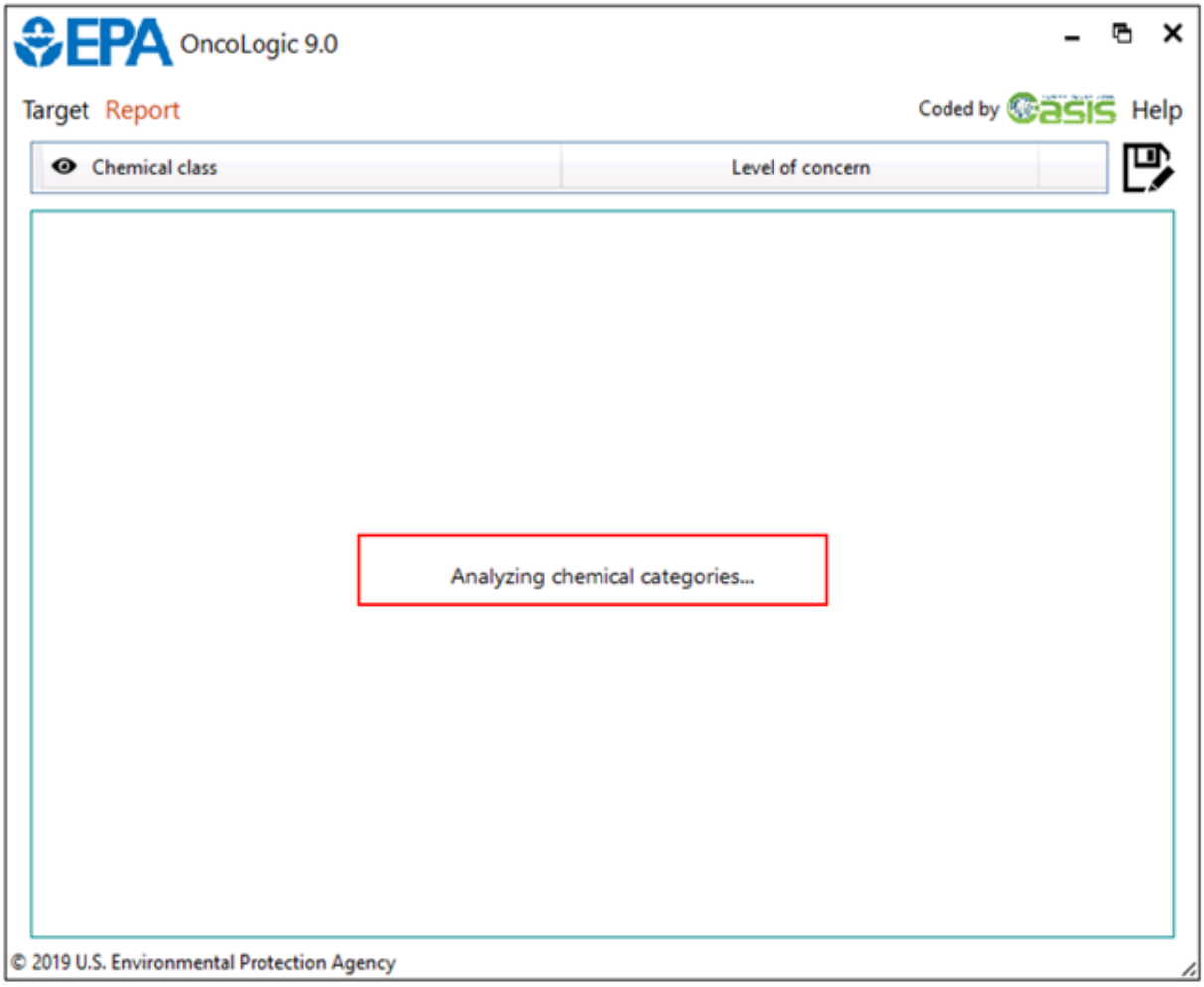


Figure 1

Second step - Evaluate

When the system has analyzed the target chemical, the relevant chemical class or classes are displayed (Figure 2). The next step is to click on *Evaluate* (1 and/ or 2).

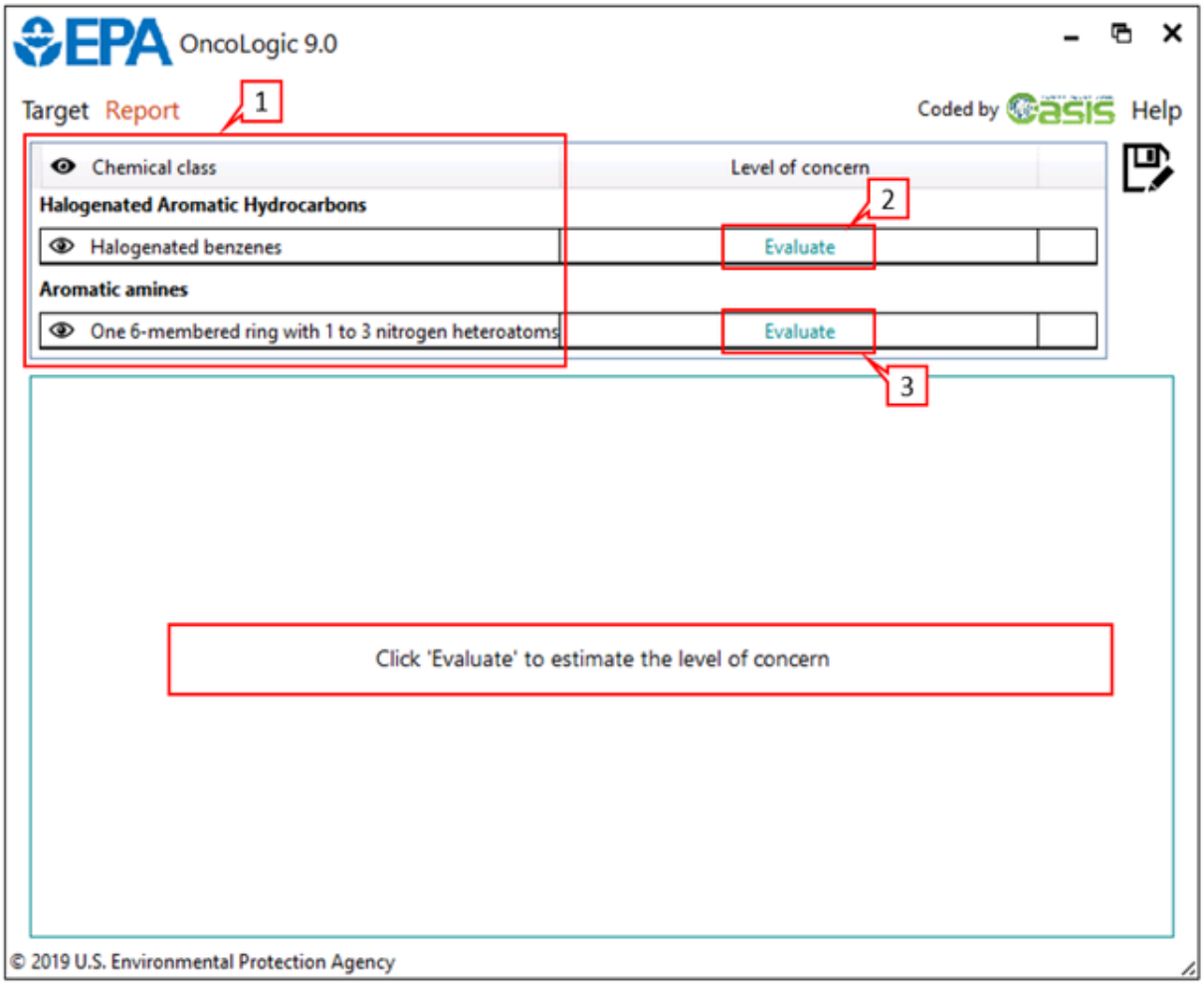


Figure 2

The evaluation may take some time and in this case a progress bar appears (Figure 3).

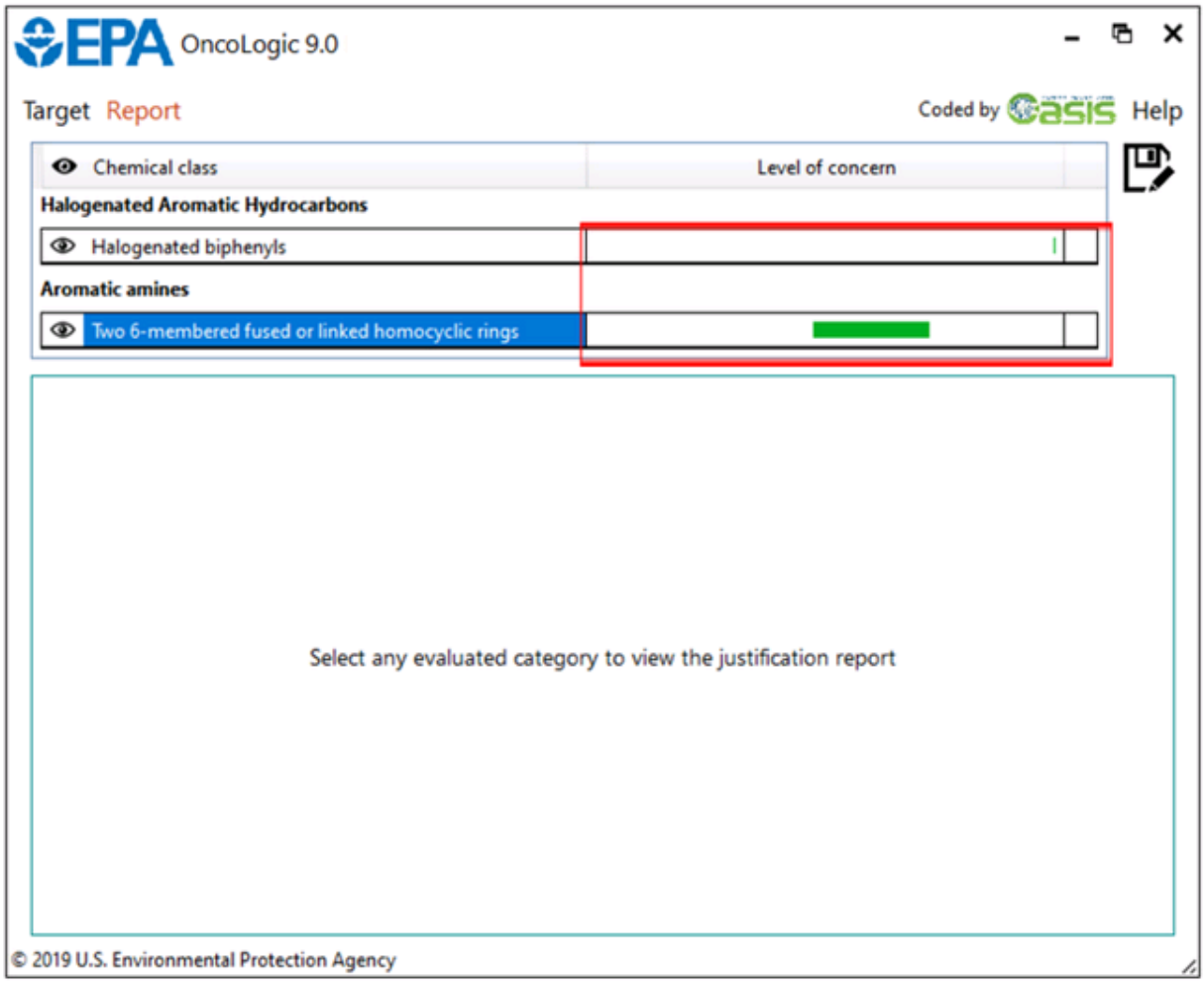


Figure 3

When the evaluation is completed, level of concern is assigned to each chemical class (Figure 4).

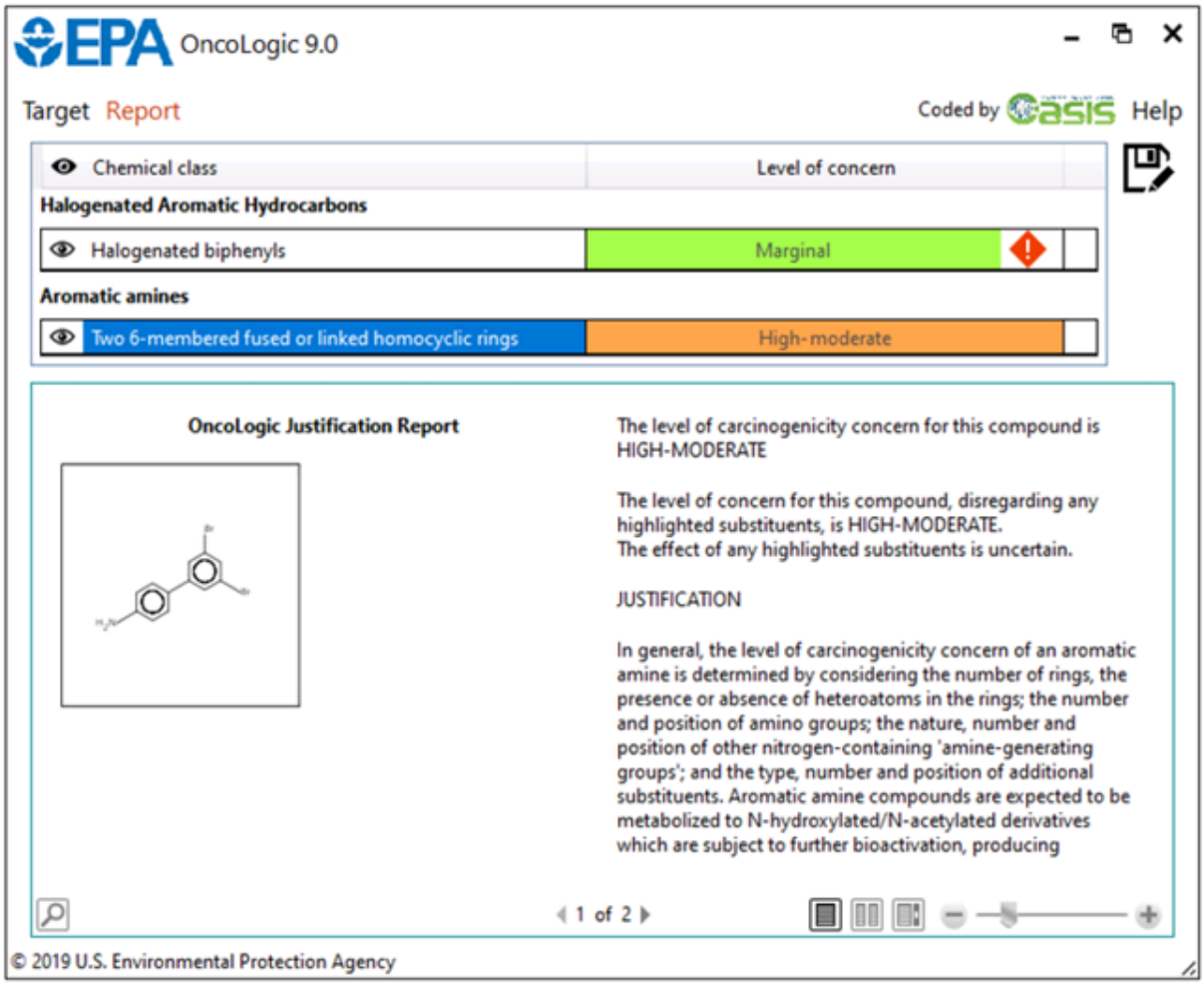

EPA OncoLogic 9.0
Target Report
Coded by Oasis
Help
Chemical class
Level of concern
Halogenated Aromatic Hydrocarbons
Halogenated biphenyls
Marginal
Aromatic amines
Two 6-membered fused or linked homocyclic rings
High-moderate
OncoLogic Justification Report
The level of carcinogenicity concern for this compound is HIGH-MODERATE
The level of concern for this compound, disregarding any highlighted substituents, is HIGH-MODERATE.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
In general, the level of carcinogenicity concern of an aromatic amine 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
1 of 2
© 2019 U.S. Environmental Protection Agency

Figure 4

-o-

4.2.2 Analyzing the prediction result

The system is fully transparent and the obtained result could be analyzed in details. The user could click on *View evaluation scheme* icon (1 or 2) (Figure 1).

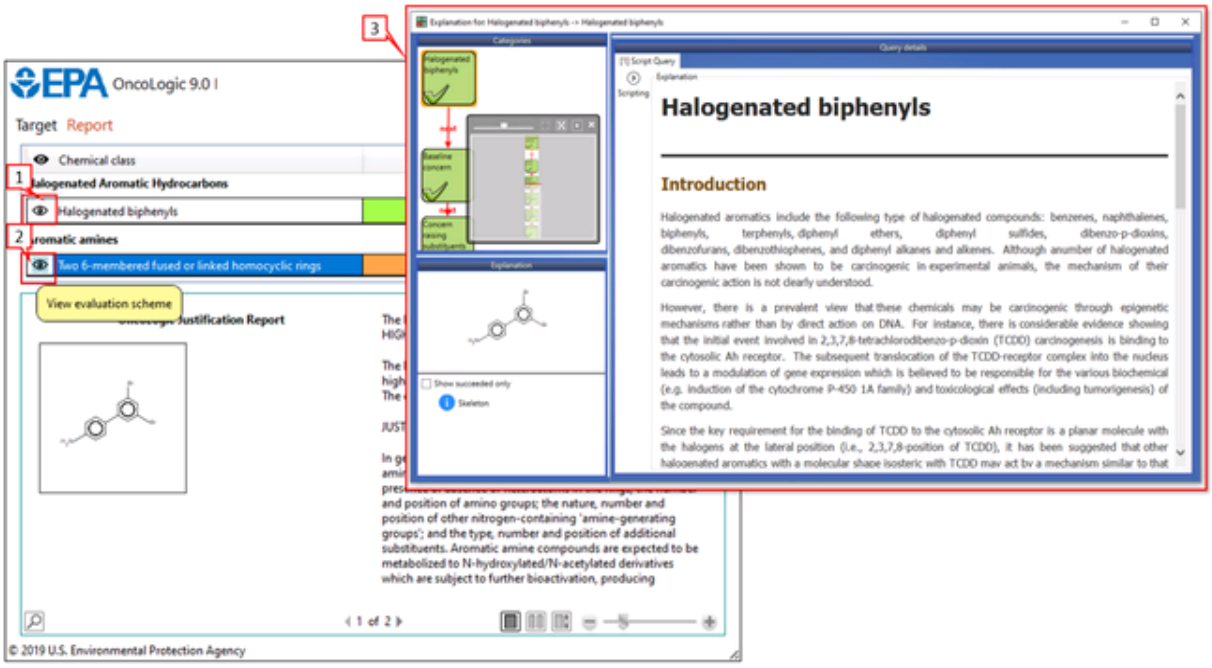


Figure 1

The evaluation scheme has the following fields (Figure 2):

- A. Node browser
- B. 2D depiction
- C. List with all possible steps
- D. Explanation field

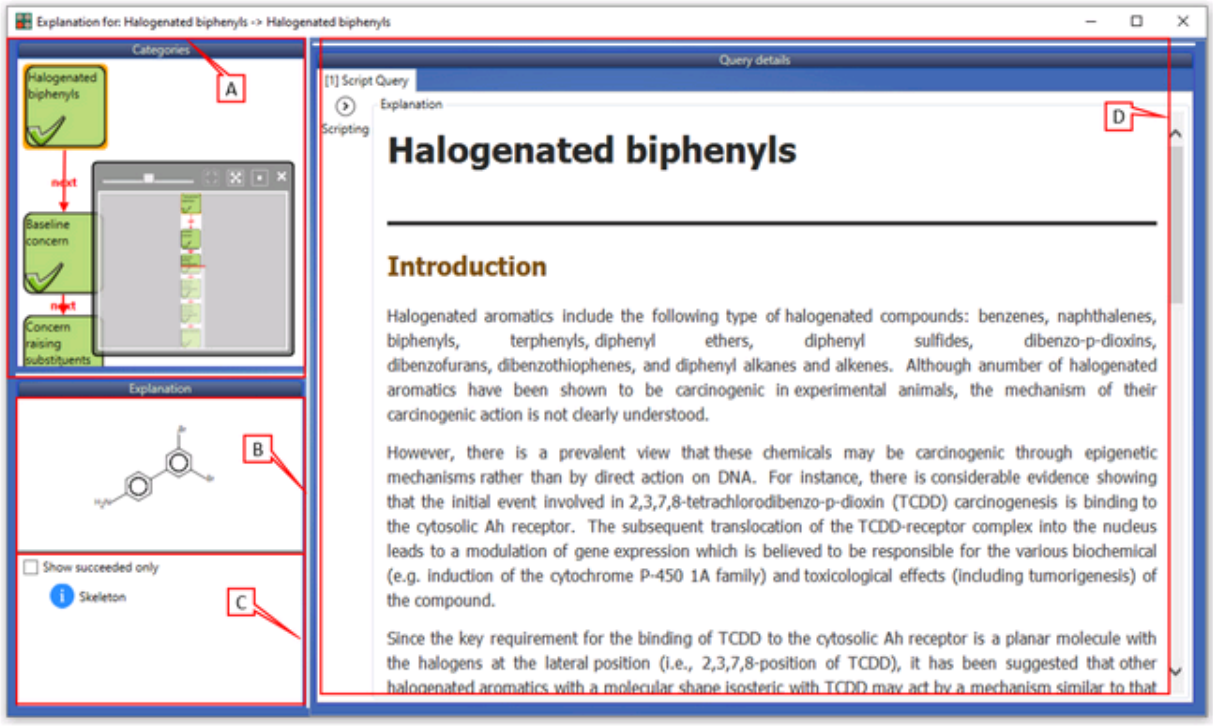

Explanation for: Halogenated biphenyls -> Halogenated biphenyls
Categories
Halogenated biphenyls
A
next
Baseline concern
next
Concern raising substituents
Explanation
B
Show succeeded only
Skeleton
C
Query details
[1] Script Query
Explanation
Scripting
D
Halogenated biphenyls
Introduction
Halogenated aromatics include the following type of halogenated compounds: benzenes, naphthalenes, biphenyls, terphenyls, diphenyl ethers, diphenyl sulfides, dibenzo-p-dioxins, dibenzofurans, dibenzothiophenes, and diphenyl alkanes and alkenes. Although anumber of halogenated aromatics have been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is not clearly understood.
However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.
Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other

Figure 2

-o-

A. Node browser

A. Node browser

Each of the migrated 33 chemical classes has its own unique scheme with rules, the same as in OncoLogic 8.0 and re-coded in the new platform. The number of the nodes can vary depending on the type of the rules related to the chemical class. In the current example, the scheme with the rules consists of six nodes:

a. Halogenated biphenyls - general information
b. Baseline concern
c. Concern raising substituents
d. Concern neutral substituents
e. Concern reducing substituents
f. Final concern

The navigation panel (1) facilitates the exploring of the scheme (2) by moving the nodes, zoom in or zoom out (Figure 1).

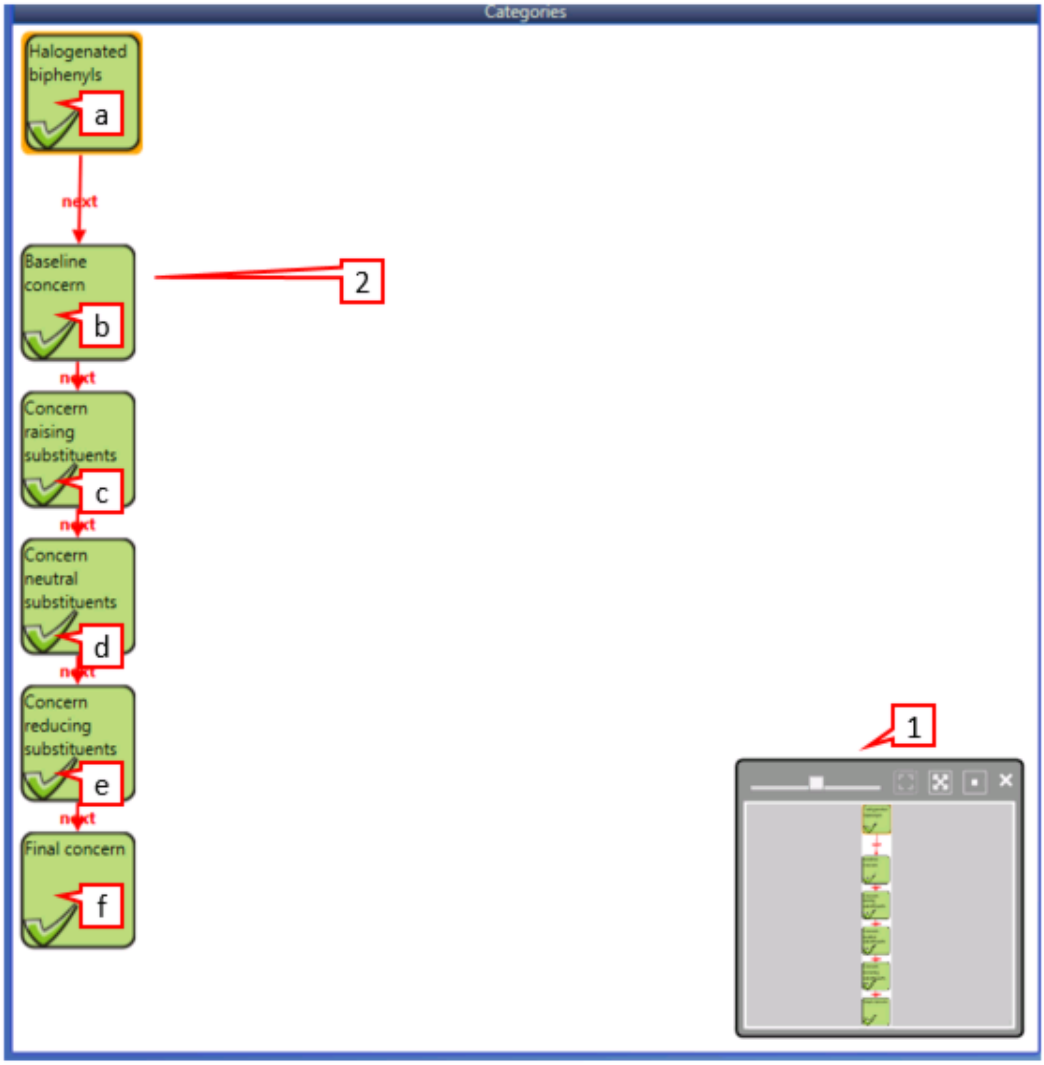


Figure 1

Clicking *Fill bounds with center* (1) moves the scheme (2) in the center of the Node browser. Right-click on the field in the navigation panel (3) allows movement of the scheme (2) to left or to right. Using the scroll bar (4) helps to zoom in or to zoom out (Figure 2) and the zoom level (4) is shown.Click on the white filed in the *Node browser* (5) helps to move the nodes up and down, too. Click on the "X" (6) closes the navigation panel.

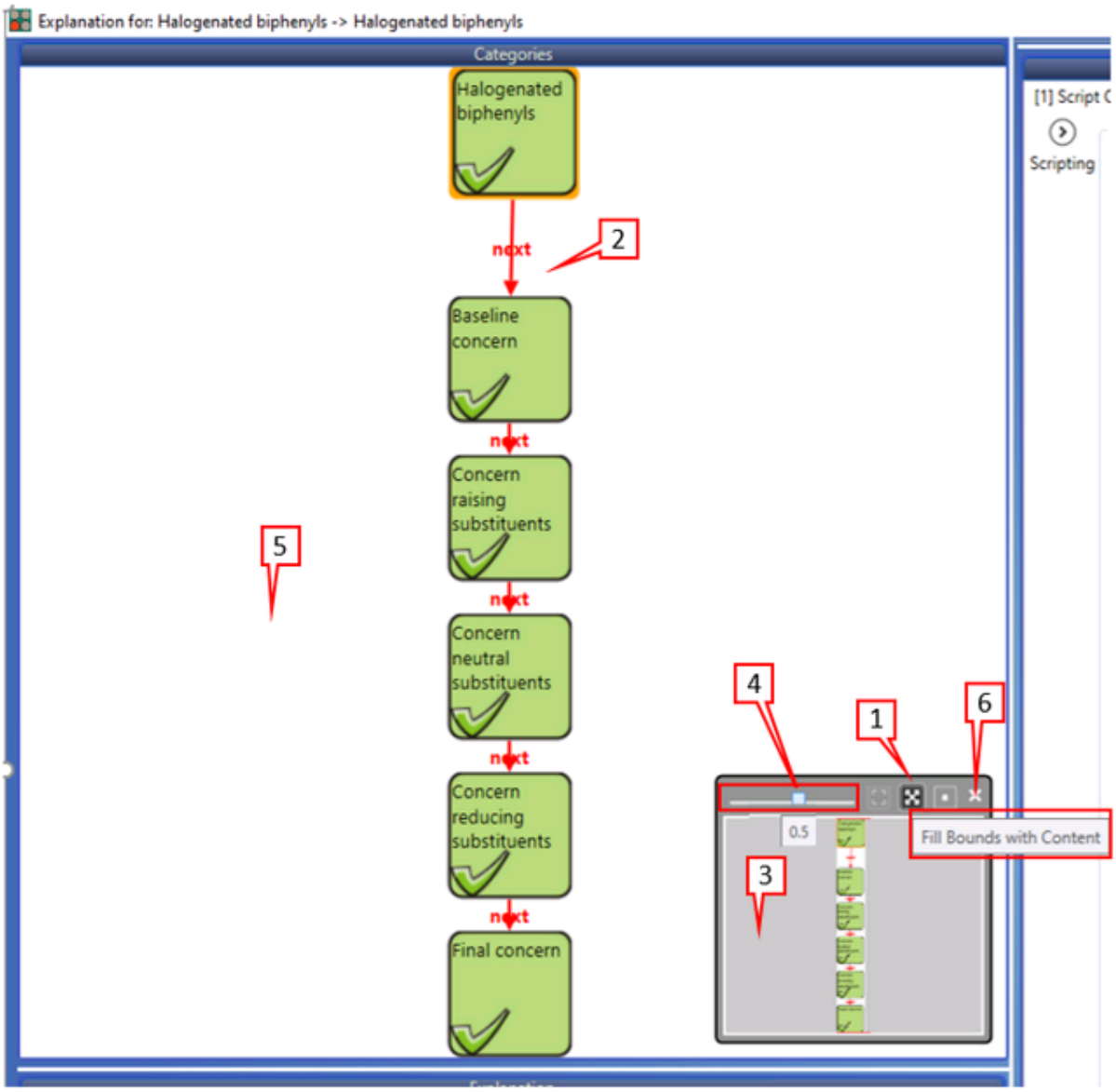


Figure 2

-o-

B. 2D depiction

B. 2D depiction

Here, the target chemical is depicted (Figure 1). This filed of the evaluation scheme is related to the *Node browser filed* and depends on the selected node there.

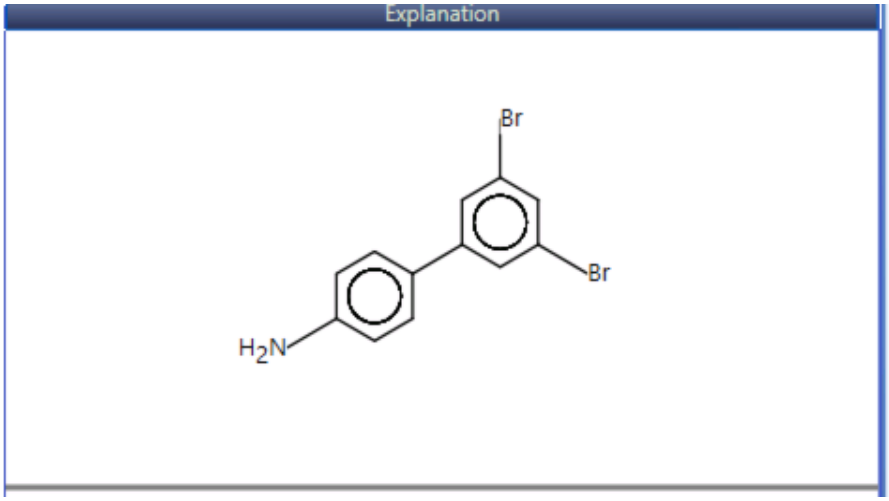


Figure 1

-o-

C. List with all possible steps

C. List with possible steps

Each of the scheme nodes has its own contain, migrated from OncoLogic 8.0. Let's go back to the example. If you click on Baseline concern node (1), the *List with all possible steps* (2) is filled with information as well as the *Explanation field* (3) (Figure 1). The blue node (3) stands for "information". The red node (4) denotes not succeeded nodes. The green nodes (5) indicate the rules that are applied successfully.

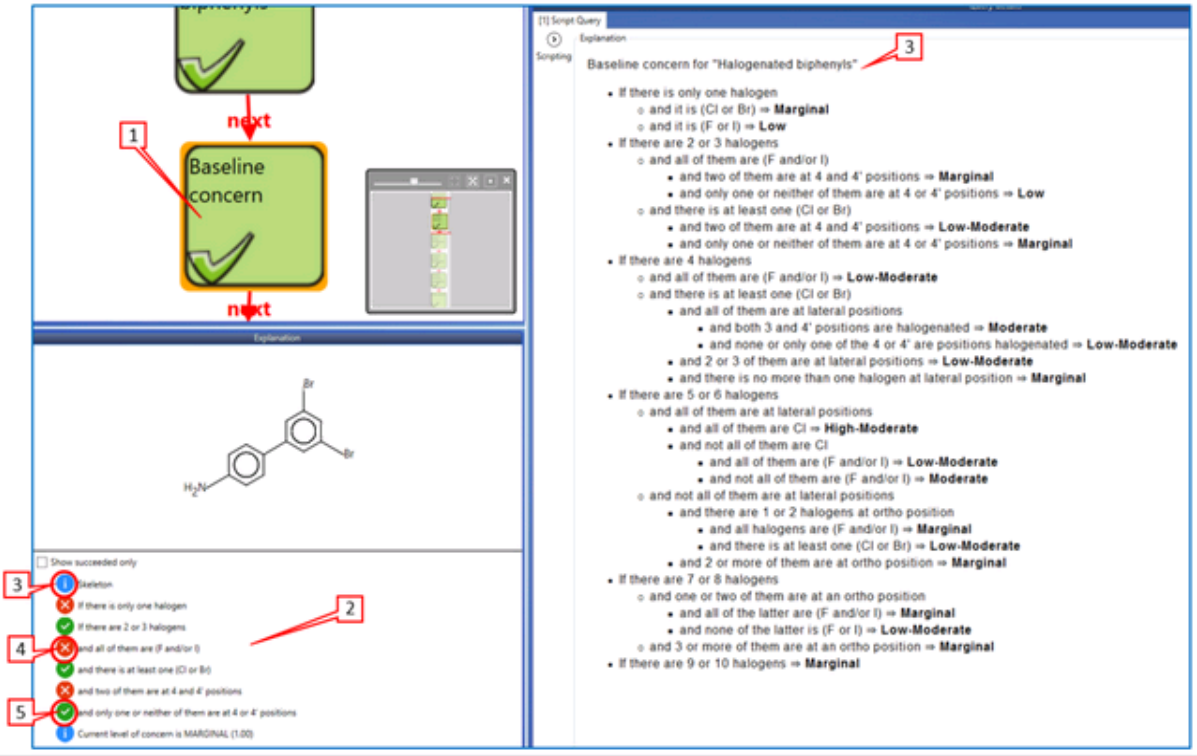


Figure 1

Click on one of the lines in the *List with all possible steps* (1) highlights the same information in the *Explanation field* (2) and in 2D depiction (3). (Figure 2 and 3).

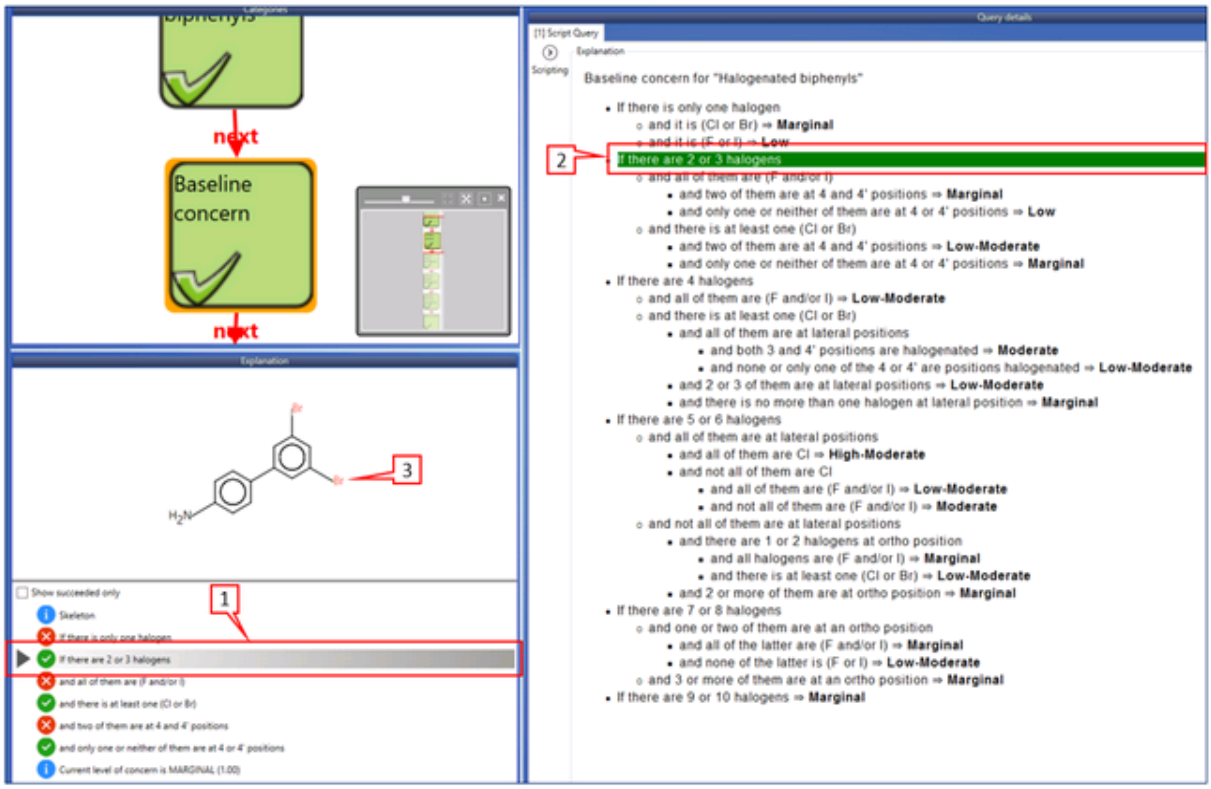


Figure 2

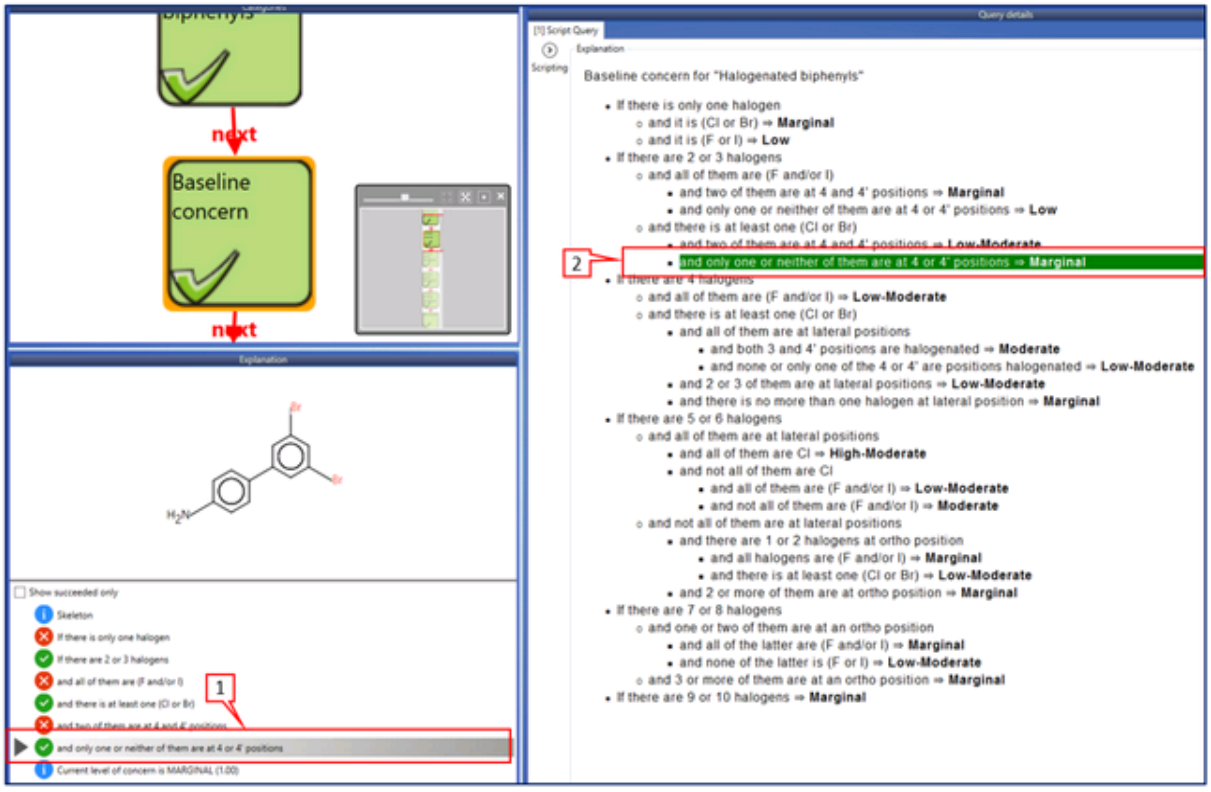


Figure 3

If *Show succeeded only* (1) is selected, only the highlighted in green steps from the list remain (Figure 4).

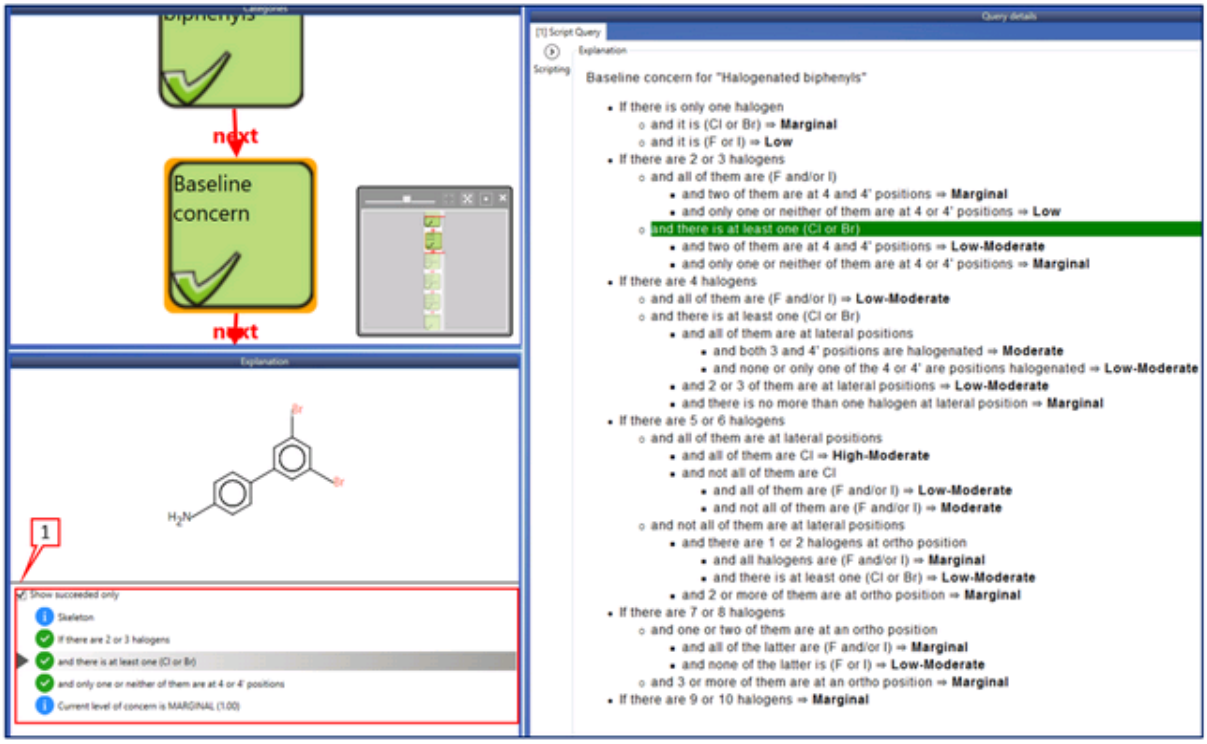


Figure 4

-o-

D. Explanation field

Each of the scheme nodes contain rules, extracted from OncoLogic 8.0 and migrated here, in OncoLogic 9.0. All rules are presented in a very transparent way. The rules (1) are displayed in the *Explanation field* and the code behind the rules can be observed (2), too (Figure 1).

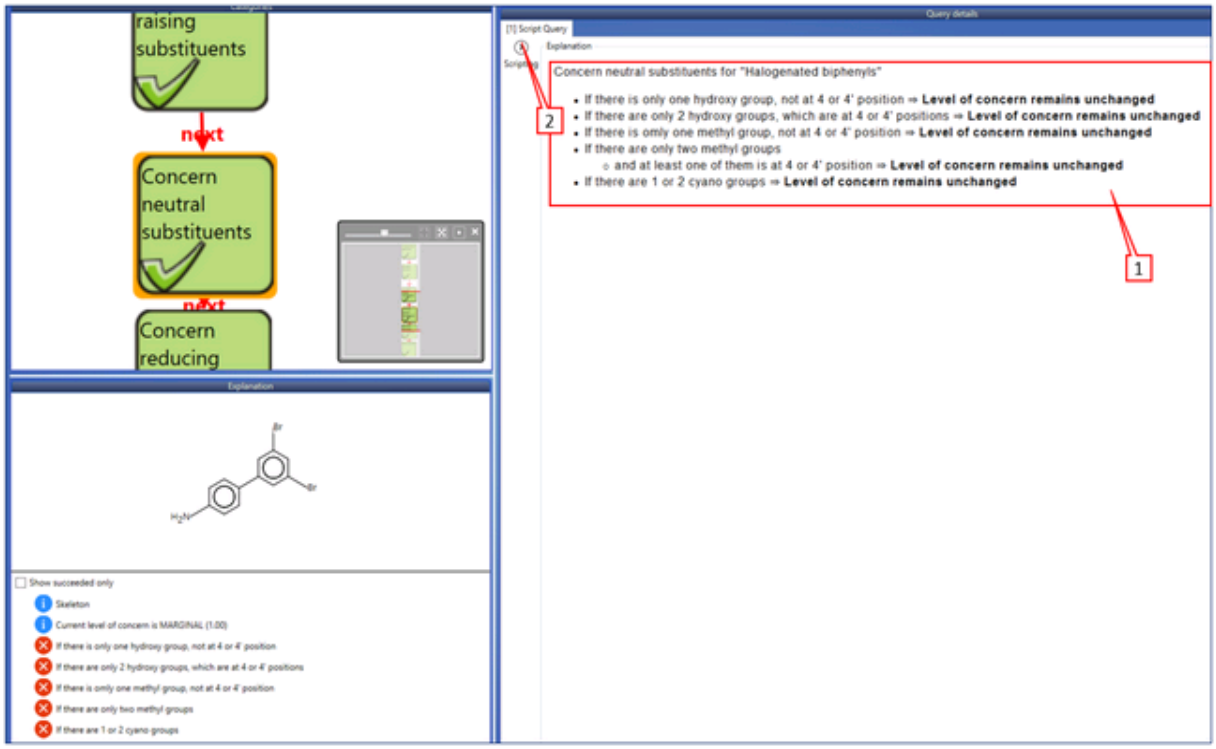


Figure 1

The script could be observed easily (Figure 2).

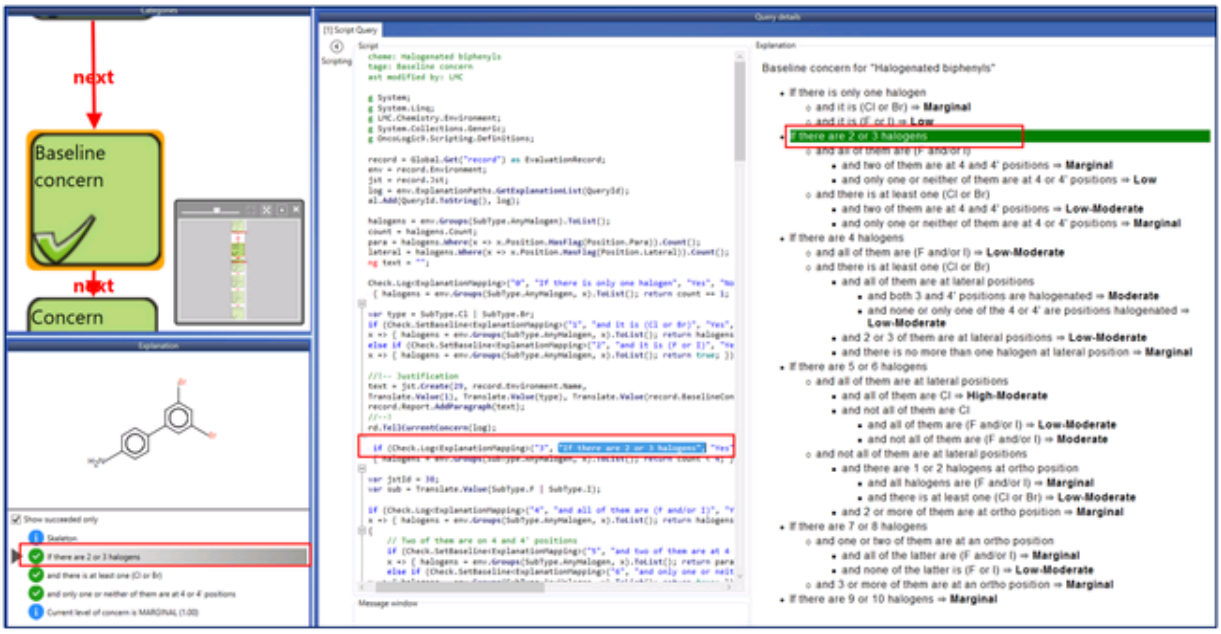

next
Baseline concern
next
Concern
Baseline concern for "Halogenated biphenyls"
If there is only one halogen
and it is (Cl or Br) ⇒ Marginal
and it is (F or I) ⇒ Low
If there are 2 or 3 halogens
and all of them are (F and/or I)
and two of them are at 4 and 4' positions ⇒ Marginal
and only one or neither of them are at 4 or 4' positions ⇒ Low
and there is at least one (Cl or Br)
and two of them are at 4 and 4' positions ⇒ Low-Moderate
and only one or neither of them are at 4 or 4' positions ⇒ Marginal
If there are 4 halogens
and all of them are (F and/or I) ⇒ Low-Moderate
and there is at least one (Cl or Br)
and all of them are at lateral positions
and both 3 and 4' positions are halogenated ⇒ Moderate
and none or only one of the 4 or 4' are positions halogenated ⇒ Low-Moderate
and 2 or 3 of them are at lateral positions ⇒ Low-Moderate
and there is no more than one halogen at lateral position ⇒ Marginal
If there are 5 or 6 halogens
and all of them are at lateral positions
and all of them are Cl ⇒ High-Moderate
and not all of them are Cl
and all of them are (F and/or I) ⇒ Low-Moderate
and not all of them are (F and/or I) ⇒ Moderate
and not all of them are at lateral positions
and there are 1 or 2 halogens at ortho position
and all halogens are (F and/or I) ⇒ Marginal
and there is at least one (Cl or Br) ⇒ Low-Moderate
and 2 or more of them are at ortho position ⇒ Marginal
If there are 7 or 8 halogens
and one or two of them are at an ortho position
and all of the latter are (F and/or I) ⇒ Marginal
and none of the latter is (F or I) ⇒ Low-Moderate
and 3 or more of them are at an ortho position ⇒ Marginal
If there are 9 or 10 halogens ⇒ Marginal

Figure 2

-o-

4.3 Report

-o-

4.3.1 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. The concern levels are listed in Table 1

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

Table 1

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.

-o-

4.3.2 Save and search the report

Once the *Evaluate* is executed, the report (1) appears on the window and could be saved (2) as pdf-file, displayed in different page mode (3, 4 and 5) and zoomed in or zoomed out (6) (Figure 1).

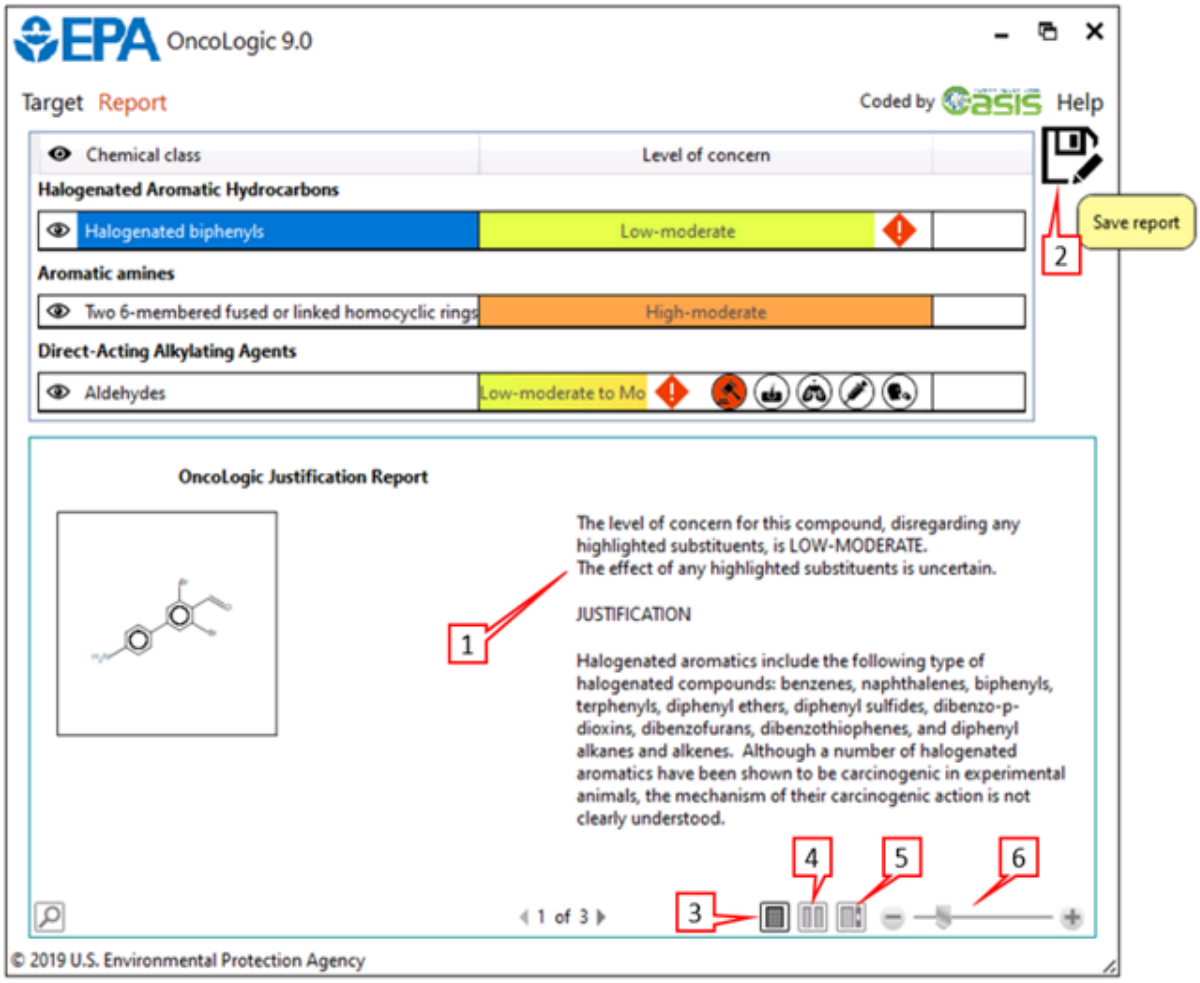


Figure 1

The text also could also be selected (1) and copied with right click (2) (Figure 2).

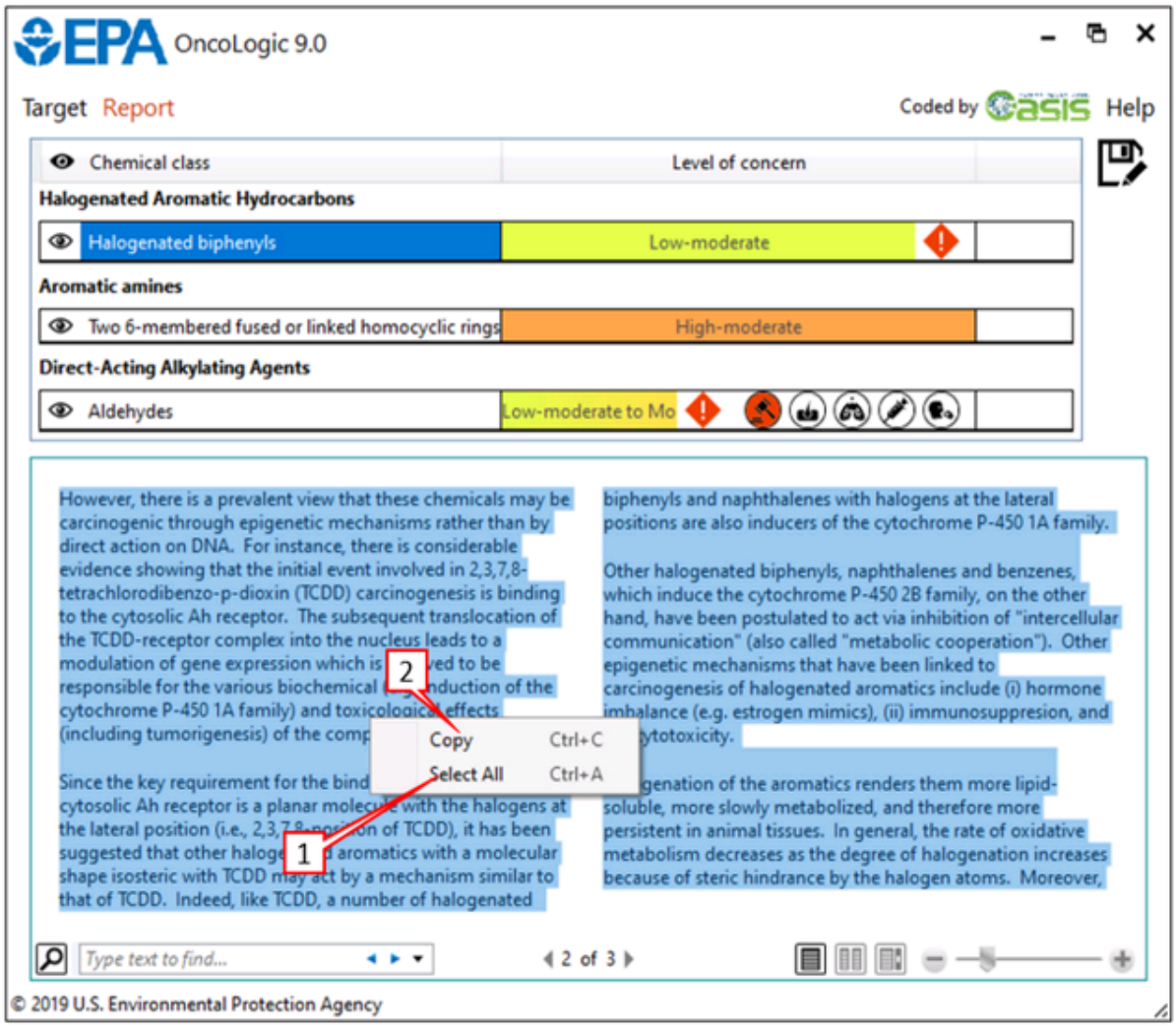


Figure 2

To search in the text first click on the magnifier icon (1), type a word to search with (2) and it is found in the text (3) (Figure 3).

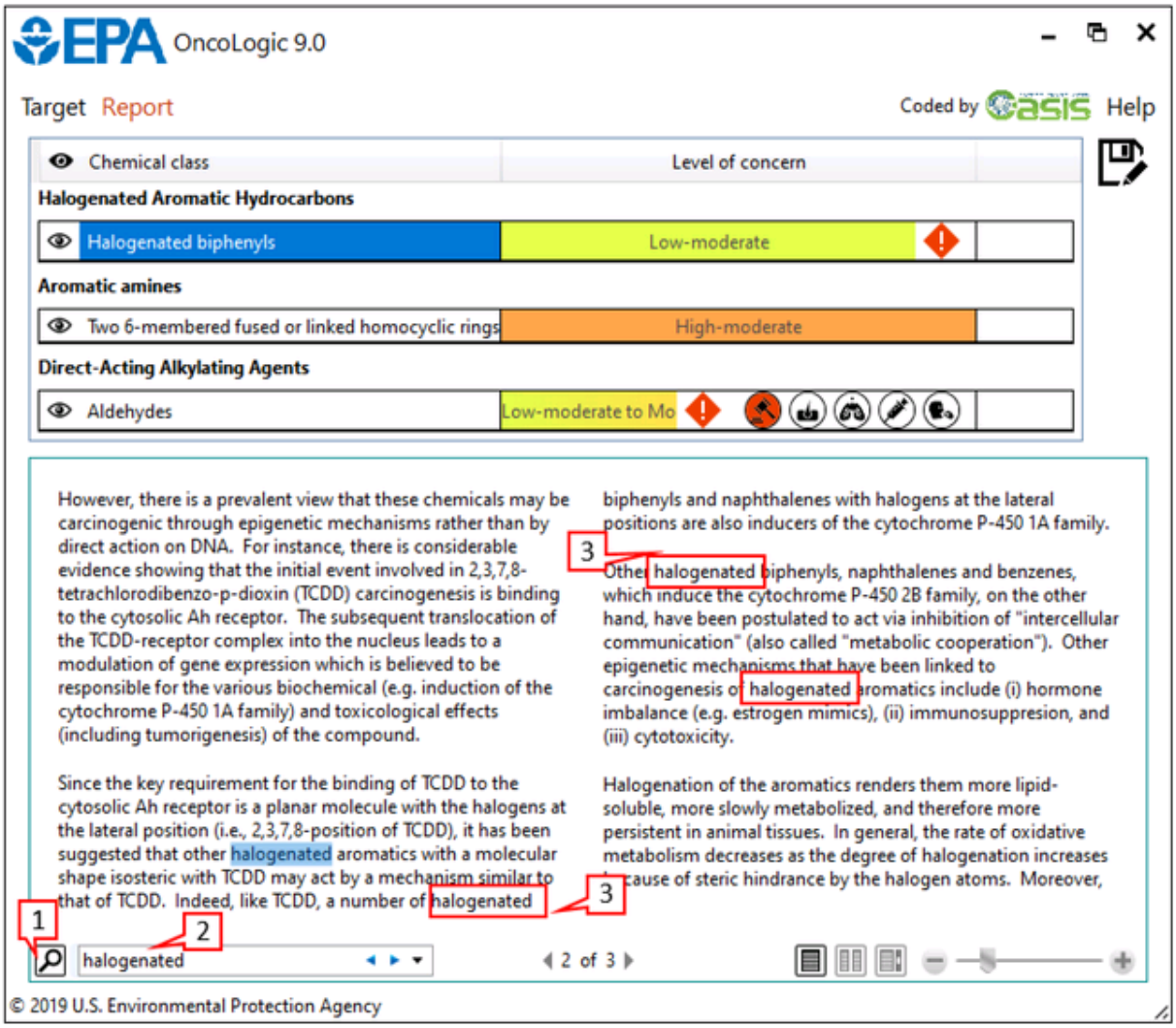

EPA OncoLogic 9.0
Target Report
Coded by oasis Help
Chemical class
Level of concern
Halogenated Aromatic Hydrocarbons
Halogenated biphenyls
Low-moderate
Aromatic amines
Two 6-membered fused or linked homocyclic rings
High-moderate
Direct-Acting Alkylating Agents
Aldehydes
Low-moderate to Mo
However, there is a prevalent view that these chemicals may be carcinogenic through epigenetic mechanisms rather than by direct action on DNA. For instance, there is considerable evidence showing that the initial event involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) carcinogenesis is binding to the cytosolic Ah receptor. The subsequent translocation of the TCDD-receptor complex into the nucleus leads to a modulation of gene expression which is believed to be responsible for the various biochemical (e.g. induction of the cytochrome P-450 1A family) and toxicological effects (including tumorigenesis) of the compound.
Since the key requirement for the binding of TCDD to the cytosolic Ah receptor is a planar molecule with the halogens at the lateral position (i.e., 2,3,7,8-position of TCDD), it has been suggested that other halogenated aromatics with a molecular shape isosteric with TCDD may act by a mechanism similar to that of TCDD. Indeed, like TCDD, a number of halogenated
biphenyls and naphthalenes with halogens at the lateral positions are also inducers of the cytochrome P-450 1A family.
Other halogenated biphenyls, naphthalenes and benzenes, which induce the cytochrome P-450 2B family, on the other hand, have been postulated to act via inhibition of "intercellular communication" (also called "metabolic cooperation"). Other epigenetic mechanisms that have been linked to carcinogenesis of halogenated aromatics include (i) hormone imbalance (e.g. estrogen mimics), (ii) immunosuppresion, and (iii) cytotoxicity.
Halogenation of the aromatics renders them more lipid-soluble, more slowly metabolized, and therefore more persistent in animal tissues. In general, the rate of oxidative metabolism decreases as the degree of halogenation increases because of steric hindrance by the halogen atoms. Moreover,
1
2
halogenated
2 of 3
3
3
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Figure 3

-o-

4.4 Main sections and symbols

The program interface includes two main modules - target module (1) and report module (2). Report module is divided into two parts - chemical class (3) and level of concern (4) (Figure 1).

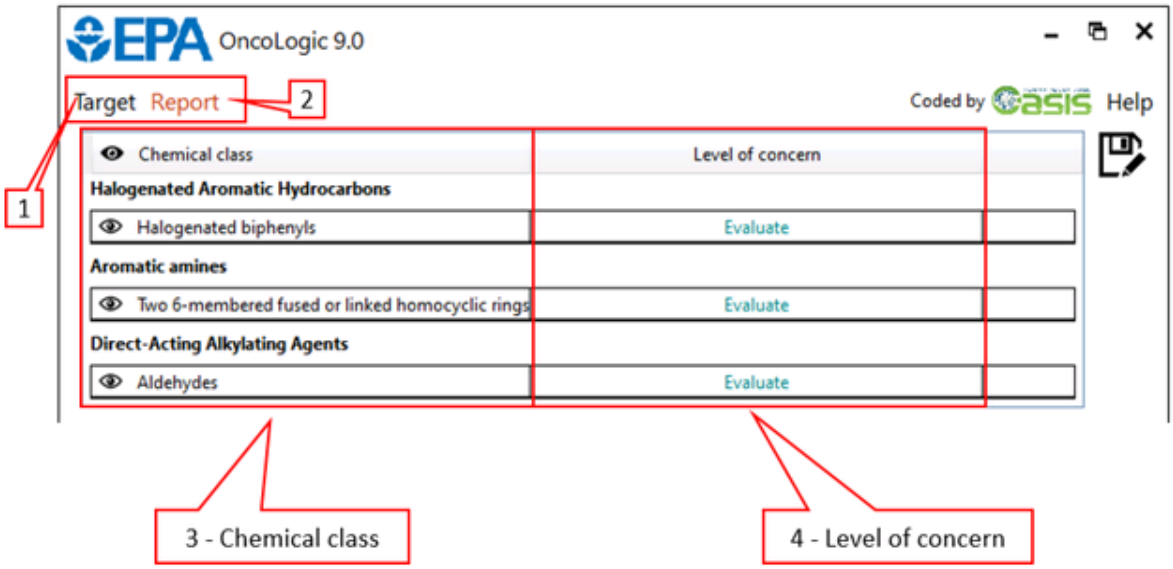

Figure 1

After the evaluation, for some chemical classes appear additional symbols such as so called "Z" group (1) and different routes of exposure (2) if available (Figure 2).
Z-group symbol pays attention on the presence of substituents in target molecule the effect of which on the final level of concern is uncertain.

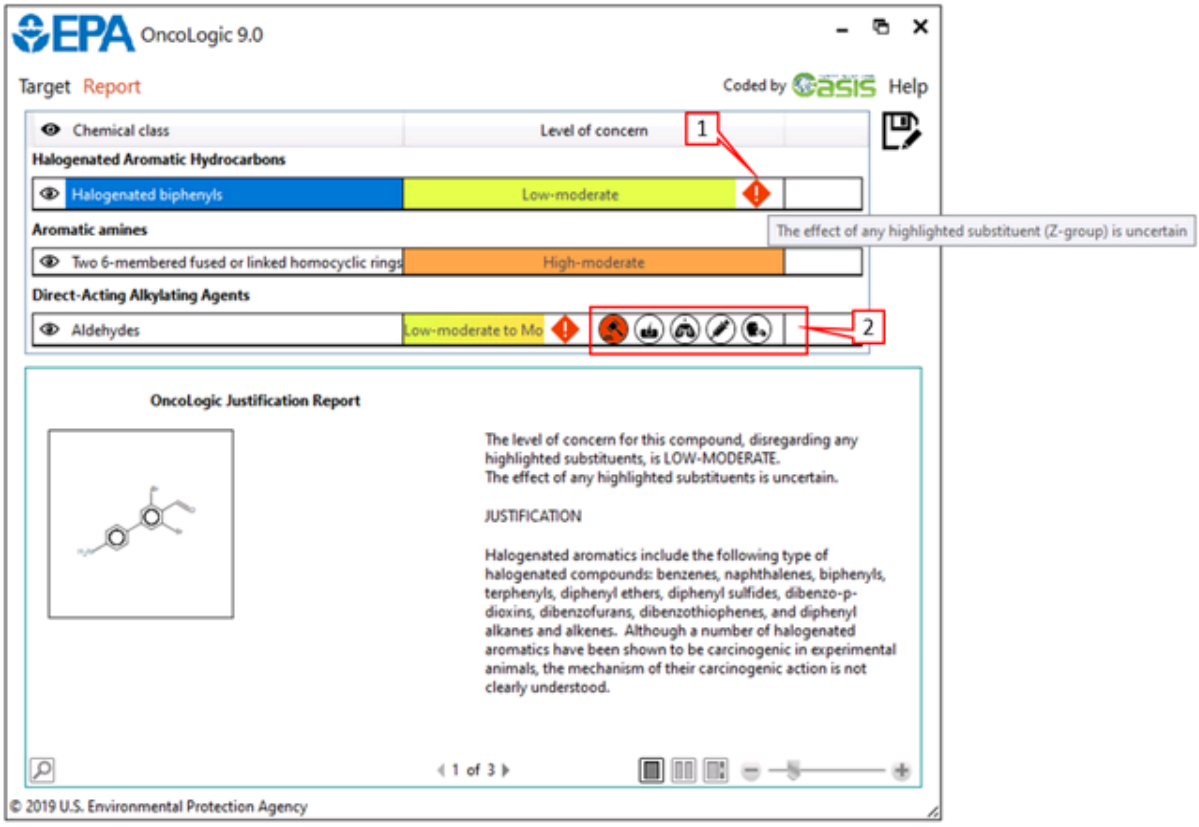

Figure 2

The routes of exposure are dermal. inhalation, injection and oral. There is a final level of concern which is the range of the variation of all routes of exposure (Figure 3).

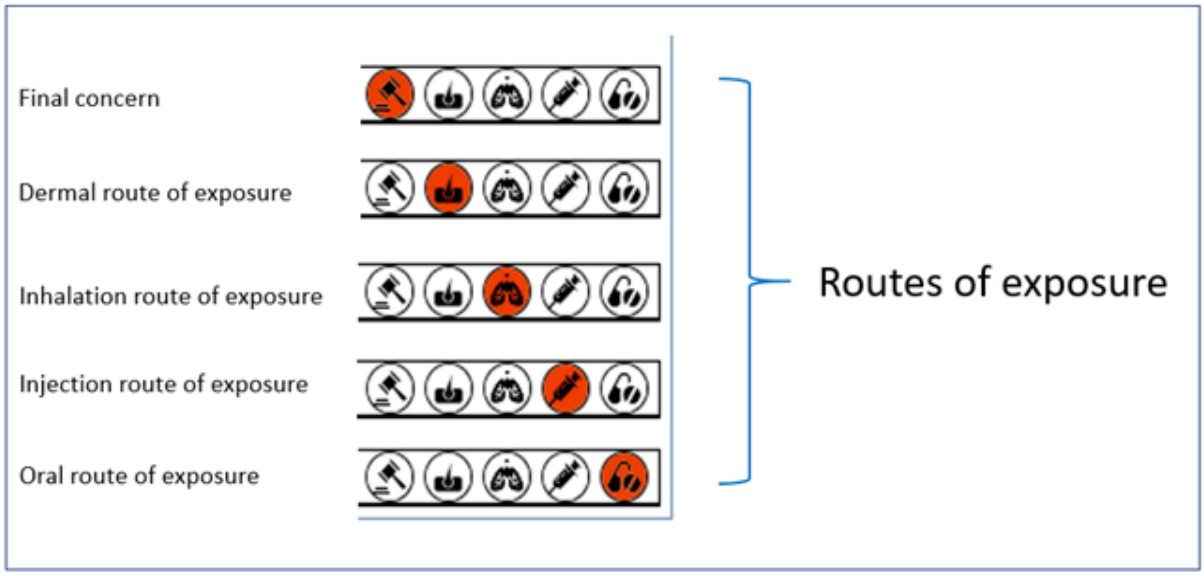

Figure 3

-o-

5. Examples

5.1 Acylating agents

1. Input a target chemical (1) and click OK (2) (Figure 1).

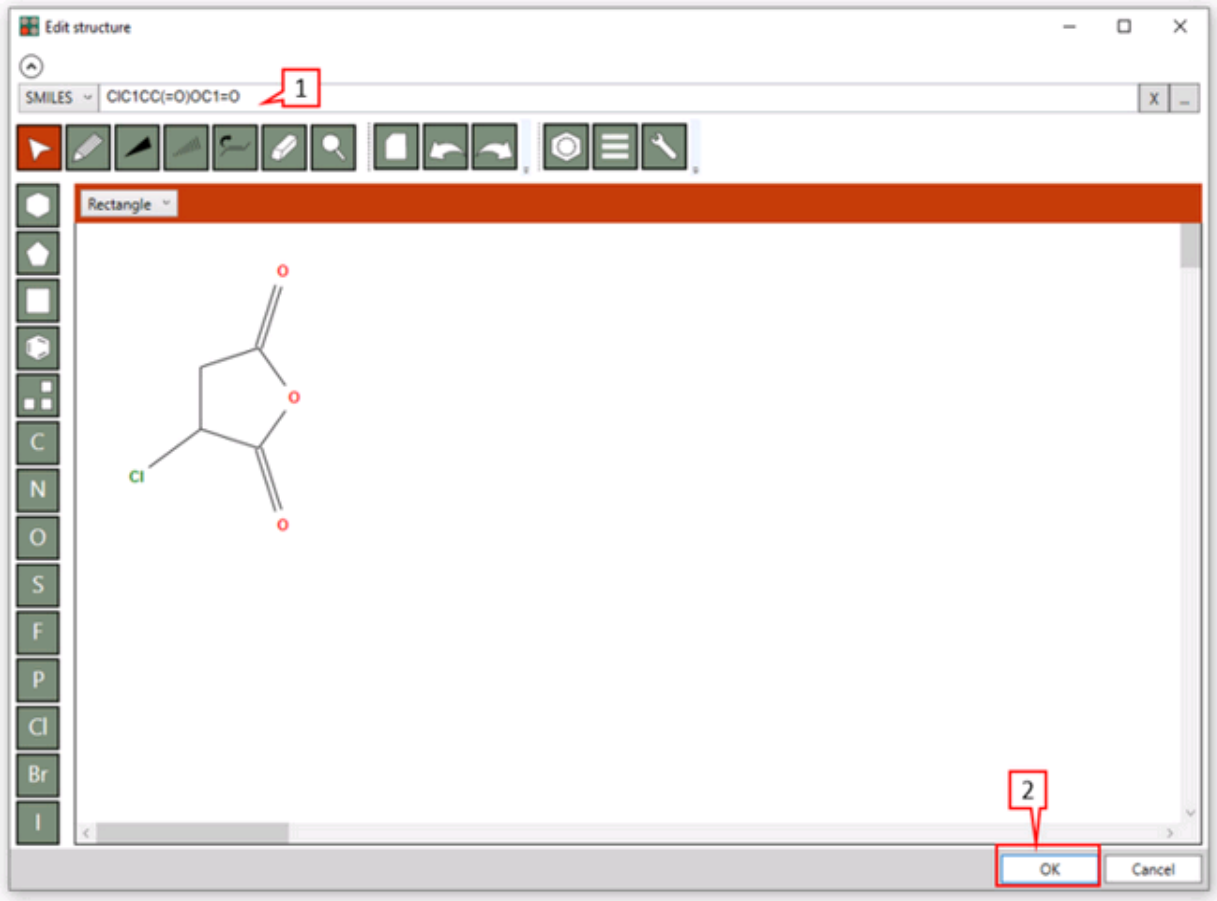

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

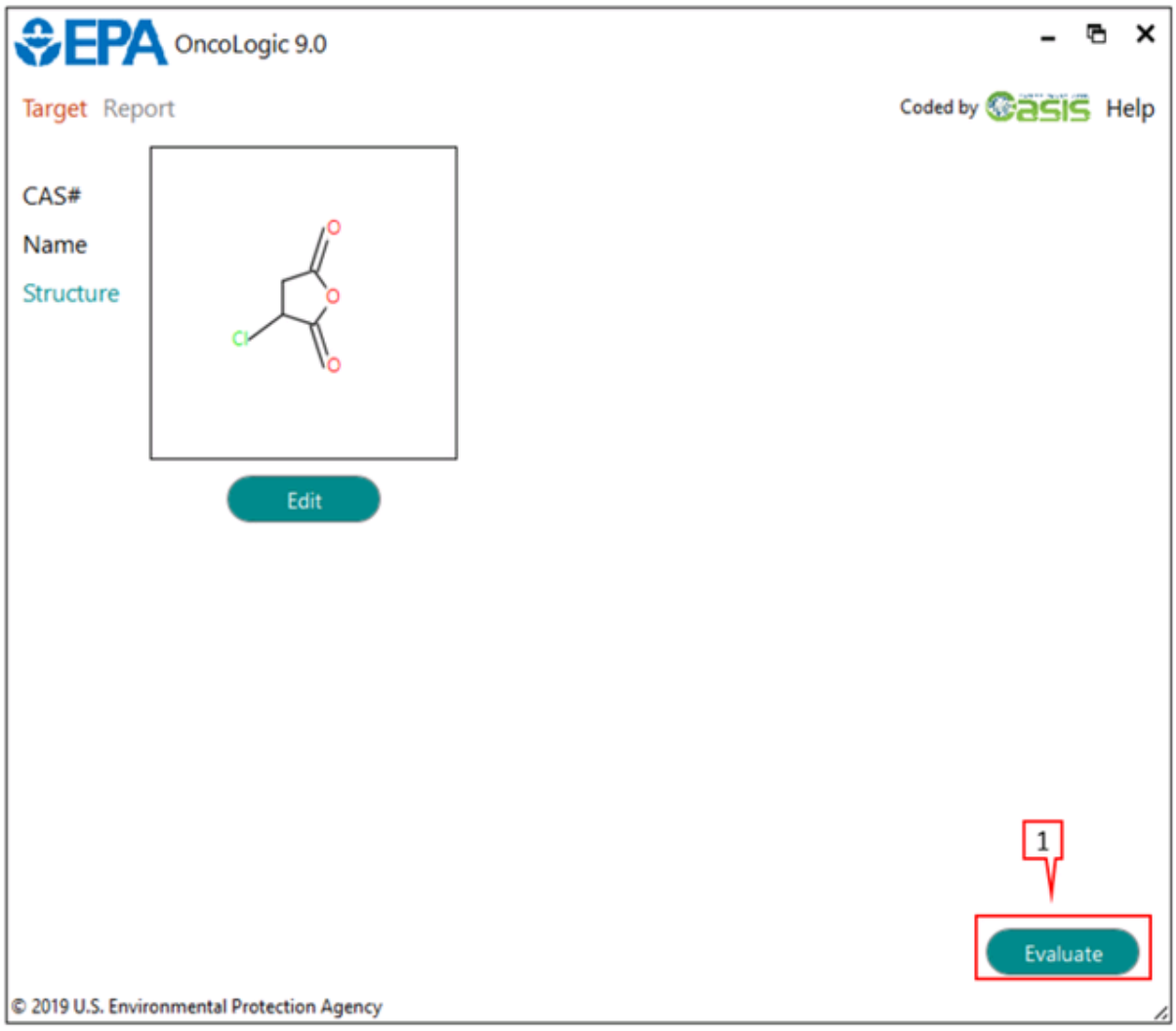

Figure 2

3. After the target chemical has been profiled as *Acylating agents/ Anhydrides* (1), click on Evaluate (2) (Figure 3).

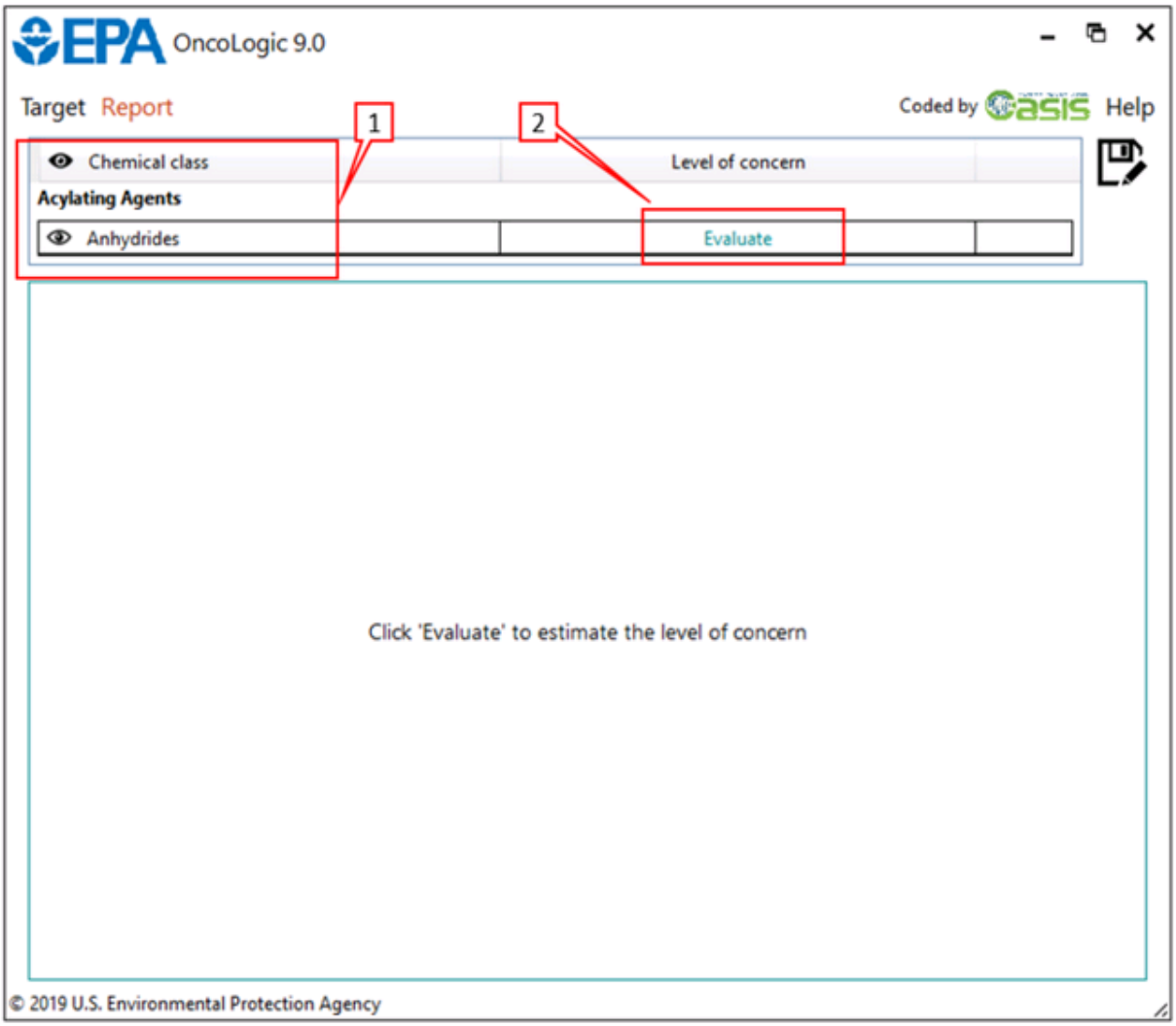

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

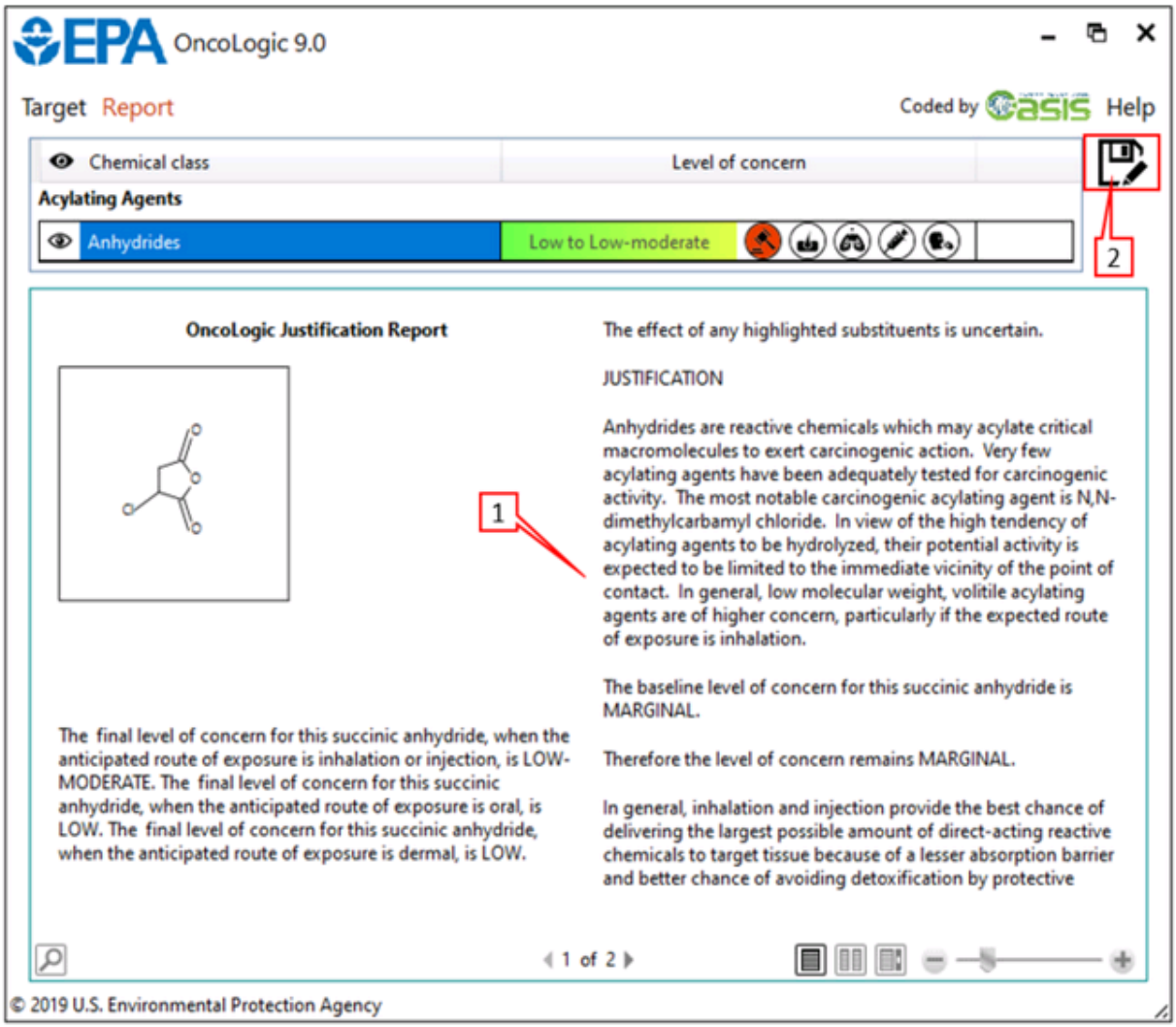
EPA OncoLogic 9.0
Target Report
Coded by OASIS Help
Chemical class
Level of concern
Acylating Agents
Anhydrides
Low to Low-moderate
2
OncoLogic Justification Report
1
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
Anhydrides are reactive chemicals which may acylate critical macromolecules to exert carcinogenic action. Very few acylating agents have been adequately tested for carcinogenic activity. The most notable carcinogenic acylating agent is N,N-dimethylcarbamyl chloride. In view of the high tendency of acylating agents to be hydrolyzed, their potential activity is expected to be limited to the immediate vicinity of the point of contact. In general, low molecular weight, volitile acylating agents are of higher concern, particularly if the expected route of exposure is inhalation.
The baseline level of concern for this succinic anhydride is MARGINAL.
Therefore the level of concern remains MARGINAL.
In general, inhalation and injection provide the best chance of delivering the largest possible amount of direct-acting reactive chemicals to target tissue because of a lesser absorption barrier and better chance of avoiding detoxification by protective
The final level of concern for this succinic anhydride, when the anticipated route of exposure is inhalation or injection, is LOW-MODERATE. The final level of concern for this succinic anhydride, when the anticipated route of exposure is oral, is LOW. The final level of concern for this succinic anhydride, when the anticipated route of exposure is dermal, is LOW.
1 of 2
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Figure 4

-o-

5.2 Aromatic amines

1. Input a target chemical (1) and click OK (2) (Figure 1).

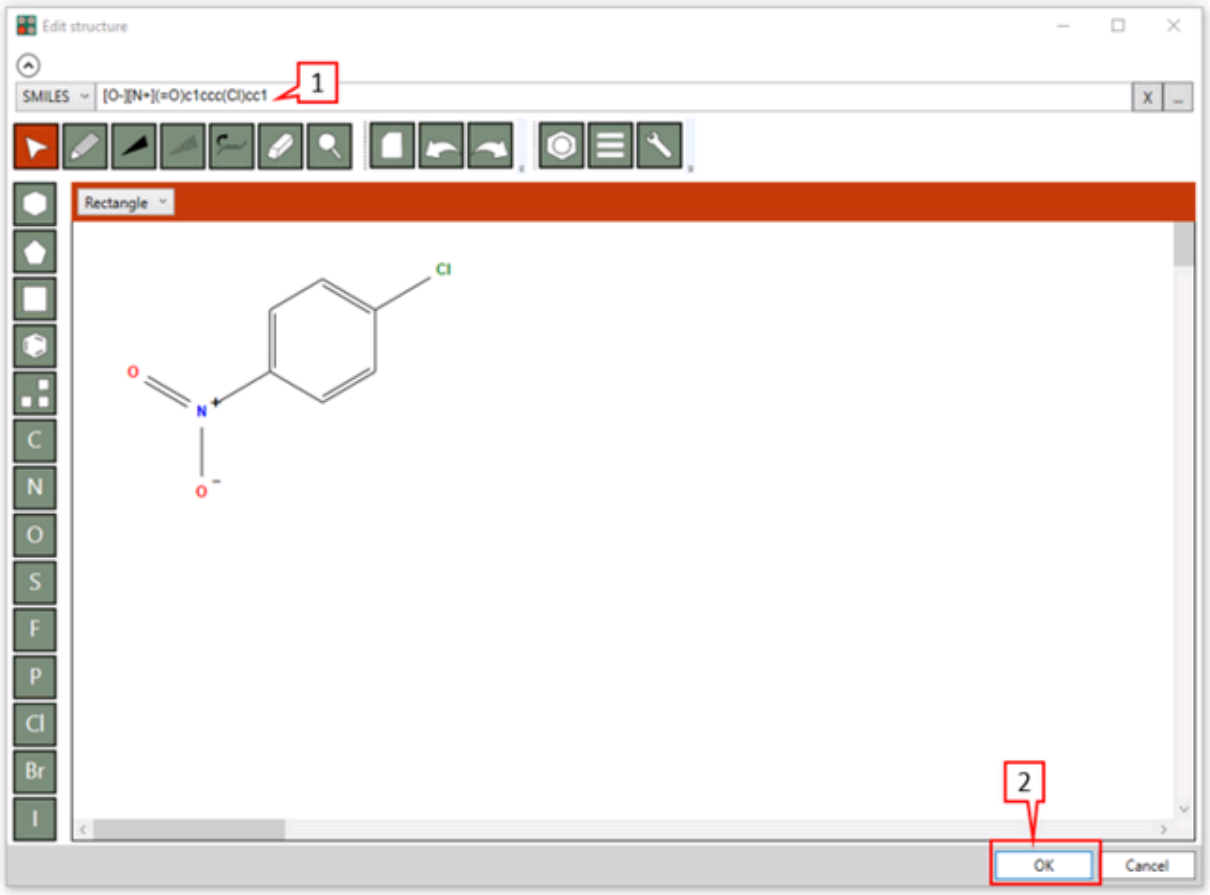

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

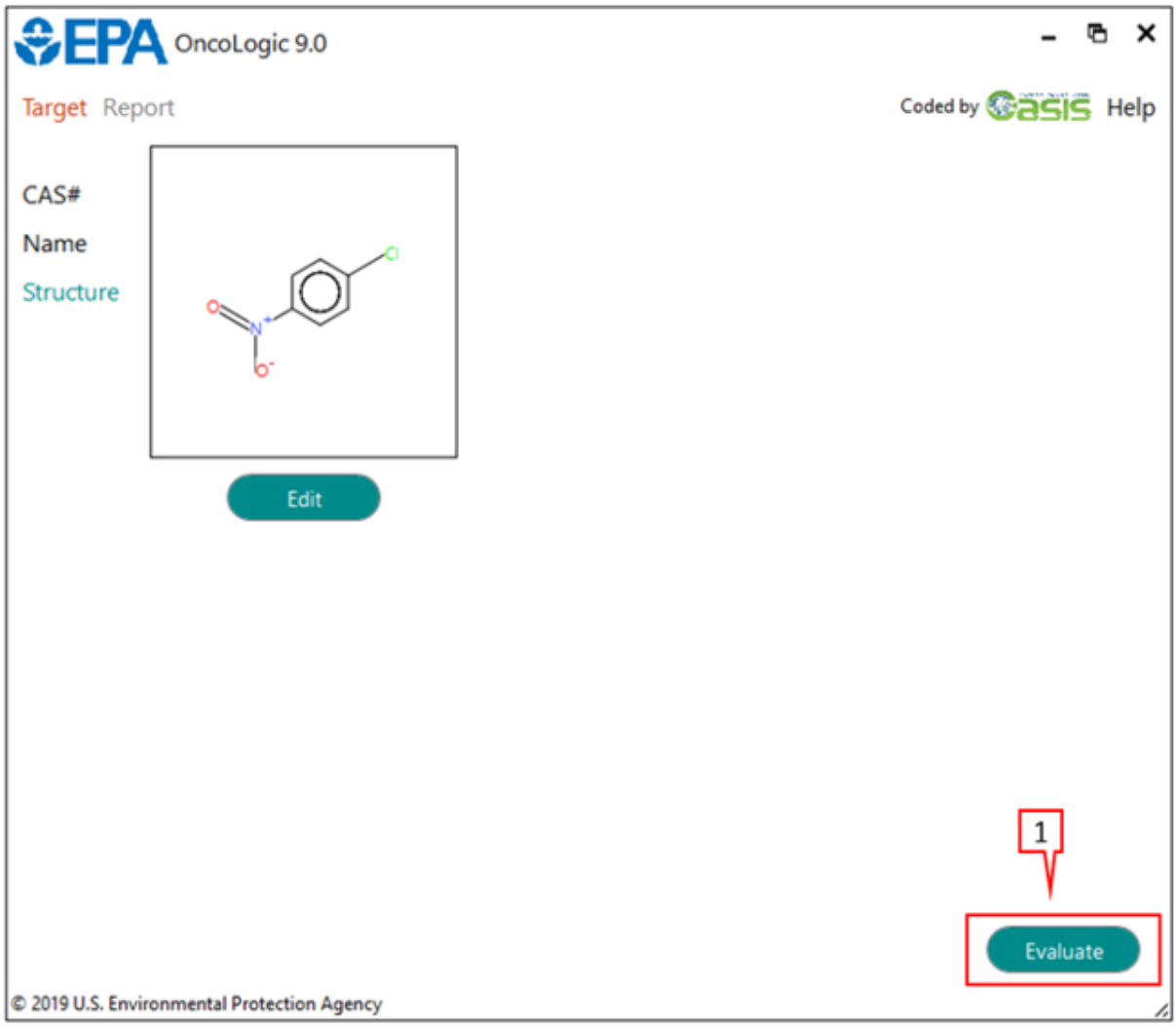

Figure 2

3. The target chemical has met the criteria of two chemical classes *Halogenated Aromatic Hydrocarbons/ Halogenated benzenes* and *Aromatic amines/ One benzene ring and one amino group* (1). Click on either of the *Evaluate* (2 or 3) (Figure 3).

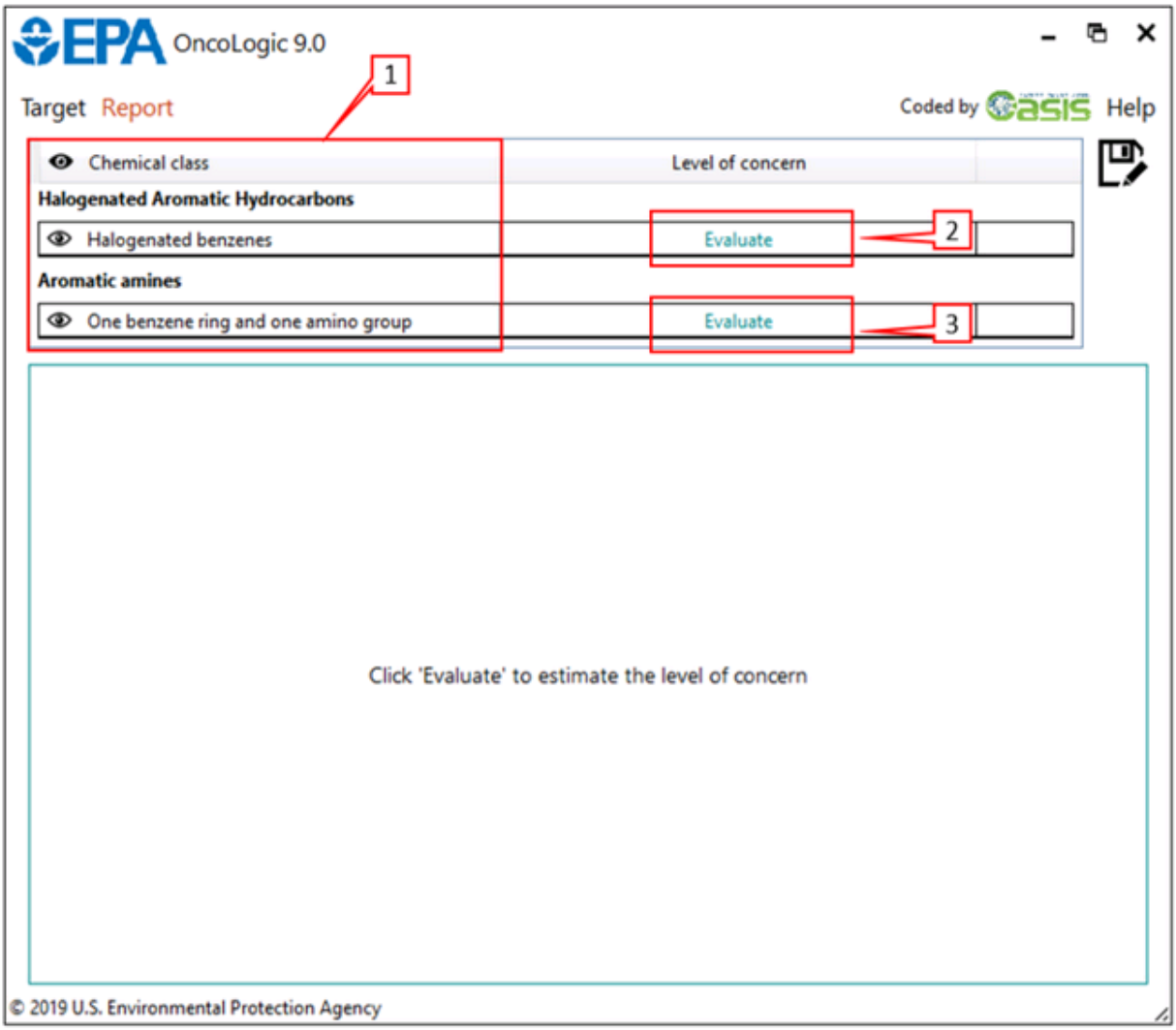

Figure 3

4. Two reports have been generated (1) and it could be saved (2) (Figure 4).

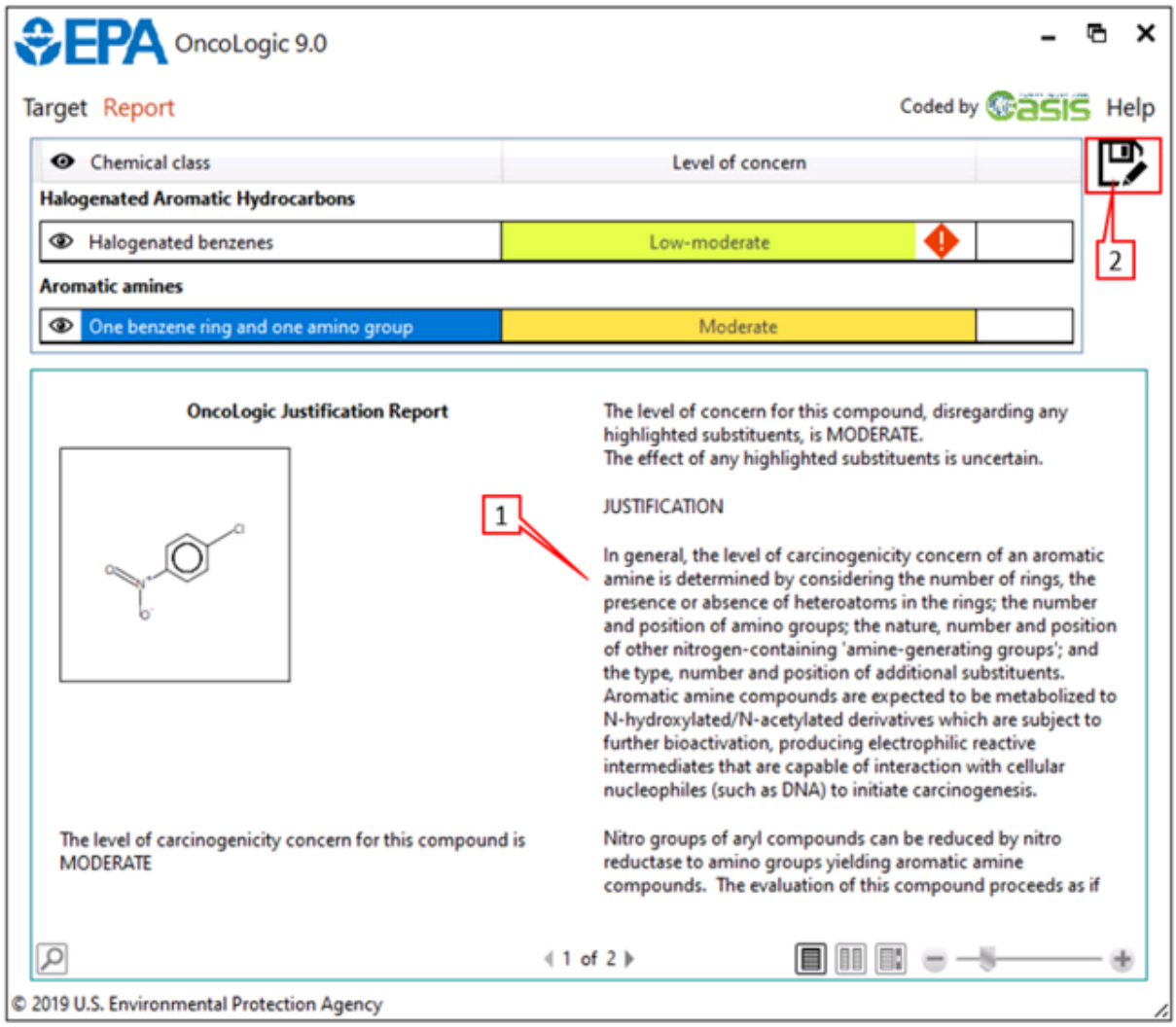
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Halogenated Aromatic Hydrocarbons
Halogenated benzenes
Low-moderate
Aromatic amines
One benzene ring and one amino group
Moderate
2
OncoLogic Justification Report
1
The level of concern for this compound, disregarding any highlighted substituents, is MODERATE.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
In general, the level of carcinogenicity concern of an aromatic amine 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.
The level of carcinogenicity concern for this compound is MODERATE
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
1 of 2
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Figure 4

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5.3 Carbamates and thiocarbamates

1. Input a target chemical (1) and click OK (2) (Figure 1).

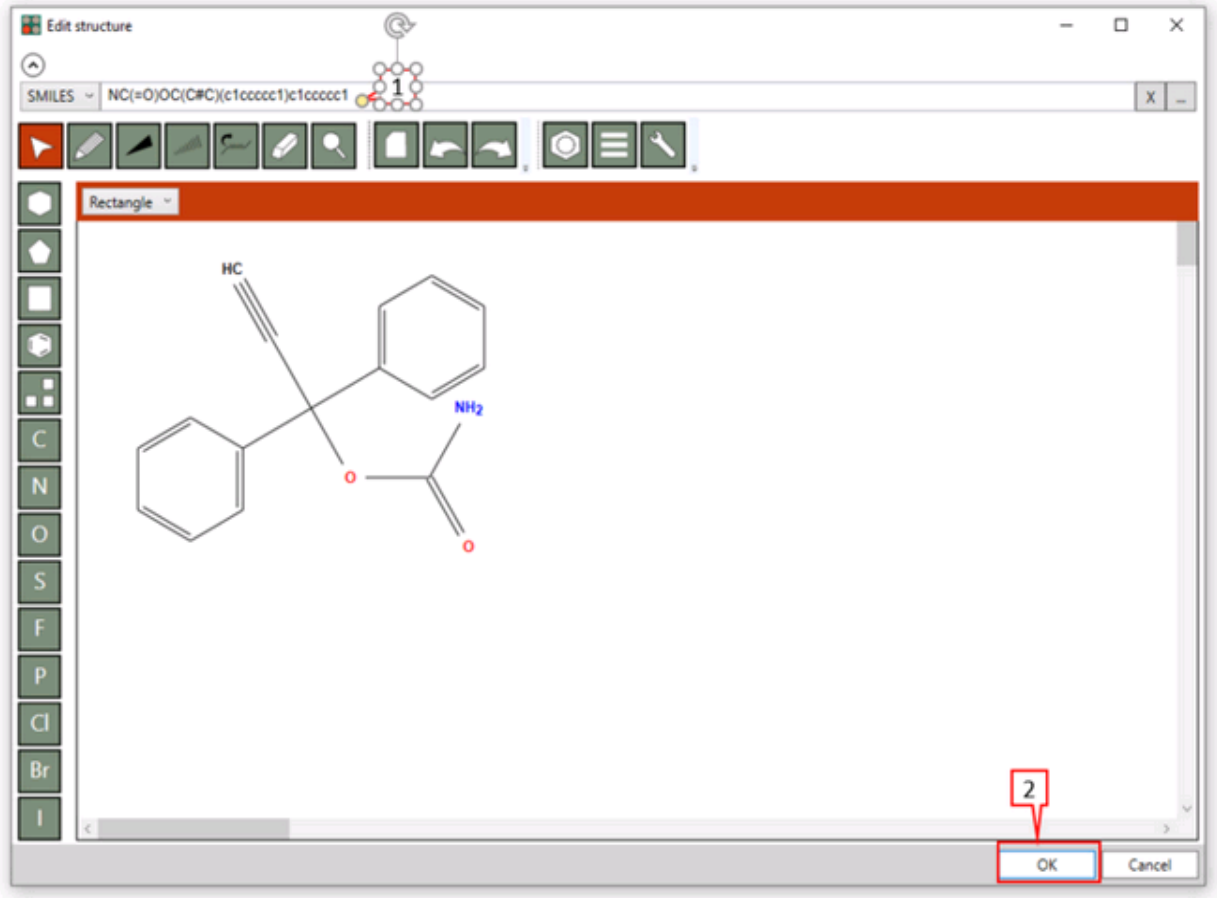

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

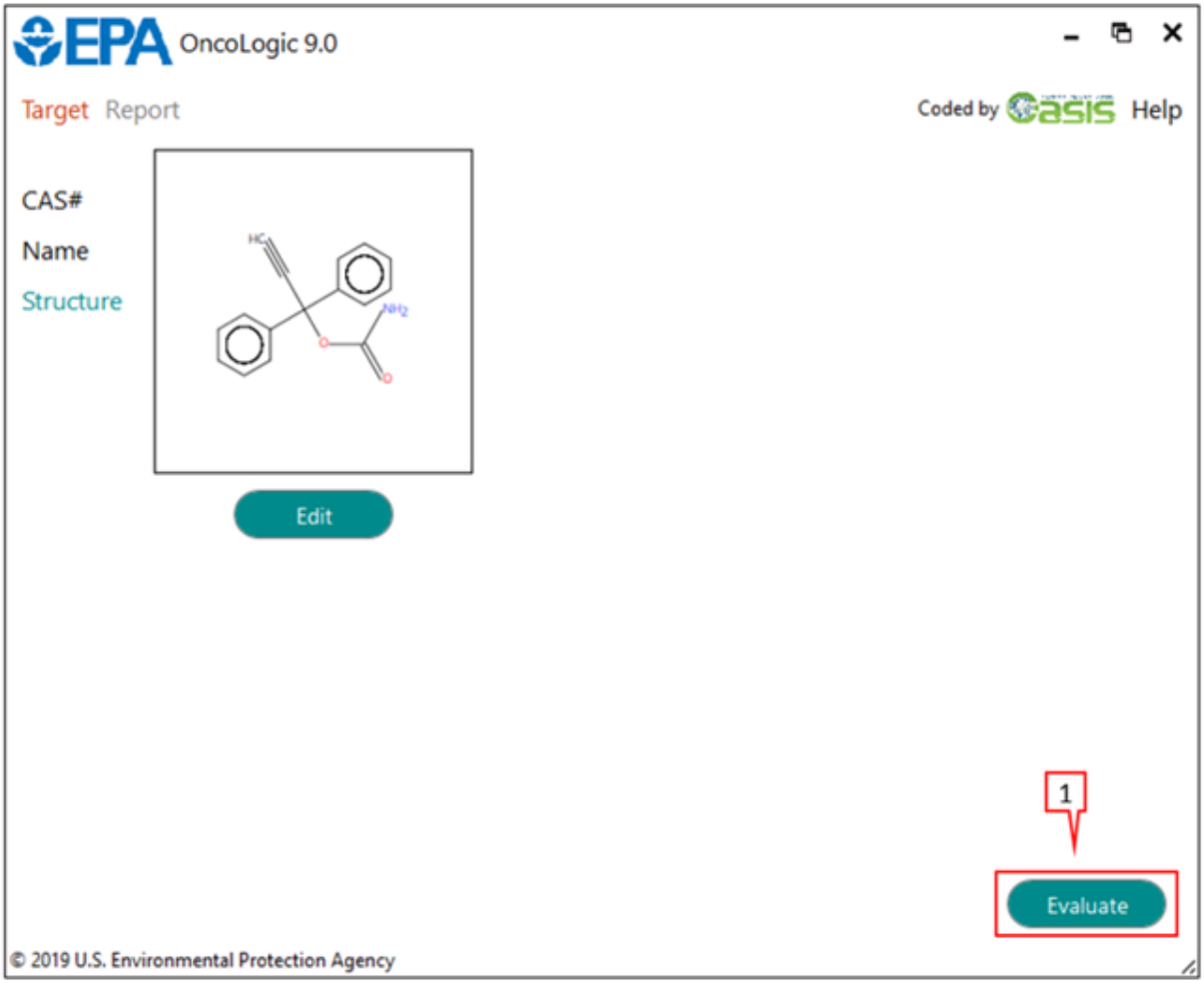

Figure 2

3. After the target chemical has been profiled as *Carbamates* (1), click on *Evaluate* (2) (Figure 3).

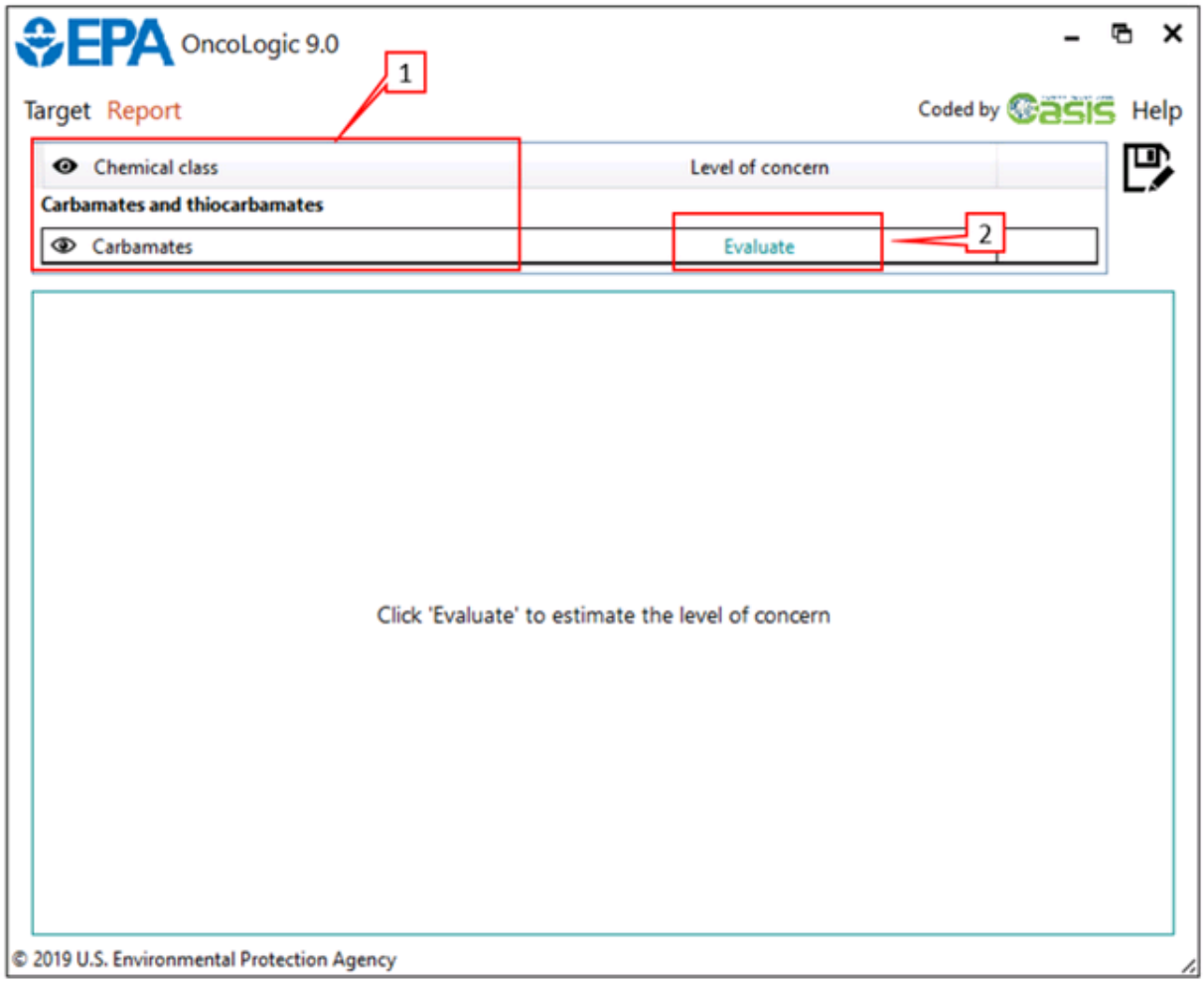

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

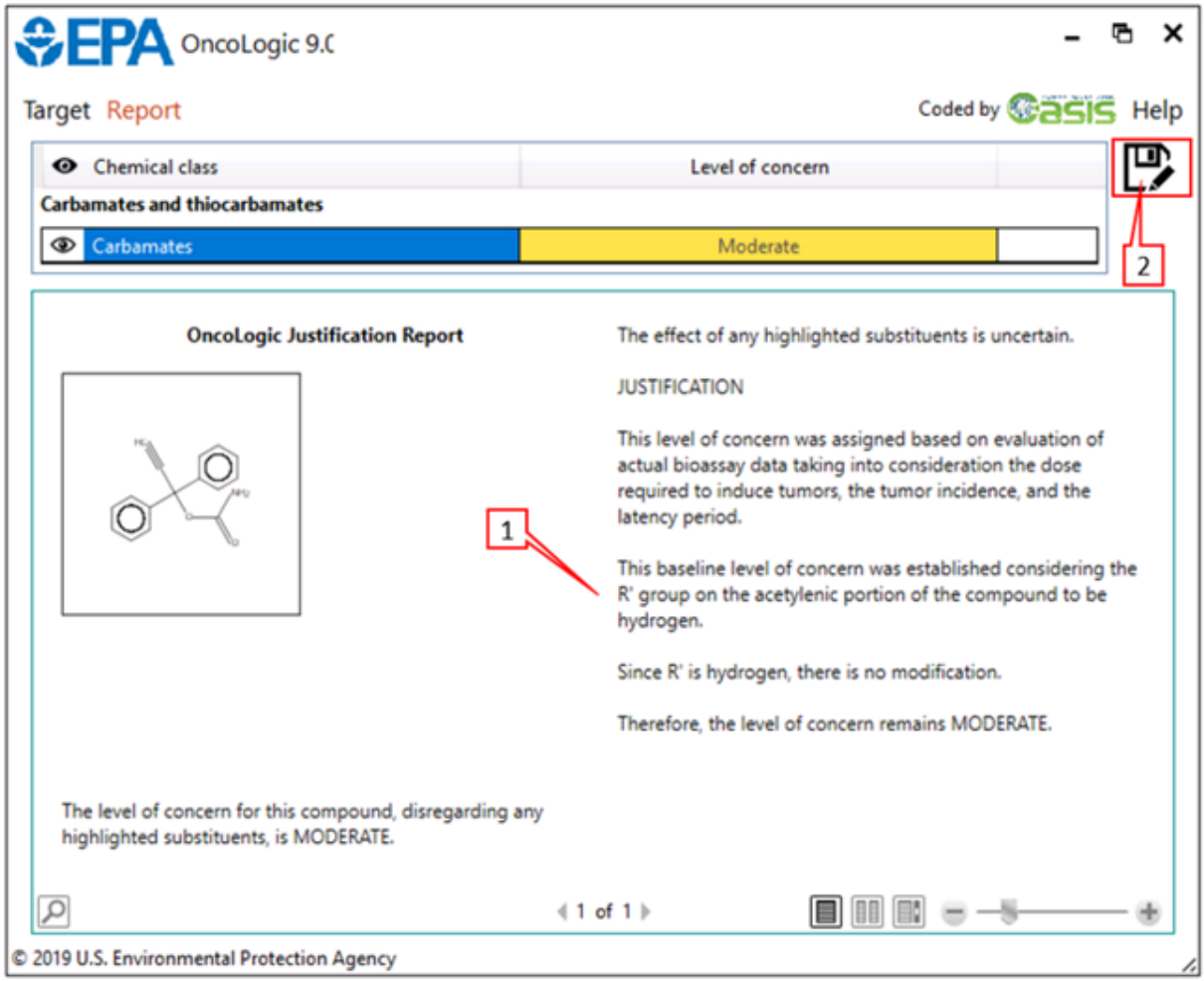
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Carbamates and thiocarbamates
Carbamates
Moderate
2
OncoLogic Justification Report
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
This level of concern was assigned based on evaluation of actual bioassay data taking into consideration the dose required to induce tumors, the tumor incidence, and the latency period.
1
This baseline level of concern was established considering the R' group on the acetylenic portion of the compound to be hydrogen.
Since R' is hydrogen, there is no modification.
Therefore, the level of concern remains MODERATE.
The level of concern for this compound, disregarding any highlighted substituents, is MODERATE.
1 of 1
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Figure 4

-o-

5.4 Direct-Acting Alkylating Agents

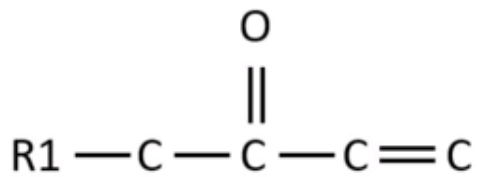
-o-

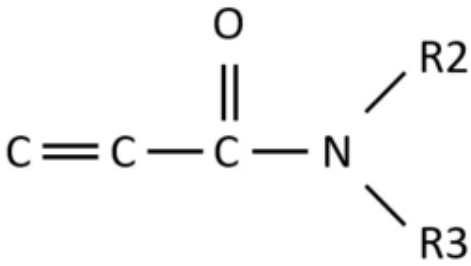
5.4.1 Normal body constituent

A. Target chemical classes with allowed normal body constituent as a part of the skeleton

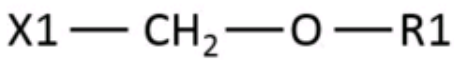
Normal body constituent could be a potential substituent (R1 or R2) in the target molecule for the following chemical classes, belonging to *Direct alkylating agents*:

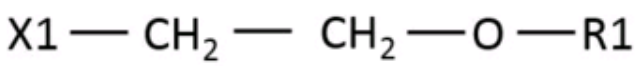
1. Acrylates, acrylamides and related compounds (3.6.1 Acrylates, acrylamides and related compounds)



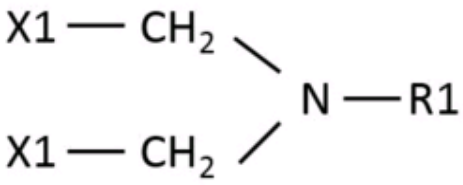


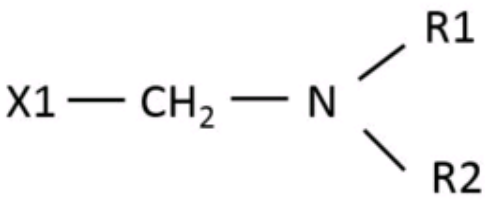
2. alpha(beta)-Haloethers (3.6.5 alpha(beta)-Haloethers)



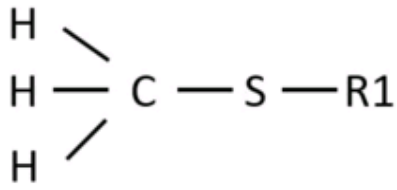


3. alpha-Haloalkylamines (3.6.6 alpha-Haloalkylamines)

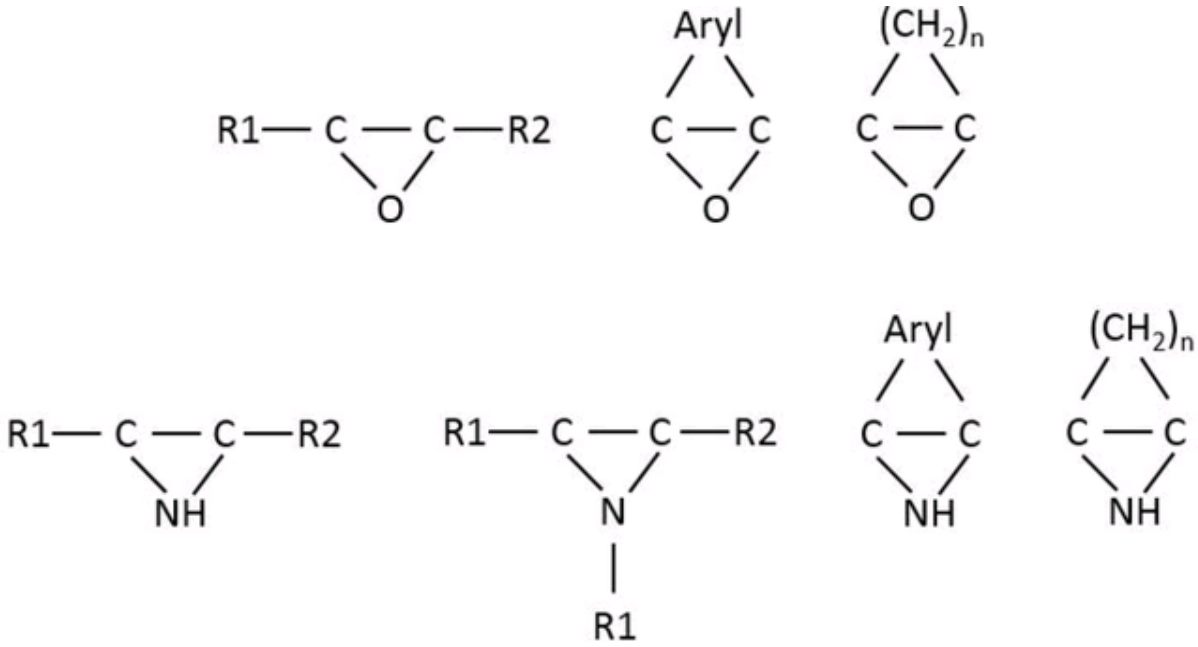




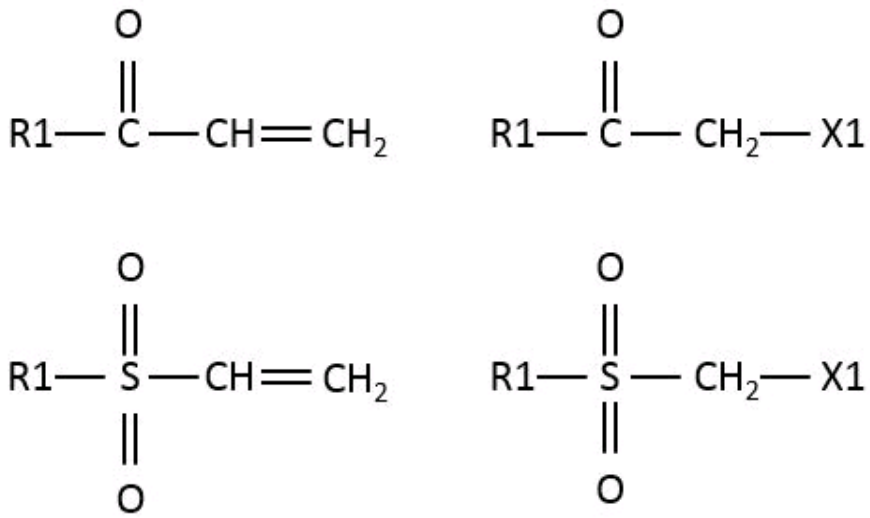
4. alpha-Halothioethers (3.6.7 alpha-Halothioethers)



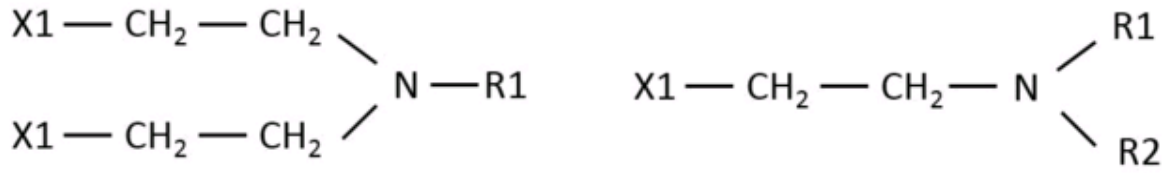
5. Epoxides and Ethyleneimines (3.6.9 Epoxides and Ethyleneimines)



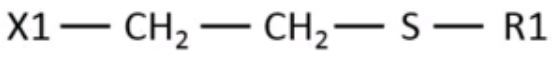
6. Ketones and Sulfones (3.6.10 Ketones and Sulfones)



7. Nitrogen Mustards (3.6.12 Nitrogen Mustards)



8. Sulfur Mustards (3.6.13 Sulfur Mustards)



B. List with normal body constituents categories:

a) Amino acid
b) Purine/ Pyrimidine Nucleoside:
- Adenosine
- Cytidine
- Cytosine
- Guanine
- Guanosine
- Thymidine
- Thymine
- Uracil
- Uridine

c) Purine/ Pyrimidine Nucleoside Analogs:
- Purine Analog
- Pyrimidine Analog
- Nucleoside Analog

d) Monosaccharide

Important note: The skeleton of the target chemical should belong to the main skeleton of the corresponding target chemical class, but could not contain explicitly the structure of any normal body constituent. The availability or not of the normal body constituents is determined by series of interactive questions to which the user should give an answer and the concern is respectively assigned (Figure 1).

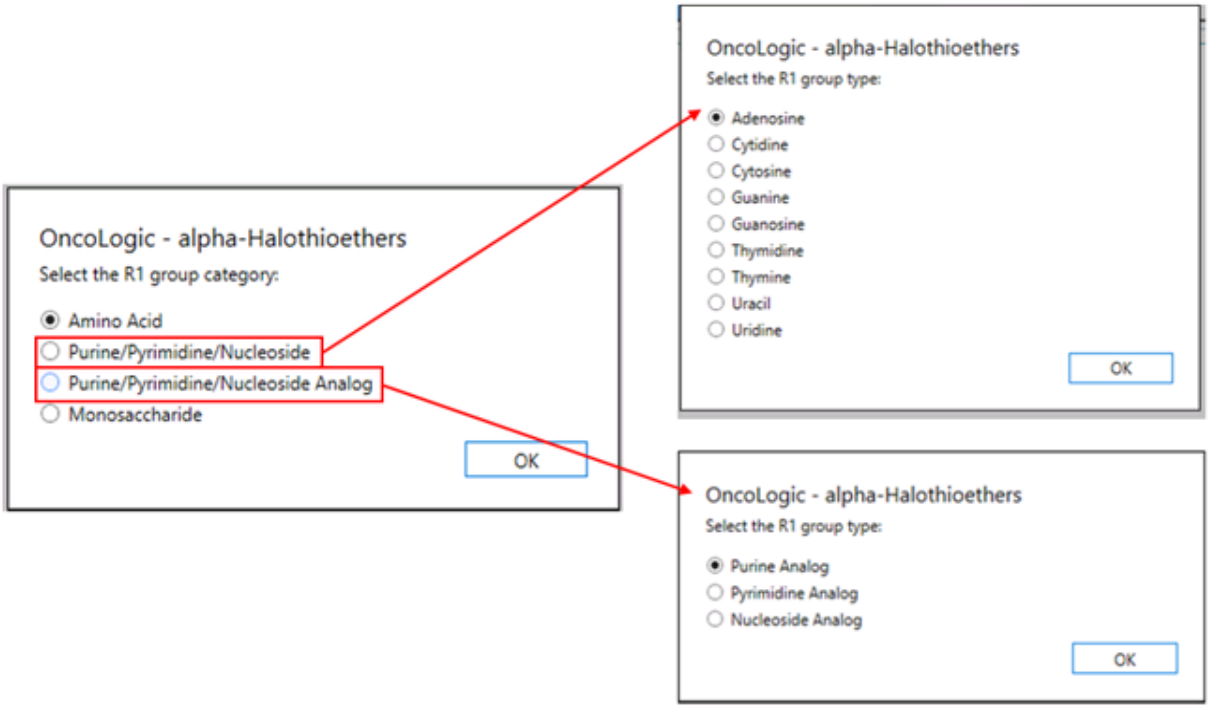

OncoLogic - alpha-Halothioethers
Select the R1 group category:
Amino Acid
Purine/Pyrimidine/Nucleoside
Purine/Pyrimidine/Nucleoside Analog
Monosaccharide
OK
OncoLogic - alpha-Halothioethers
Select the R1 group type:
Adenosine
Cytidine
Cytosine
Guanine
Guanosine
Thymidine
Thymine
Uracil
Uridine
OK
OncoLogic - alpha-Halothioethers
Select the R1 group type:
Purine Analog
Pyrimidine Analog
Nucleoside Analog
OK

Figure 1

-o-

5.4.2 Acrylates, acrylamides and related compounds

1. Input a target chemical (1) and click OK (2) (Figure 1).

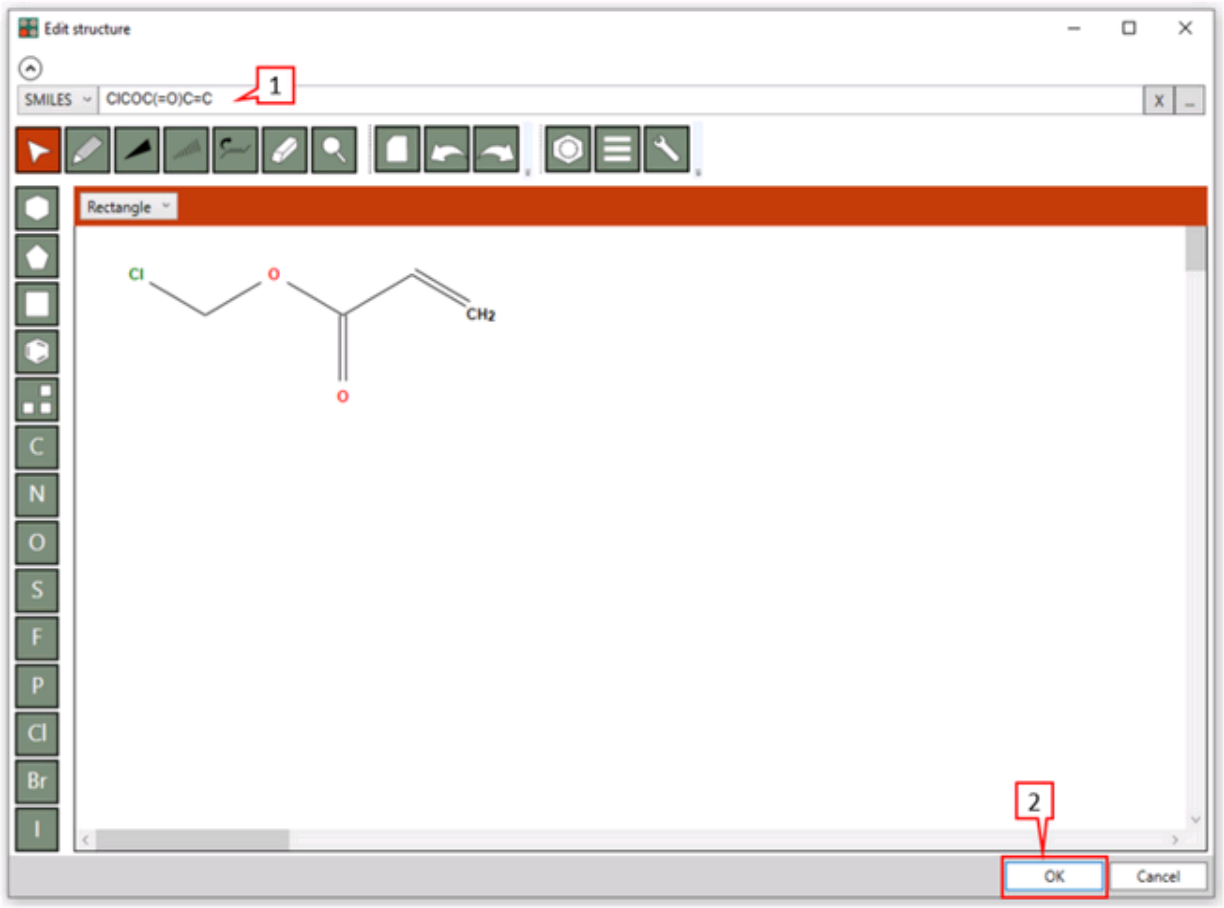


Figure 1

2. Click on *Evaluate* (1) (Figure 2).

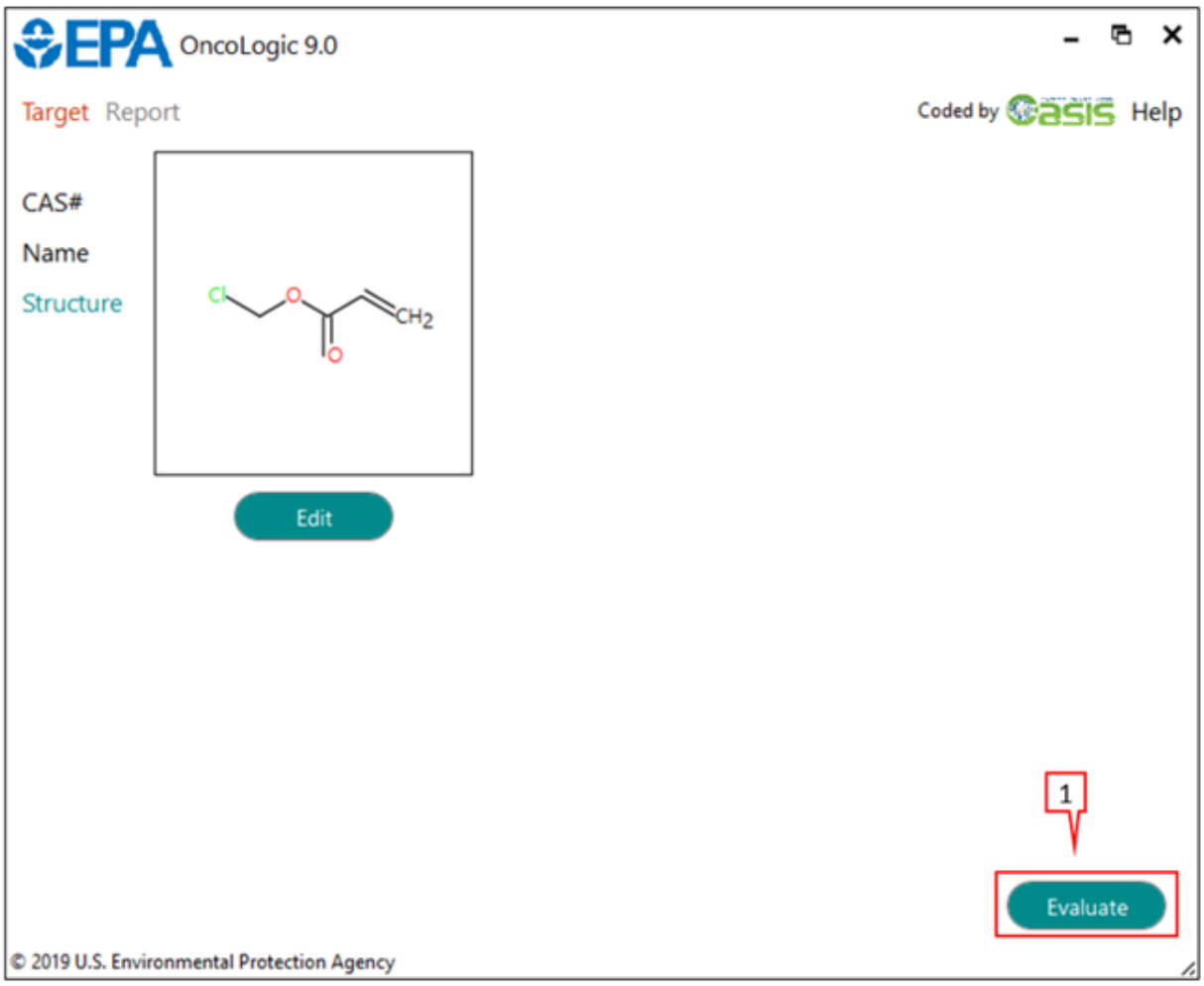
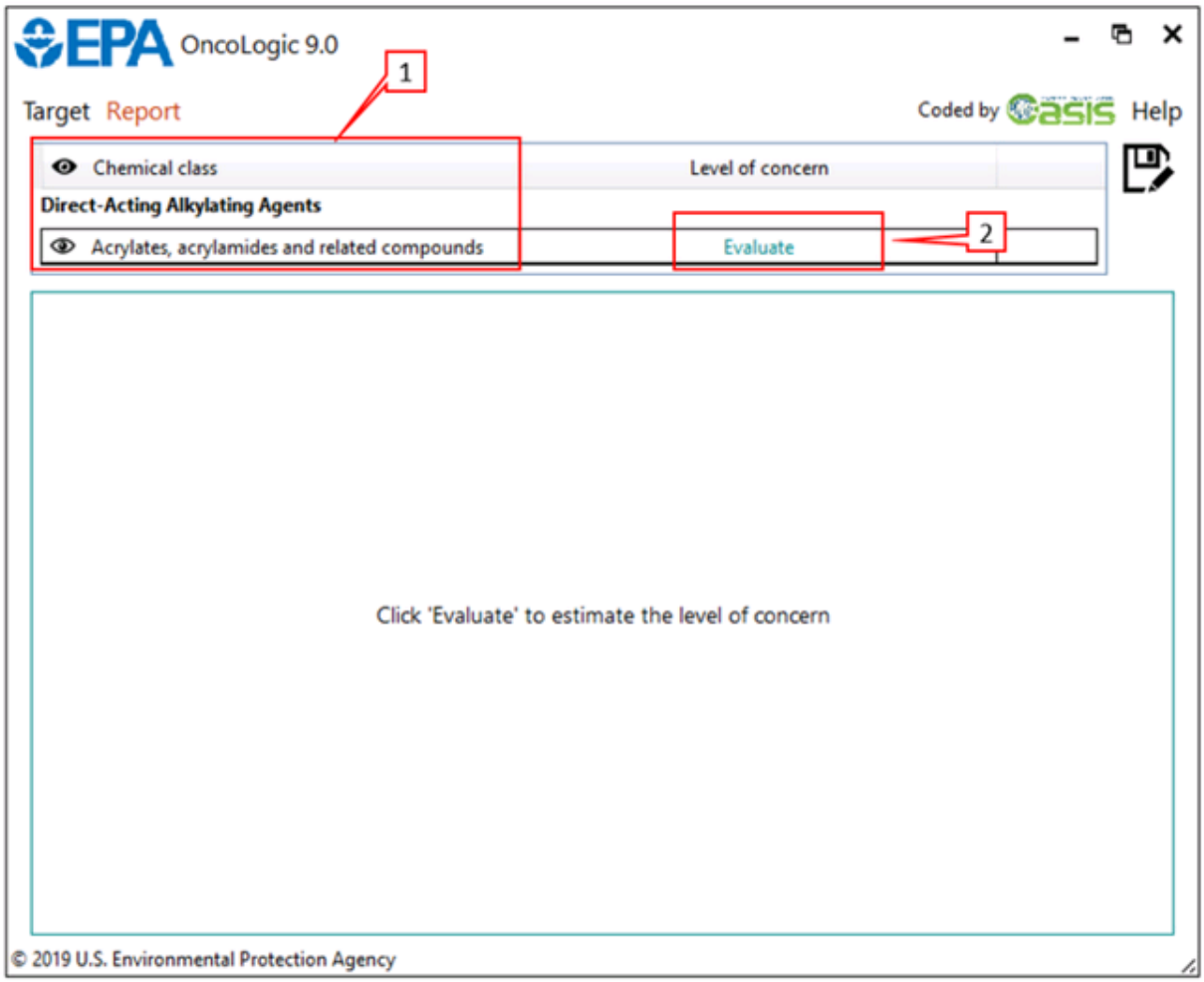


Figure 2

3. After the target chemical has been profiled as *Direct Alkylating Agents/ Acrylates, acrylamides and related compounds* (1), click on Evaluate (2) (Figure 3).


EPA OncoLogic 9.0
1
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Direct-Acting Alkylating Agents
Acrylates, acrylamides and related compounds
Evaluate
2
Click 'Evaluate' to estimate the level of concern
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-o-

5.4.2.1 Scenario 1

Scenario 1 - there isn't a normal body constituent in the skeleton

An interactive windows with the question: *Is the R1 group a normal body constituent?* (Figure 1) appears.

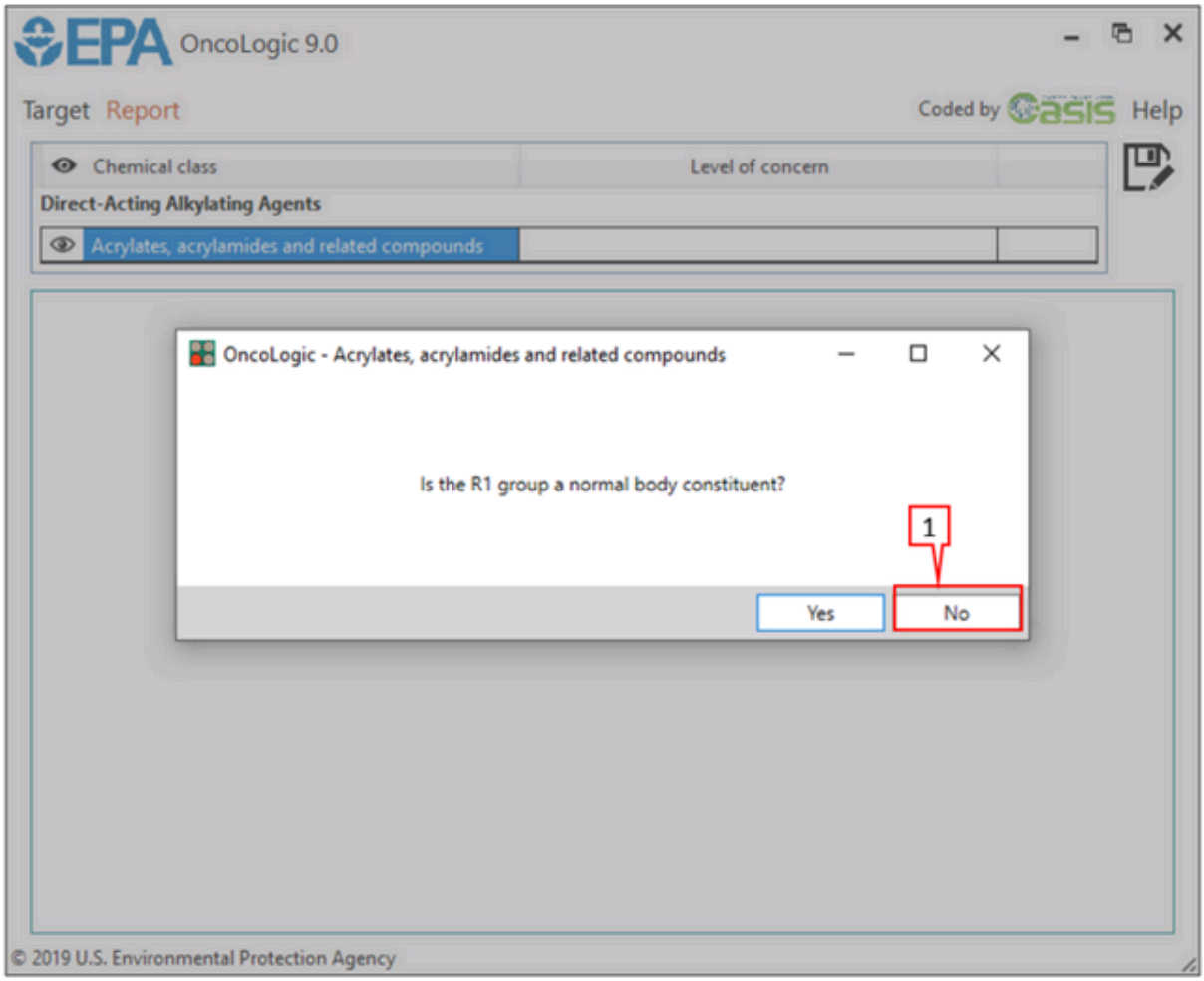

Figure 1

Scenario 1A

The next interactive quotation asks: *Is the molecule to which the reactive functional group is attached know to be NOT bioavailable by the anticipated route of exposure?* (Figure 2).

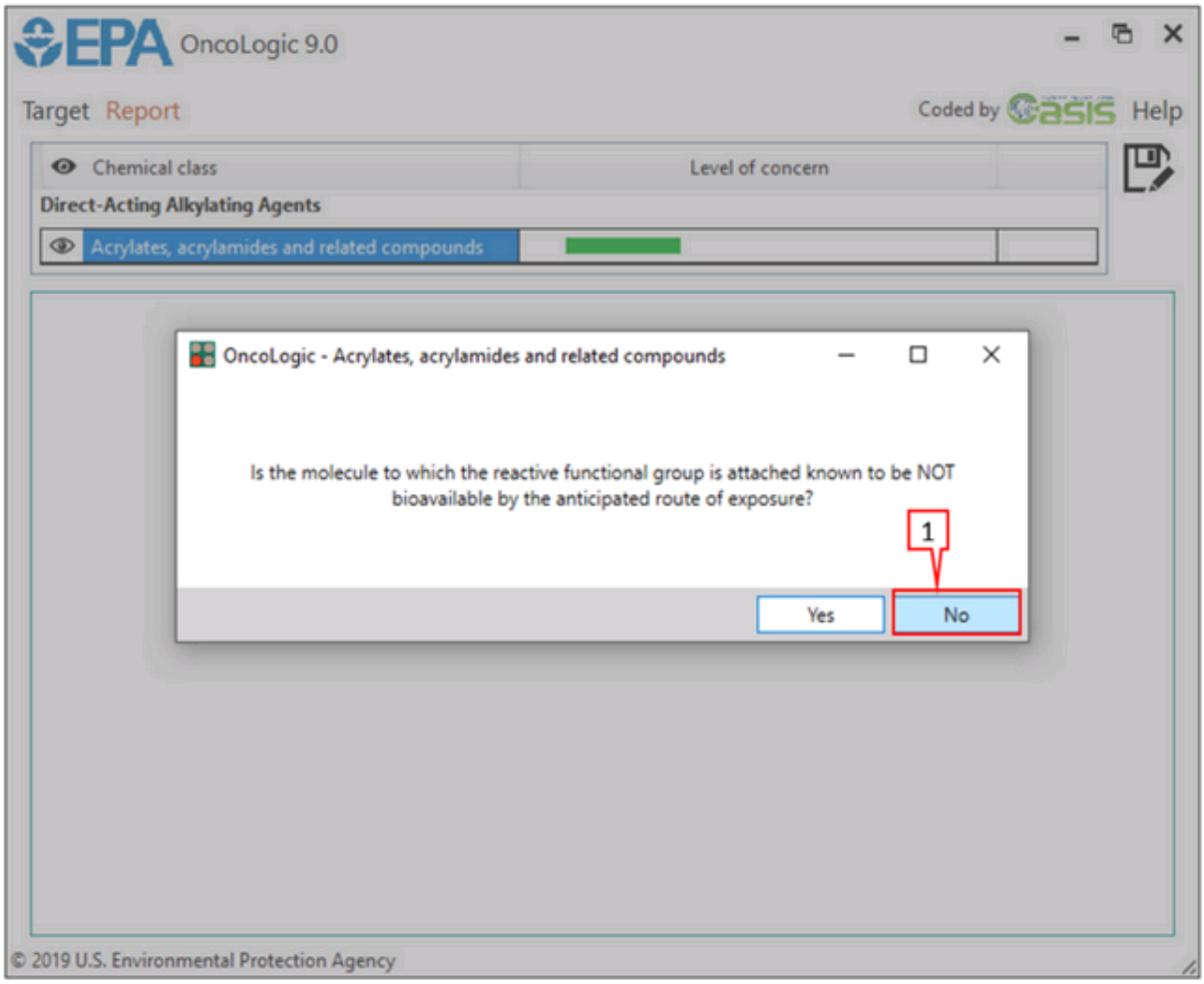

Figure 2

The report has been generated (1) and it could be saved (2) (Figure 3).

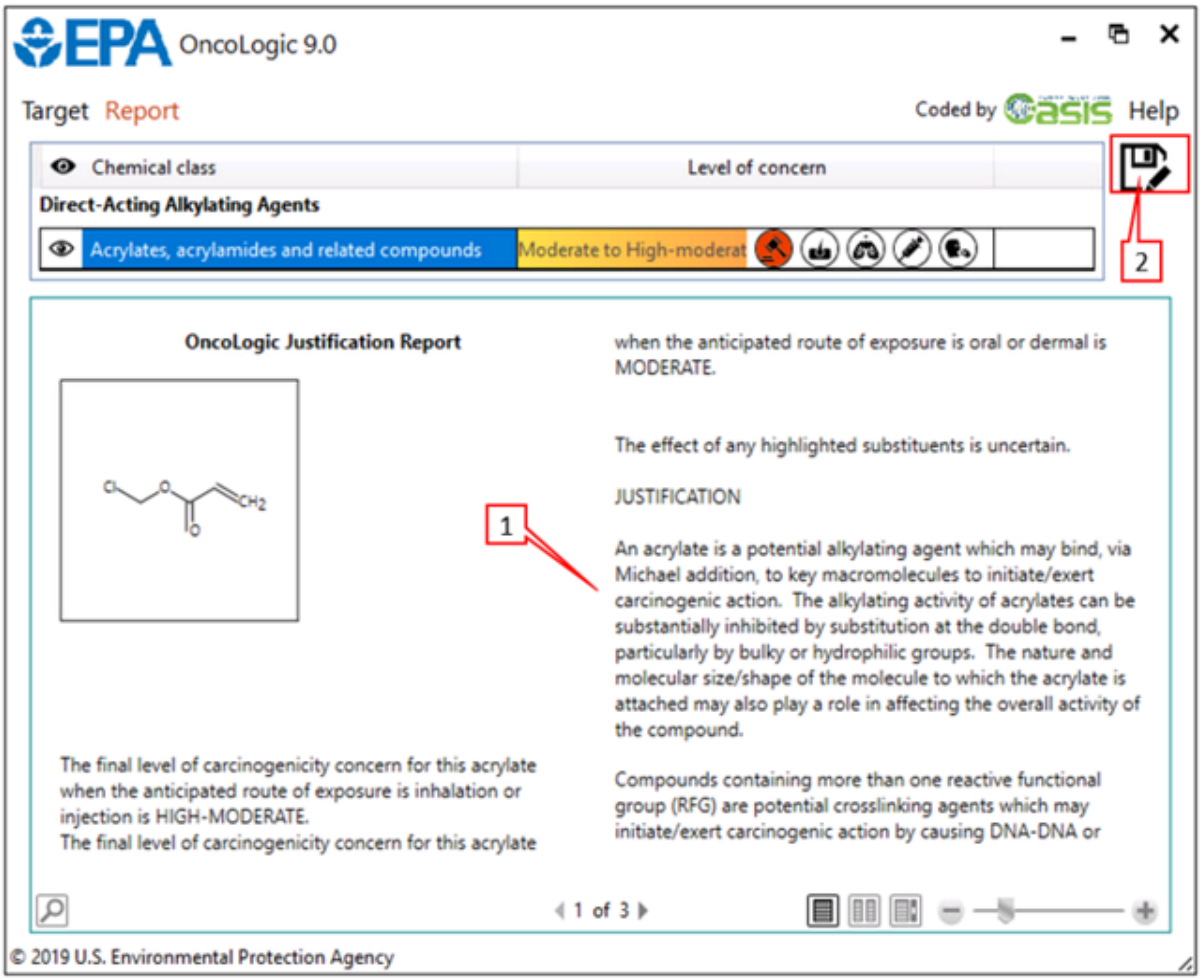

Figure 3

Scenario 1B

If the answer to: *Is the molecule to which the reactive functional group is attached know to be NOT bioavailable by the anticipated route of exposure?* is *Yes (Figure 4)*, the report is generated (1) and could be saved (2) (Figure 5).

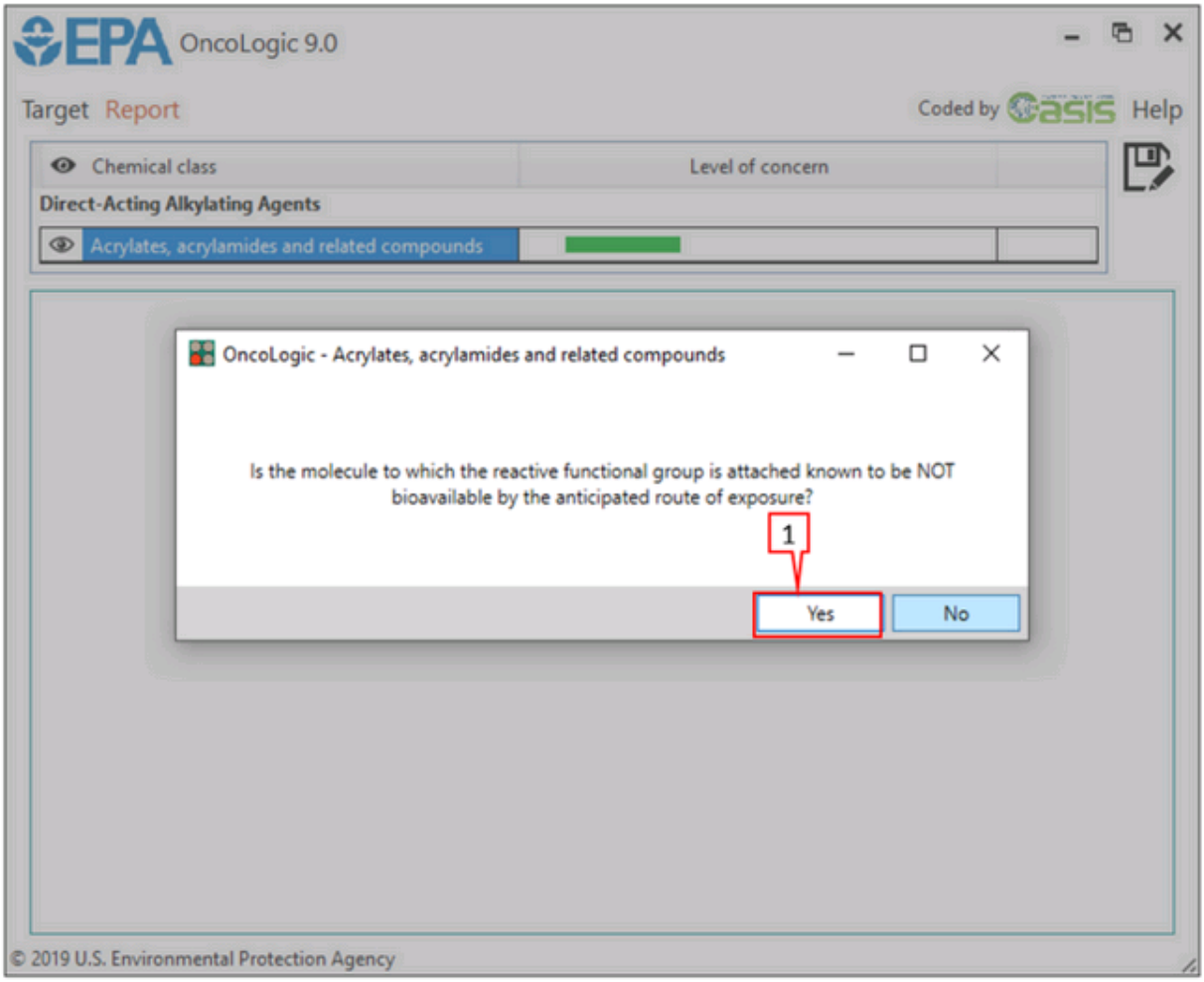
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Direct-Acting Alkylating Agents
Acrylates, acrylamides and related compounds
OncoLogic - Acrylates, acrylamides and related compounds
Is the molecule to which the reactive functional group is attached known to be NOT bioavailable by the anticipated route of exposure?
1
Yes
No
© 2019 U.S. Environmental Protection Agency

Figure 4

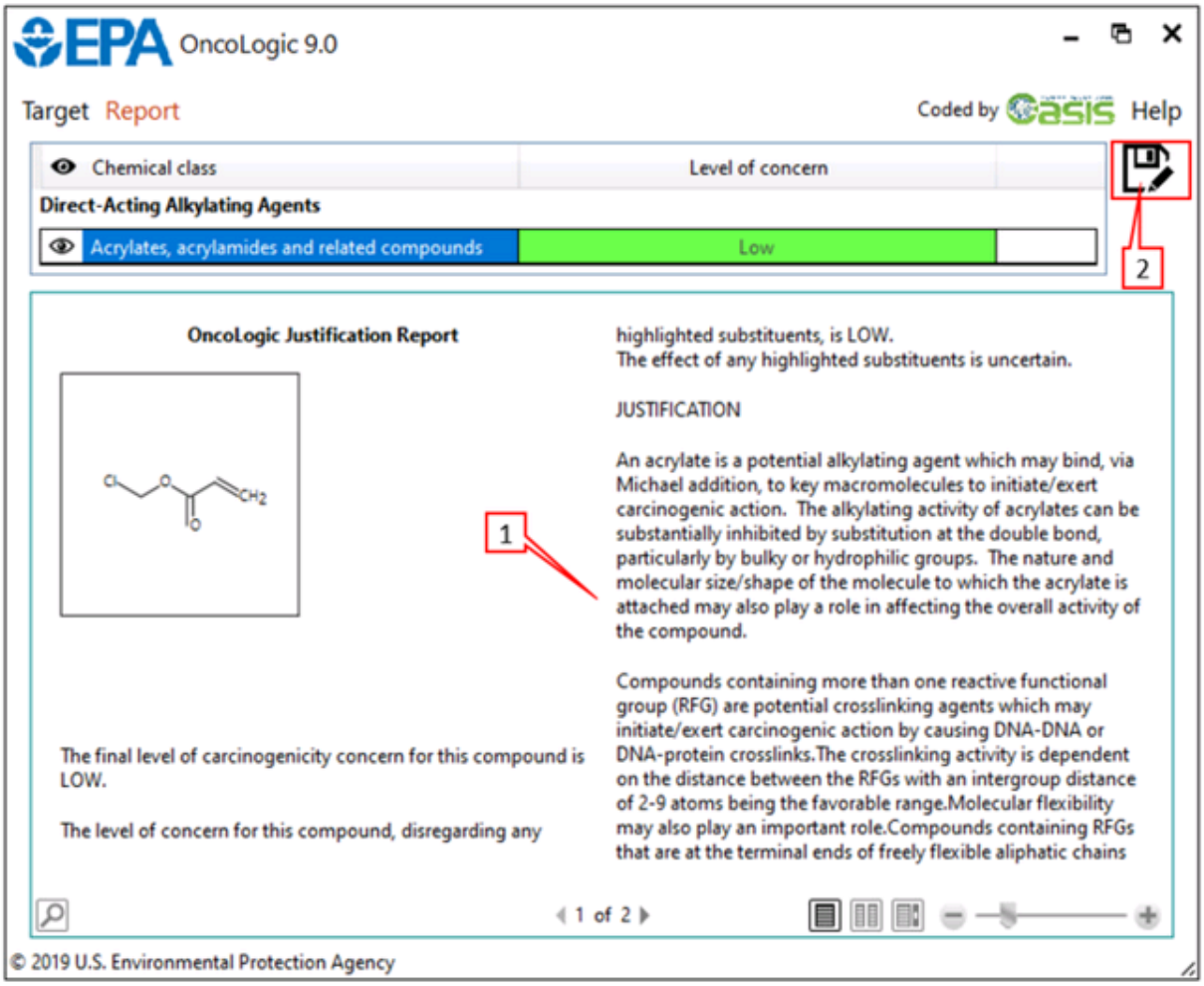
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Direct-Acting Alkylating Agents
Acrylates, acrylamides and related compounds
Low
2
OncoLogic Justification Report
highlighted substituents, is LOW.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
1
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. The nature and molecular size/shape of the molecule to which the acrylate is attached may also play a role in affecting the overall activity of the compound.
Compounds containing more than one reactive functional group (RFG) are potential crosslinking agents which may initiate/exert carcinogenic action by causing DNA-DNA or DNA-protein crosslinks.The crosslinking activity is dependent on the distance between the RFGs with an intergroup distance of 2-9 atoms being the favorable range.Molecular flexibility may also play an important role.Compounds containing RFGs that are at the terminal ends of freely flexible aliphatic chains
The final level of carcinogenicity concern for this compound is LOW.
The level of concern for this compound, disregarding any
1 of 2
© 2019 U.S. Environmental Protection Agency

Figure 5

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5.4.2.2 Scenario 2

Scenario 2 - there is a normal body constituent in the skeleton

An interactive windows with the question: *Is the R1 group a normal body constituent?* (Figure 1) appears.

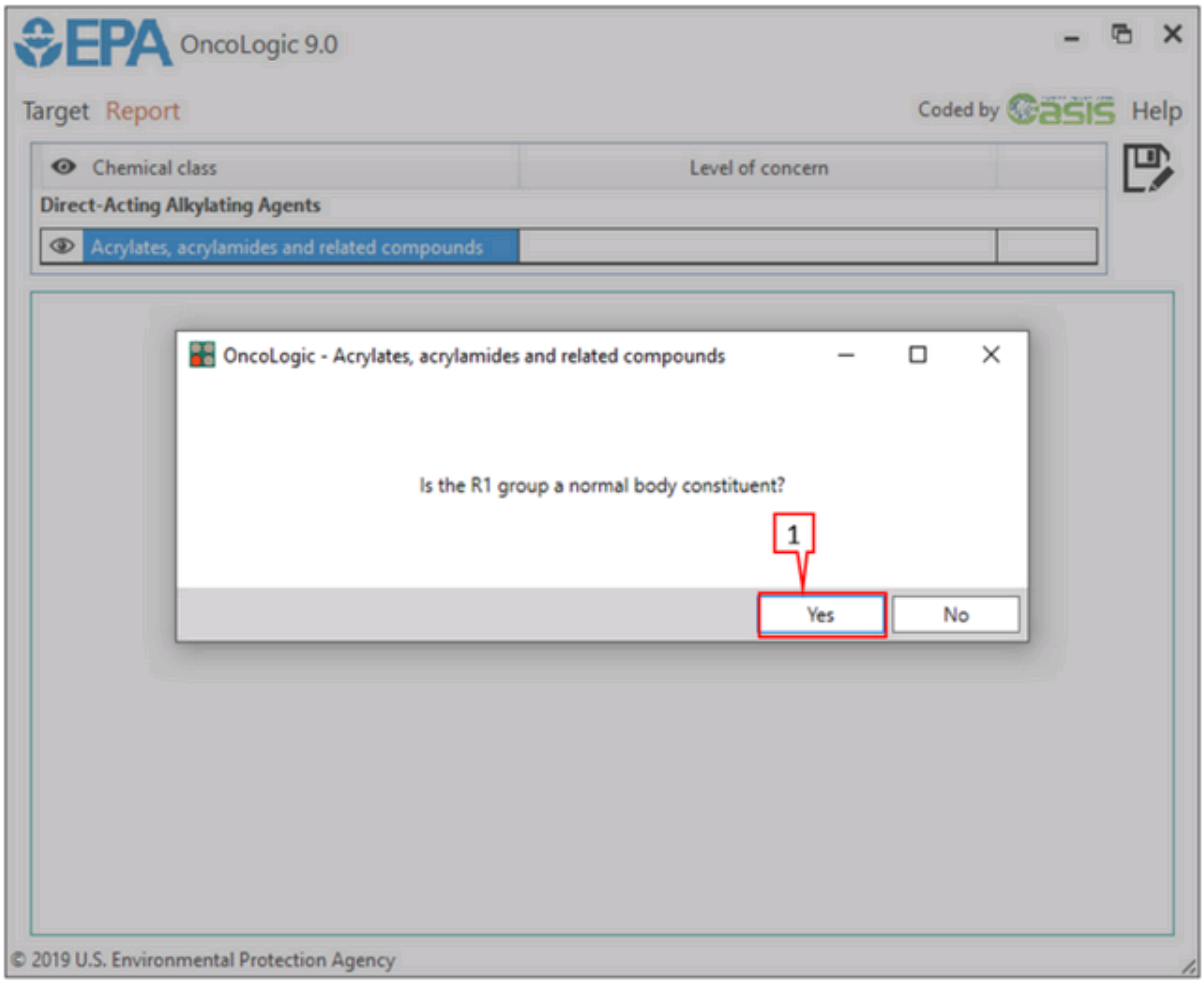

Figure 1

The next interactive quotations try to determine the type of the R1 group. In the current example *Purine/ Pyrimidine/ Nucleoside/ Guanine* is selected (Figure 2 and 3).

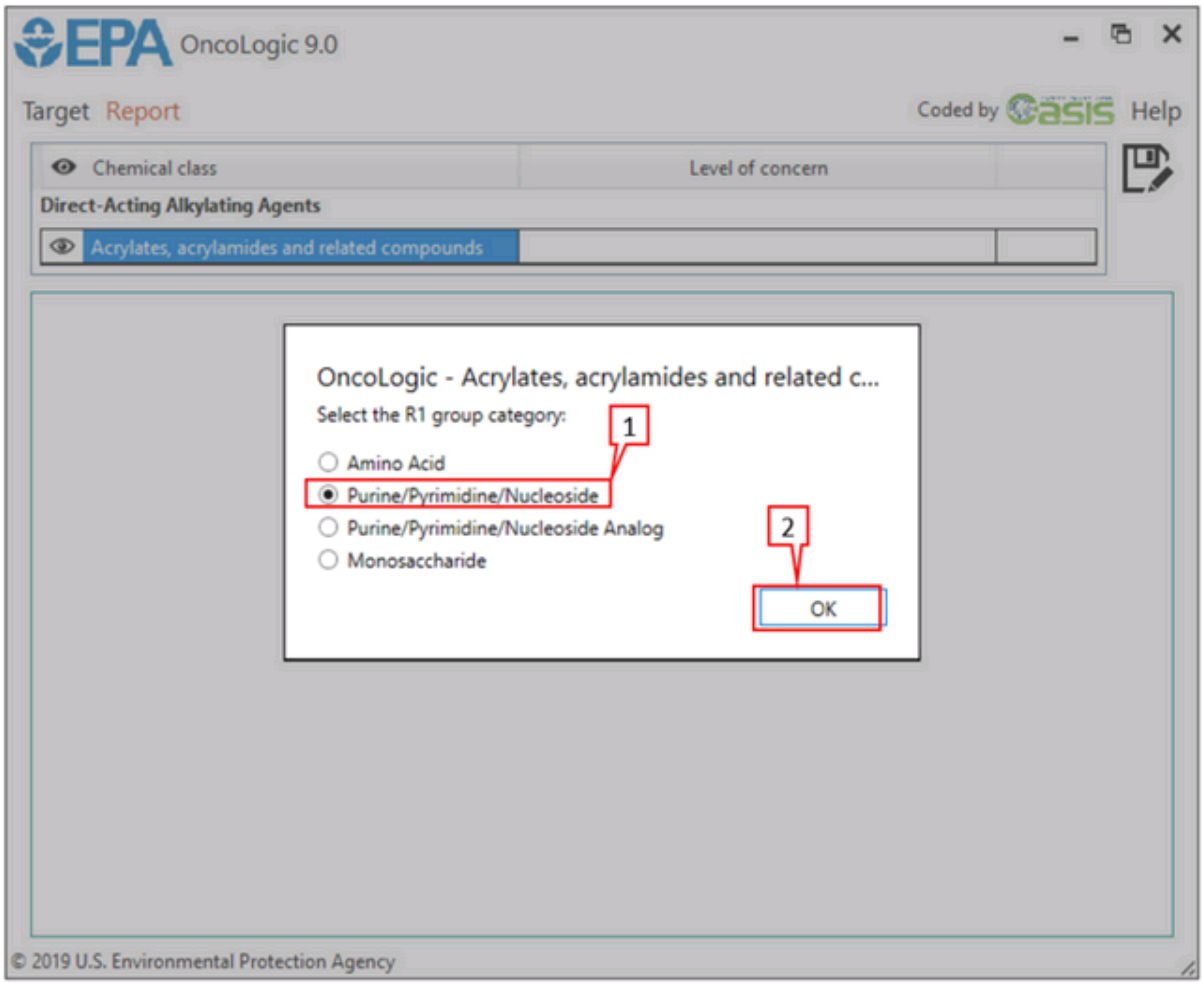
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Direct-Acting Alkylating Agents
Acrylates, acrylamides and related compounds
OncoLogic - Acrylates, acrylamides and related c...
Select the R1 group category:
1
Amino Acid
Purine/Pyrimidine/Nucleoside
Purine/Pyrimidine/Nucleoside Analog
Monosaccharide
2
OK
© 2019 U.S. Environmental Protection Agency

Figure 2

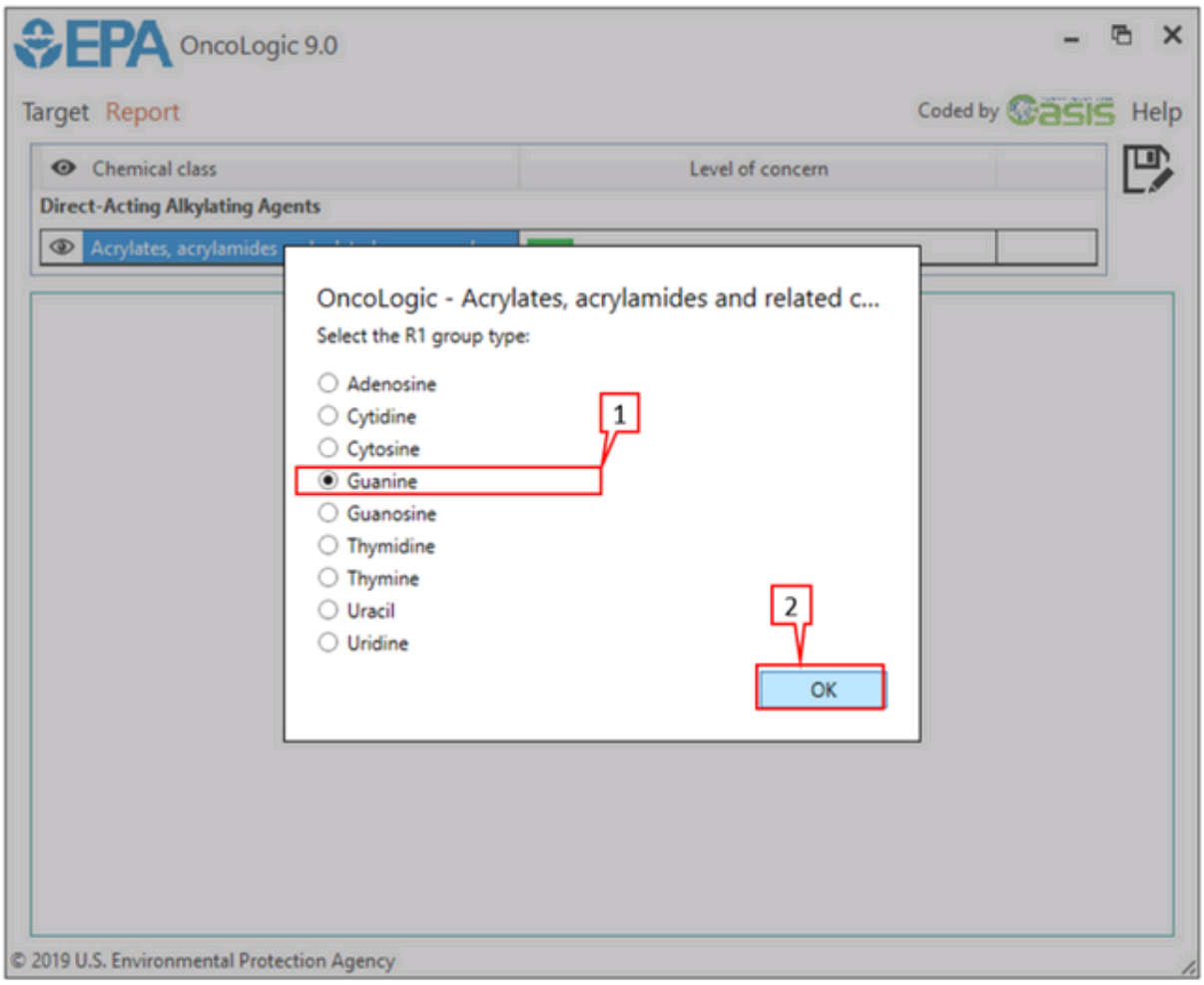

Figure 3

Scenario 2A

The next interactive quotation asks: *Is the molecule to which the reactive functional group is attached know to be NOT bioavailable by the anticipated route of exposure?* (Figure 4).

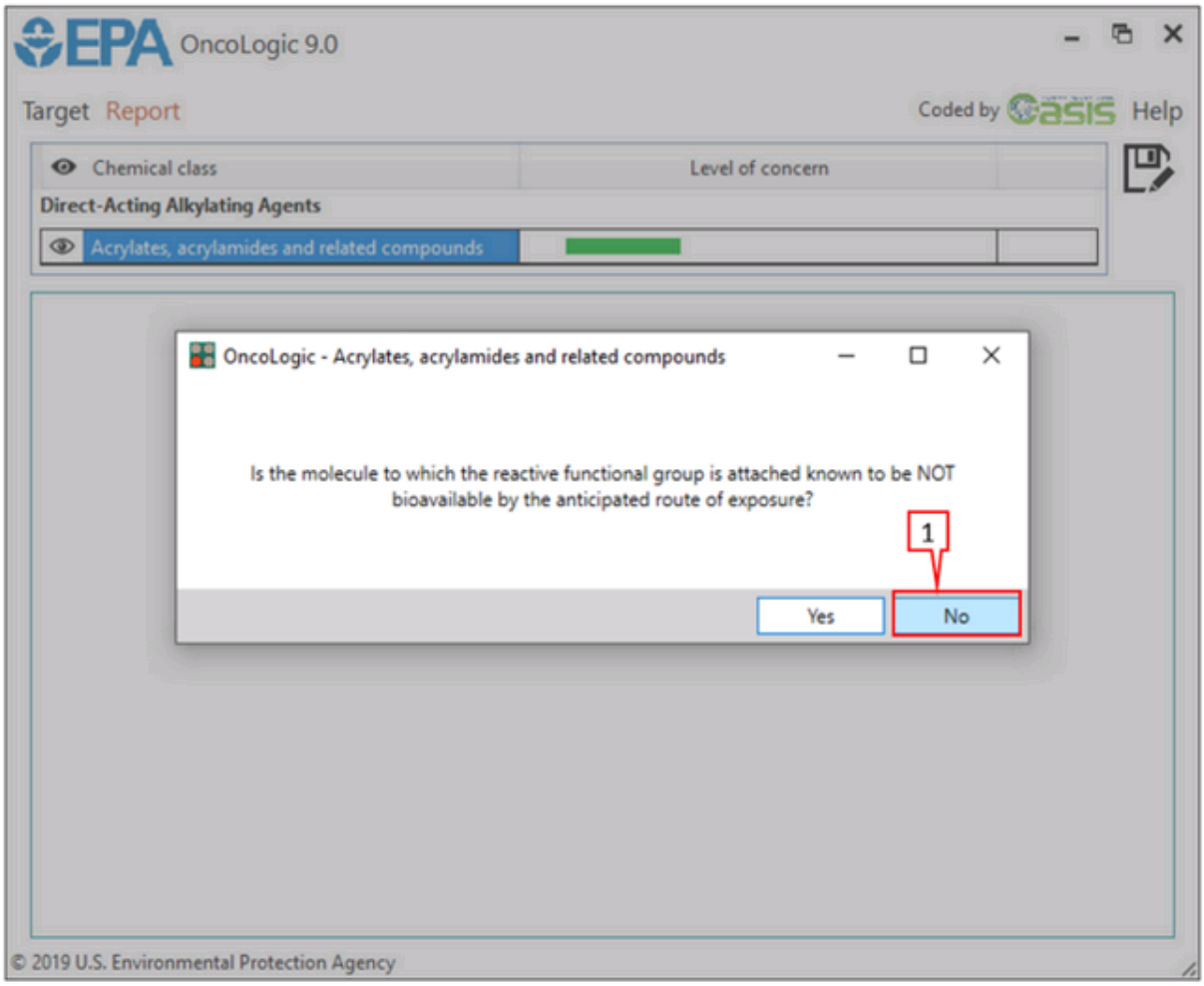

Figure 4

The report has been generated (1) and it could be saved (2) (Figure 5).

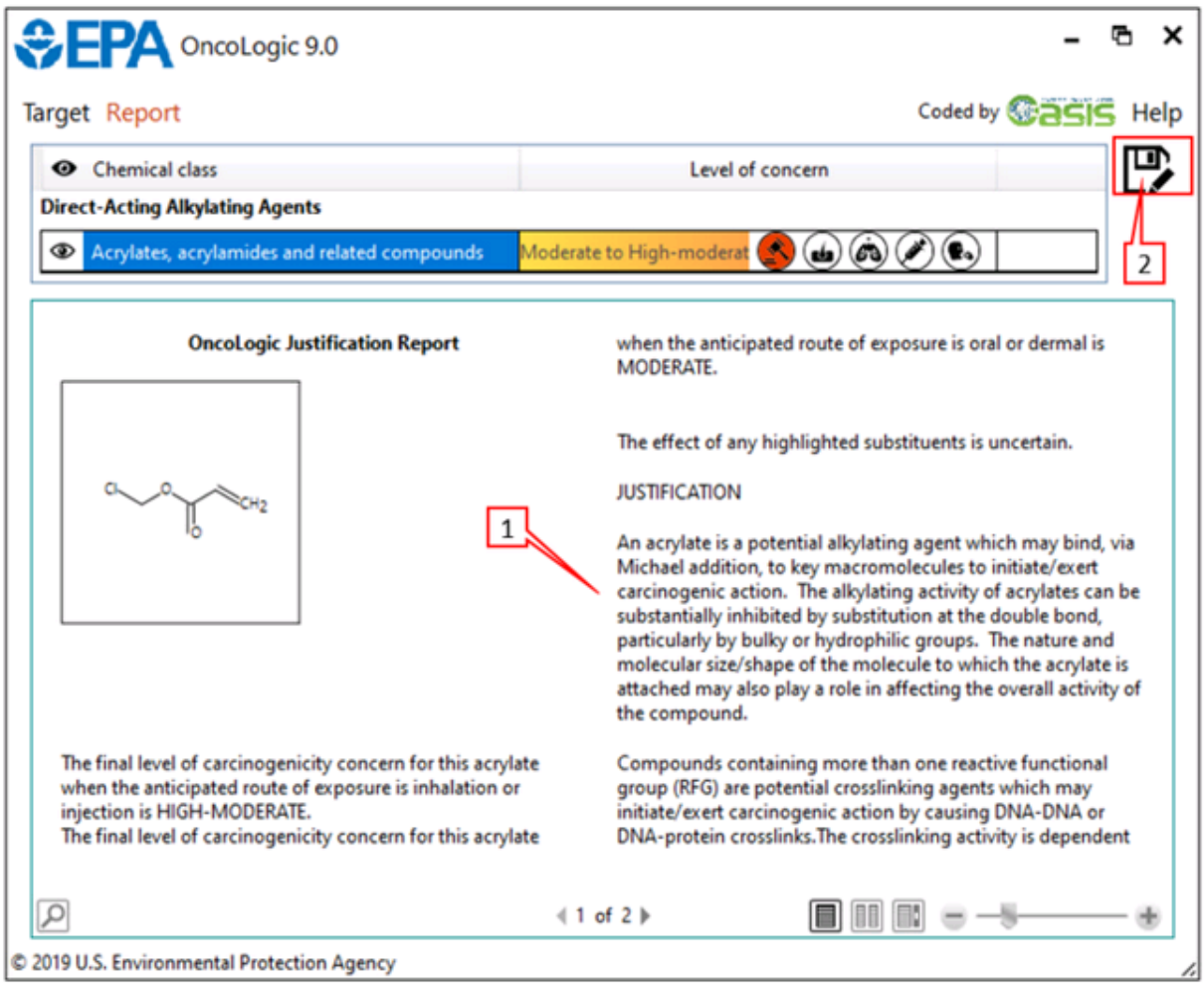

Figure 5

Scenario 2B

If the answer to: *Is the molecule to which the reactive functional group is attached know to be NOT bioavailable by the anticipated route of exposure?* is *Yes* (Figure 6), the report is generated (1) and could be saved (2) (Figure 7).

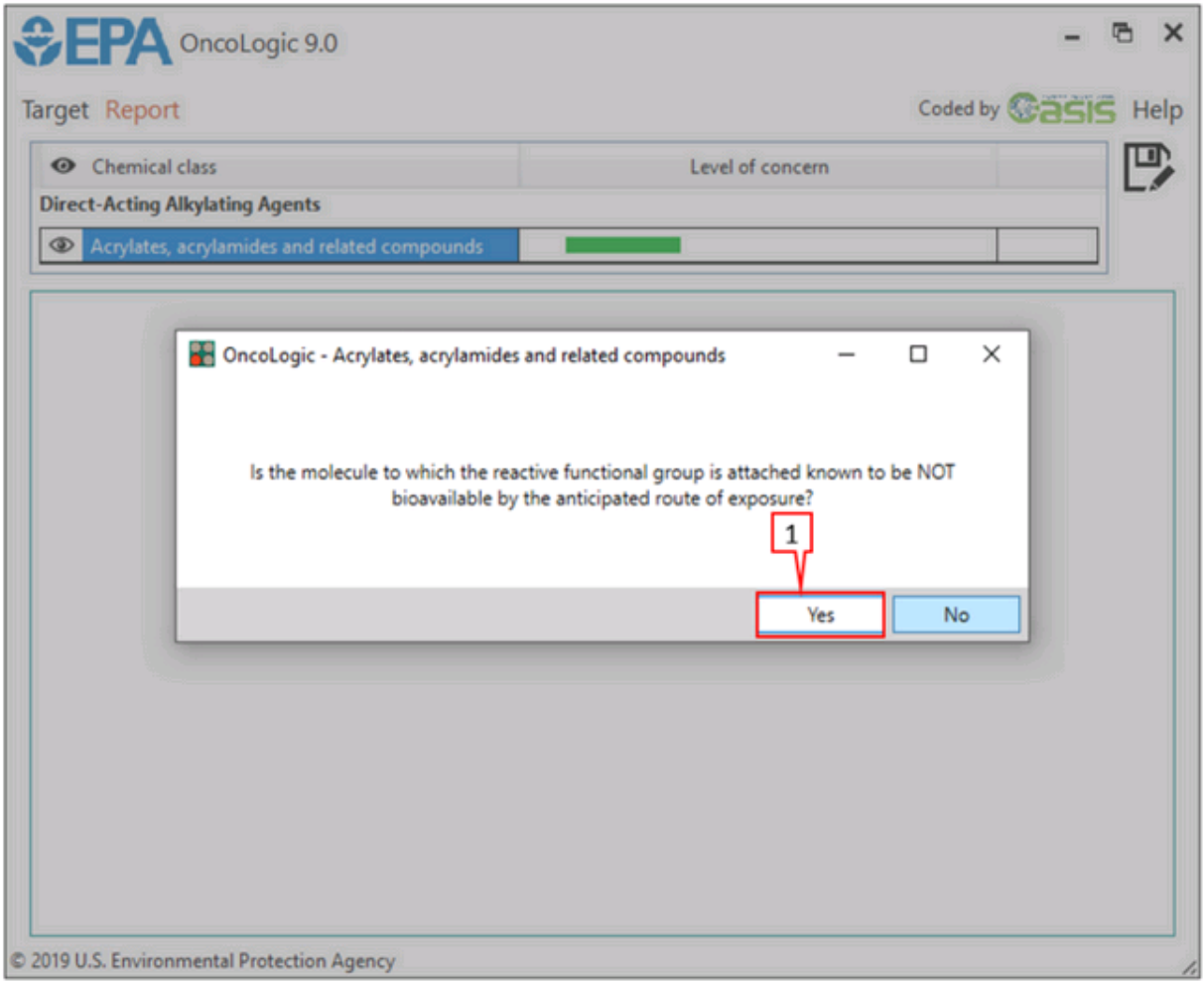
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Direct-Acting Alkylating Agents
Acrylates, acrylamides and related compounds
OncoLogic - Acrylates, acrylamides and related compounds
Is the molecule to which the reactive functional group is attached known to be NOT bioavailable by the anticipated route of exposure?
1
Yes
No
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Figure 6

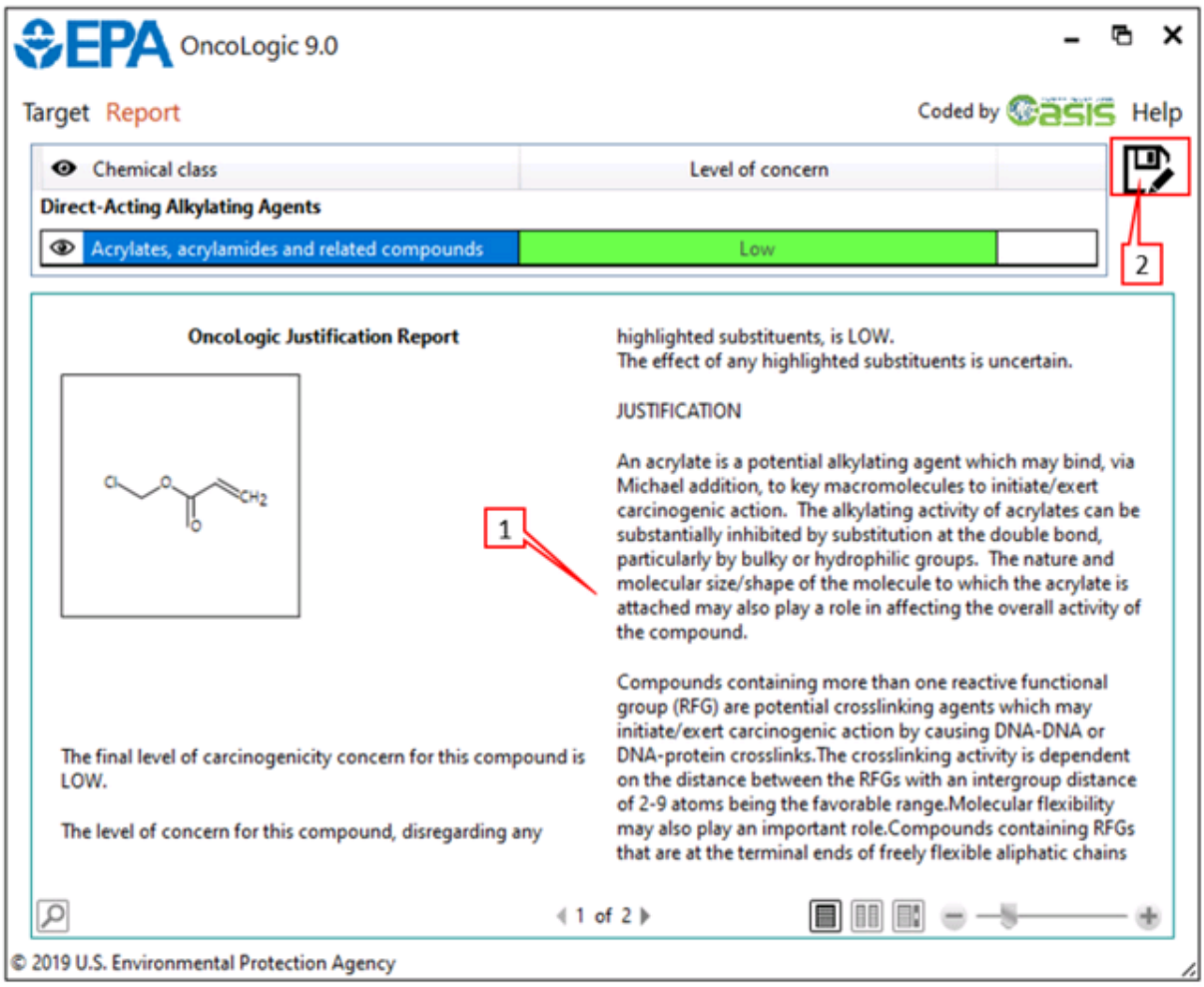
EPA OncoLogic 9.0
Target Report
Coded by oasis Help
Chemical class
Level of concern
Direct-Acting Alkylating Agents
Acrylates, acrylamides and related compounds
Low
2
OncoLogic Justification Report
1
The final level of carcinogenicity concern for this compound is LOW.
The level of concern for this compound, disregarding any
highlighted substituents, is LOW.
The effect of any highlighted substituents is uncertain.
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. The nature and molecular size/shape of the molecule to which the acrylate is attached may also play a role in affecting the overall activity of the compound.
Compounds containing more than one reactive functional group (RFG) are potential crosslinking agents which may initiate/exert carcinogenic action by causing DNA-DNA or DNA-protein crosslinks.The crosslinking activity is dependent on the distance between the RFGs with an intergroup distance of 2-9 atoms being the favorable range.Molecular flexibility may also play an important role.Compounds containing RFGs that are at the terminal ends of freely flexible aliphatic chains
1 of 2
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Figure 7

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5.5 Direct-Acting Arylating Agents

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5.5.1 Aryldiazonium Salts

1. Input a target chemical (1) and click OK (2) (Figure 1).

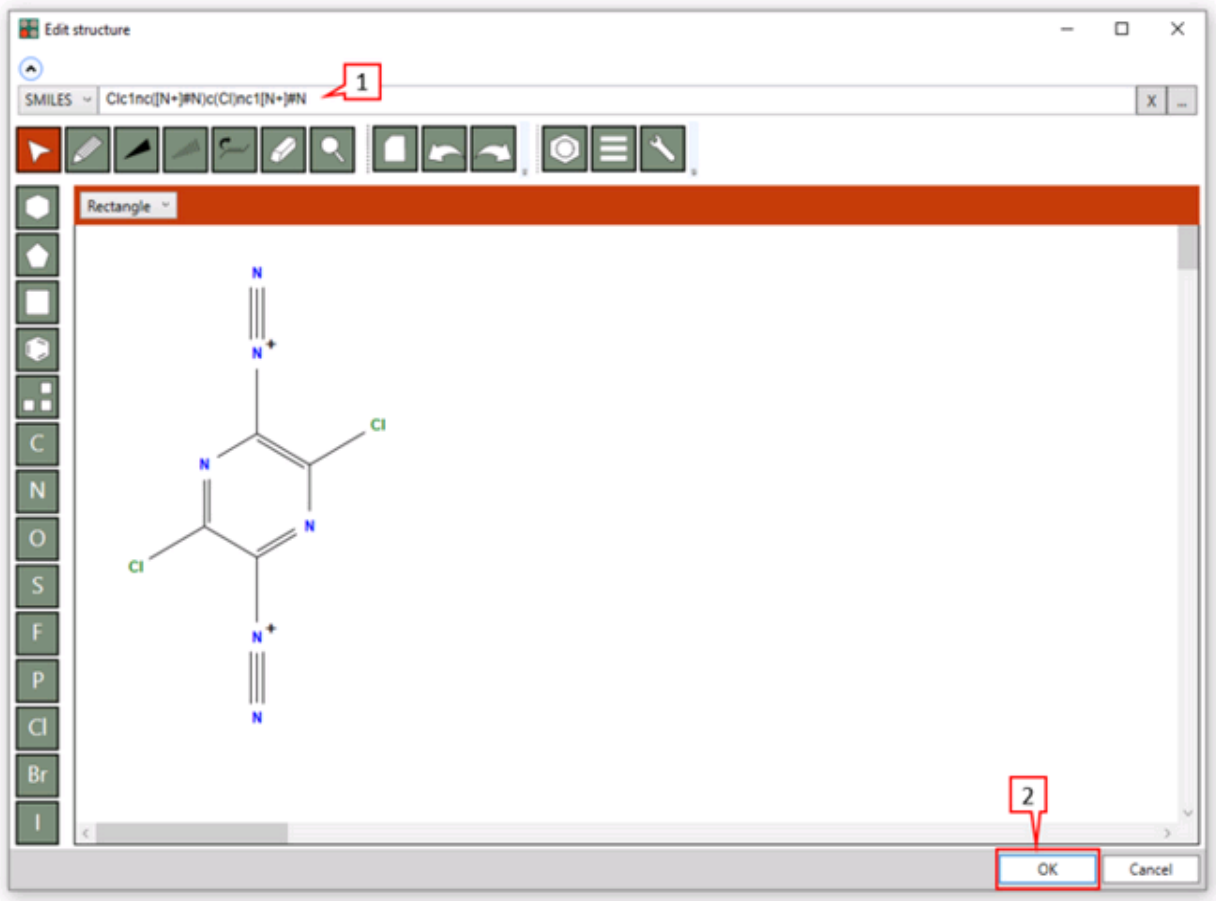

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

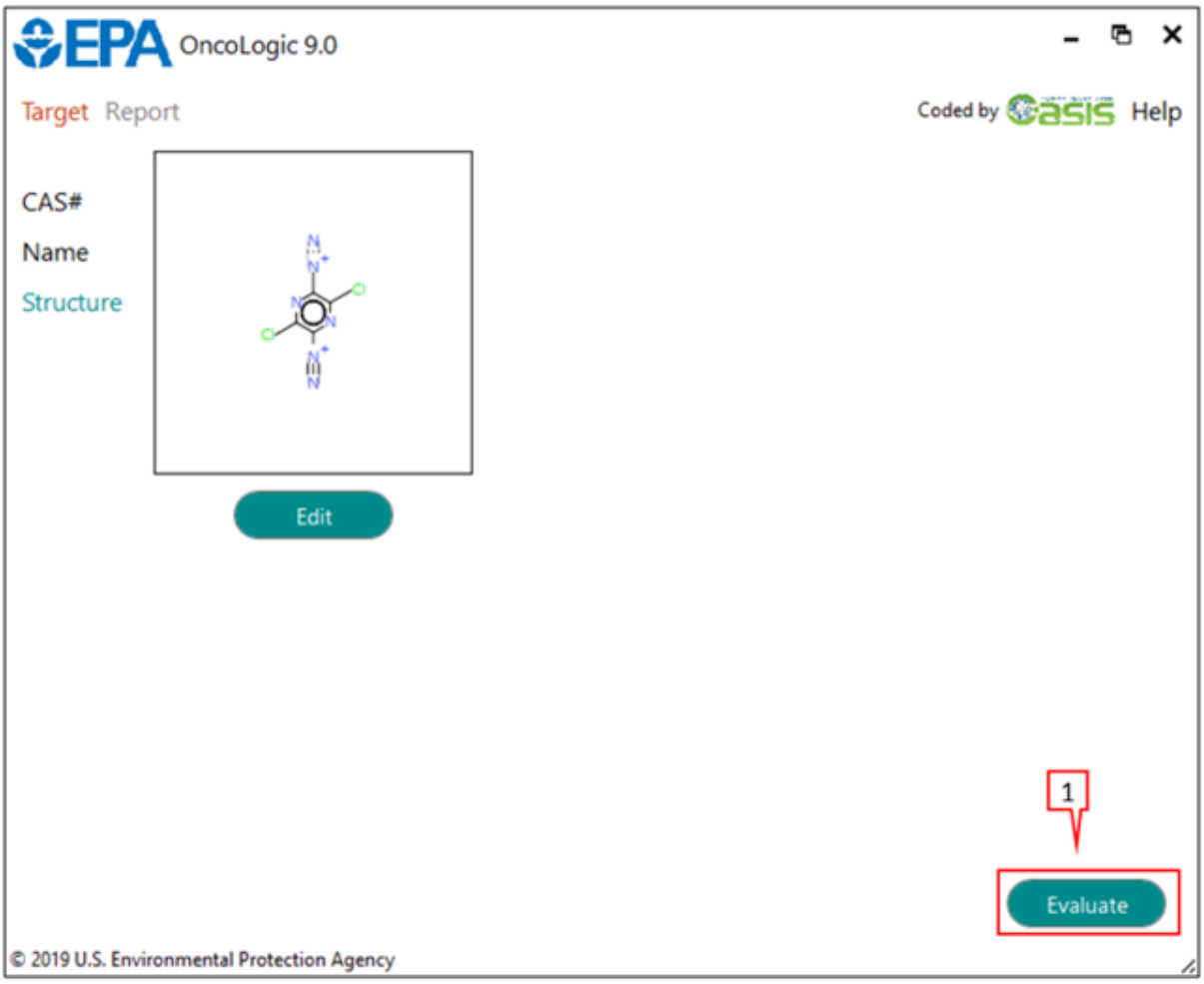

Figure 2

3. After the target chemical has been profiled as *Direct-acting Arylating Agents/ Aryldiazonium Salts, O-Halogenated Heterocyclics and Halogenated Nitroaromatics* (1), click on *Evaluate* (2) (Figure 3).

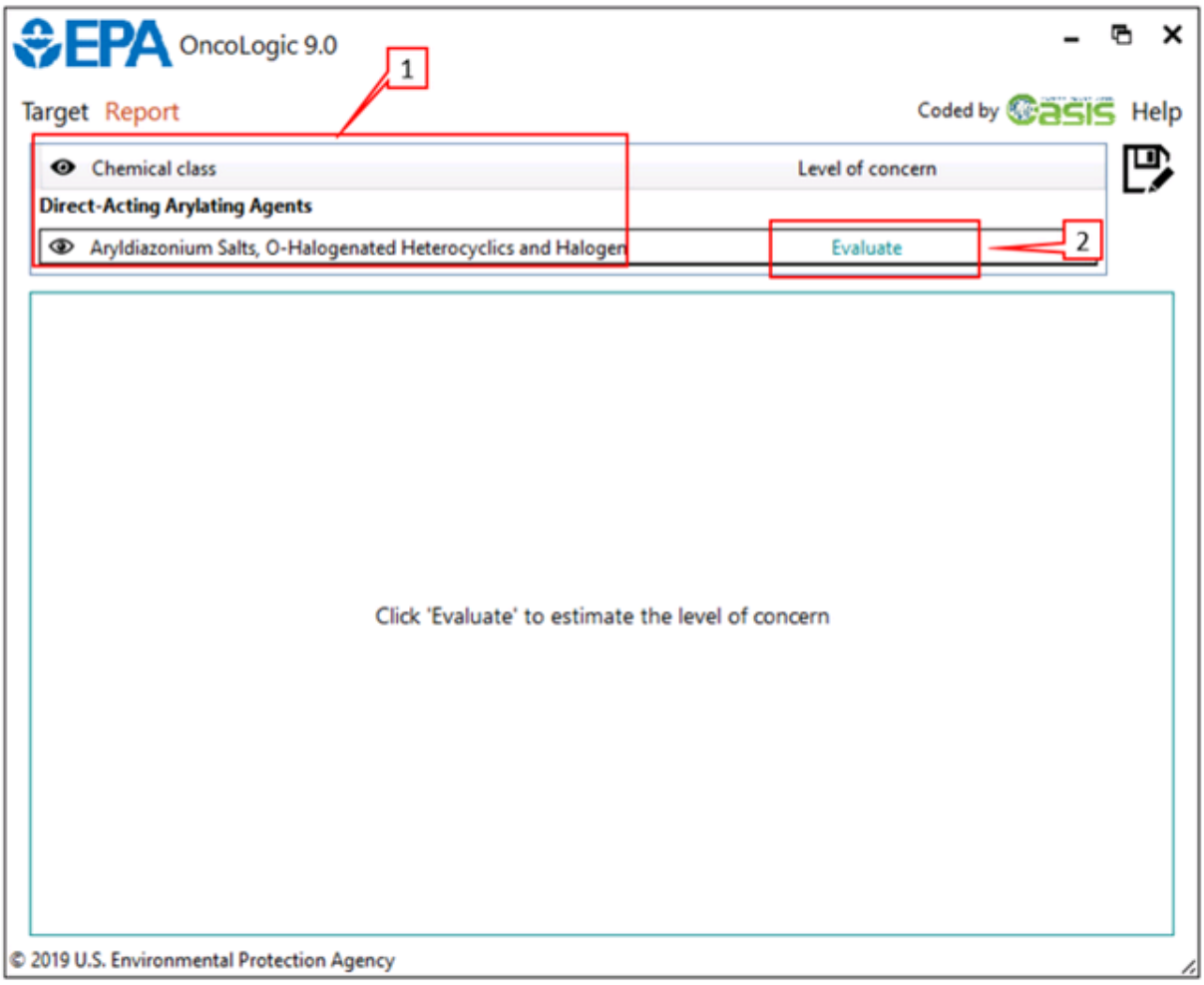

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

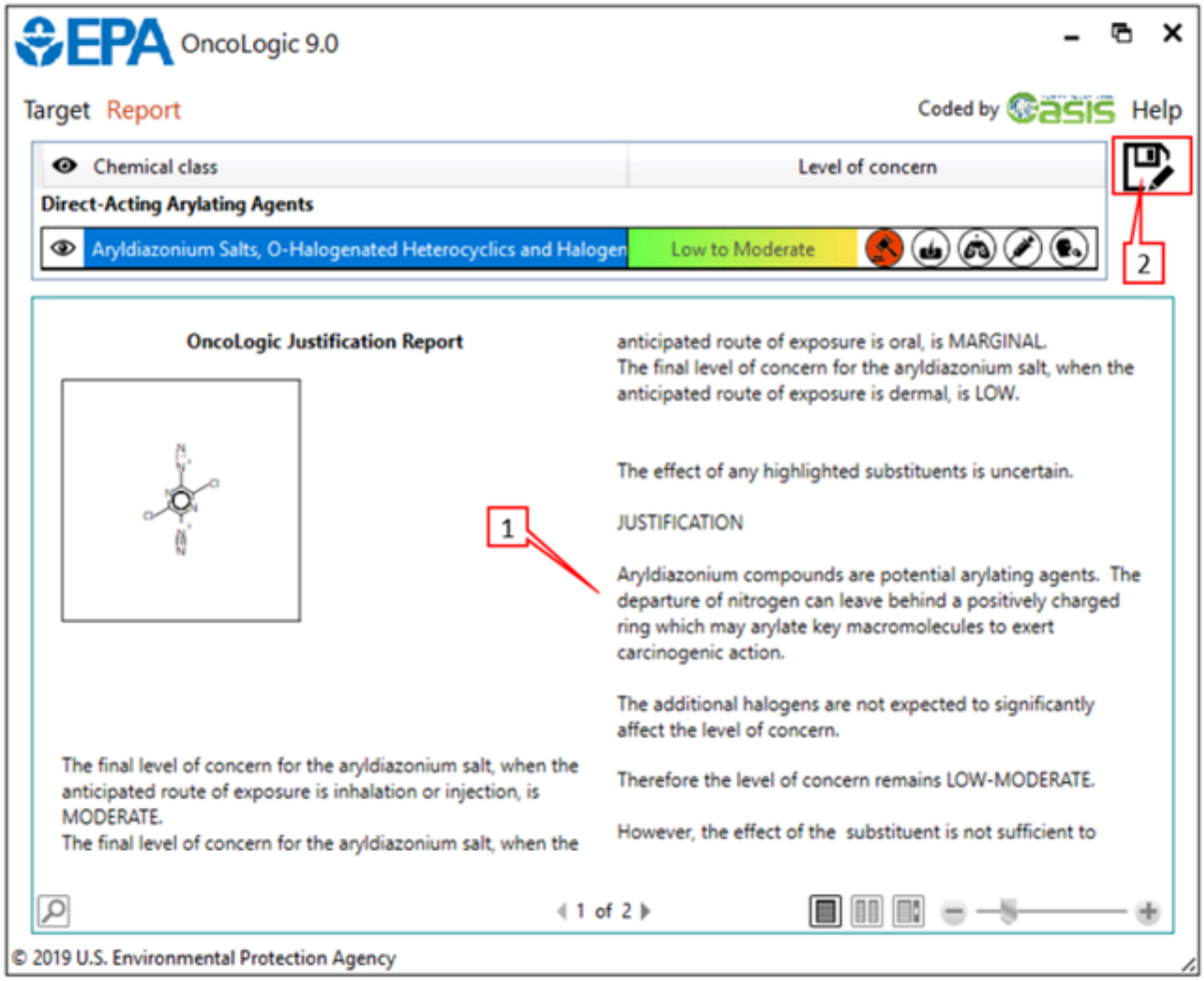
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Direct-Acting Arylating Agents
Aryldiazonium Salts, O-Halogenated Heterocyclics and Halogen
Low to Moderate
2
OncoLogic Justification Report
1
anticipated route of exposure is oral, is MARGINAL.
The final level of concern for the aryldiazonium salt, when the anticipated route of exposure is dermal, is LOW.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
Aryldiazonium compounds are potential arylating agents. The departure of nitrogen can leave behind a positively charged ring which may arylate key macromolecules to exert carcinogenic action.
The additional halogens are not expected to significantly affect the level of concern.
Therefore the level of concern remains LOW-MODERATE.
However, the effect of the substituent is not sufficient to
The final level of concern for the aryldiazonium salt, when the anticipated route of exposure is inhalation or injection, is MODERATE.
The final level of concern for the aryldiazonium salt, when the
1 of 2
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Figure 4

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5.6 Halogenated Cycloalkanes and Cycloalkenes

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5.6.1 Halogenated cyclohexadienes

1. Input a target chemical (1) and click OK (2) (Figure 1).

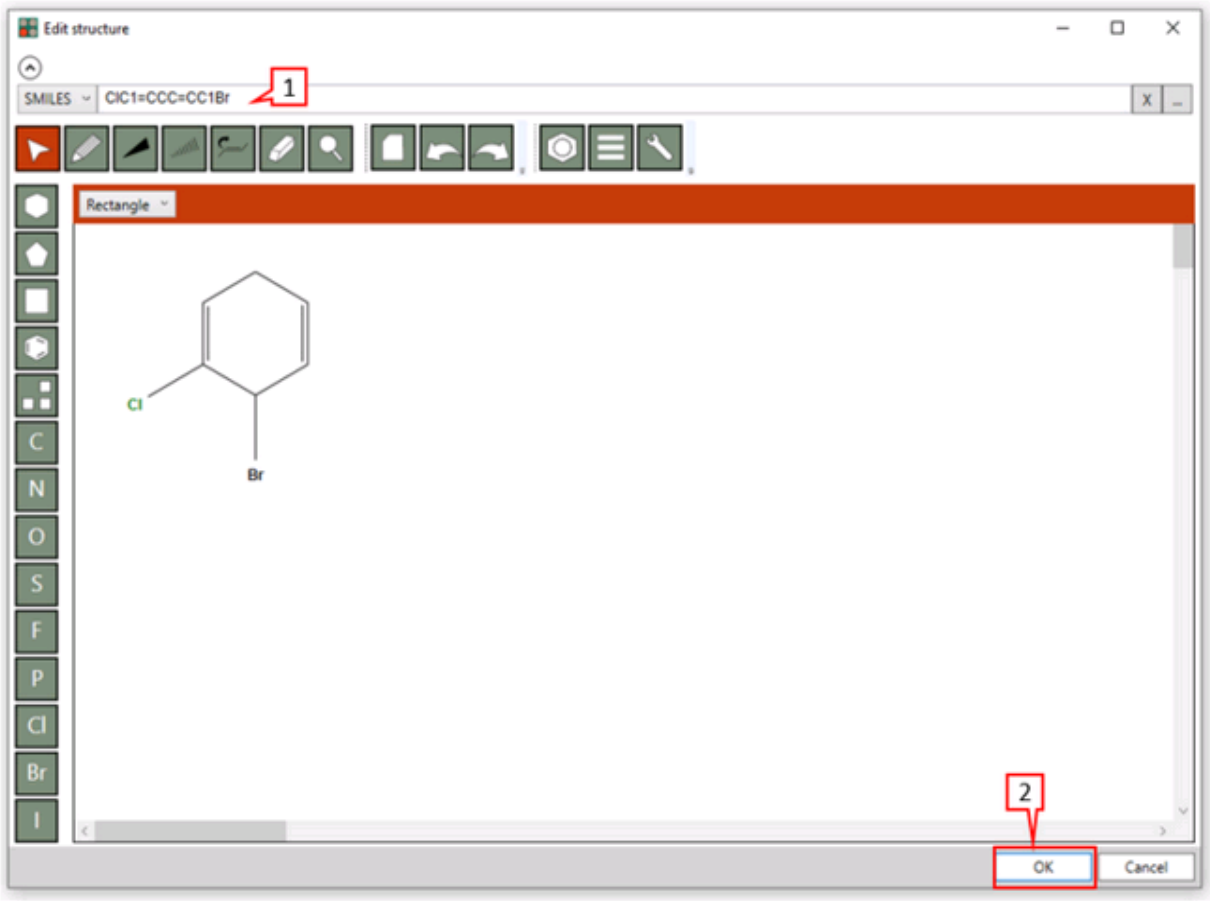

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

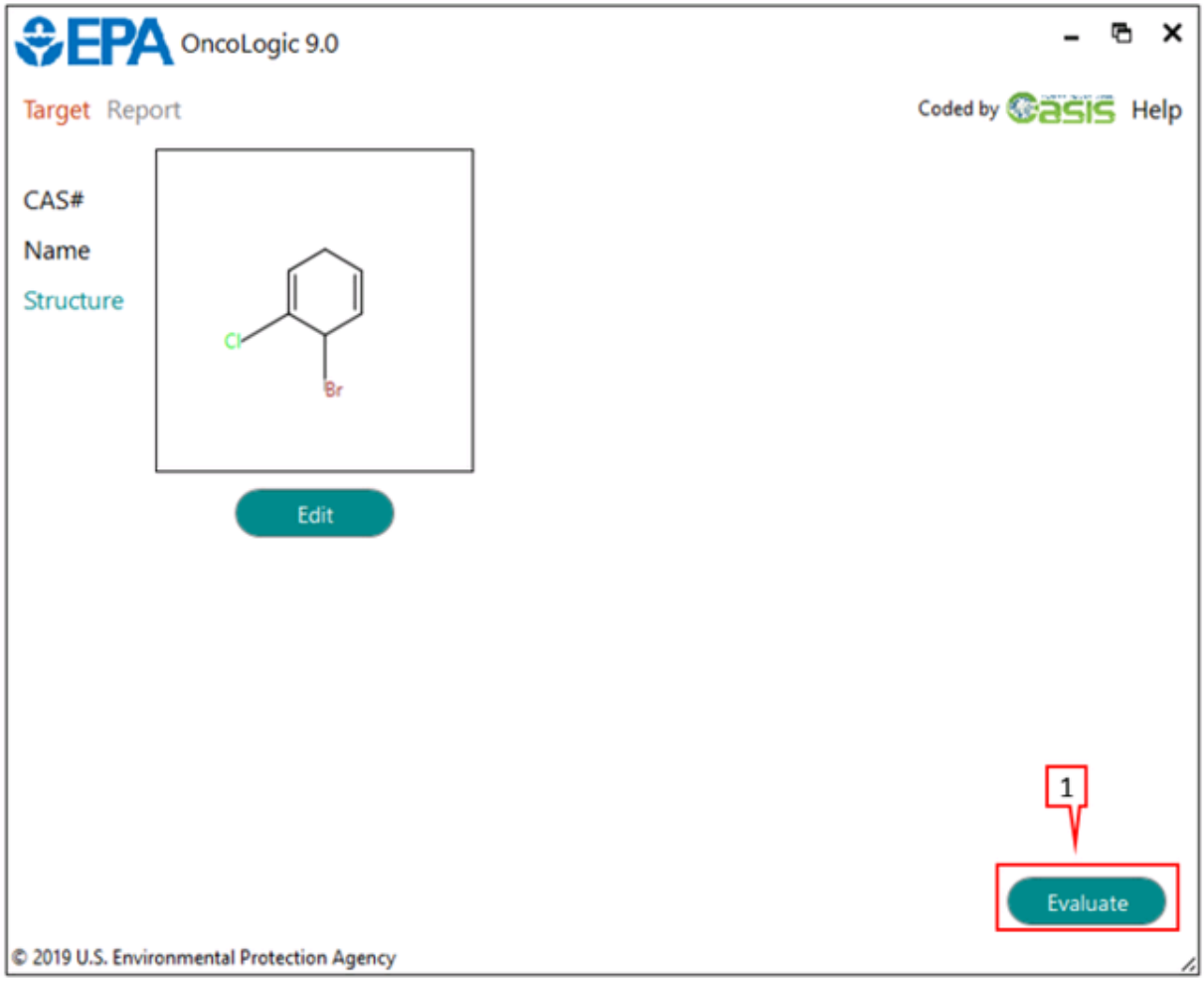

Figure 2

3. After the target chemical has been profiled as *Halogenated Cycloalkanes and Cycloalkenes/ Halogenated cyclohexadienes* (1), click on Evaluate (2) (Figure 3).

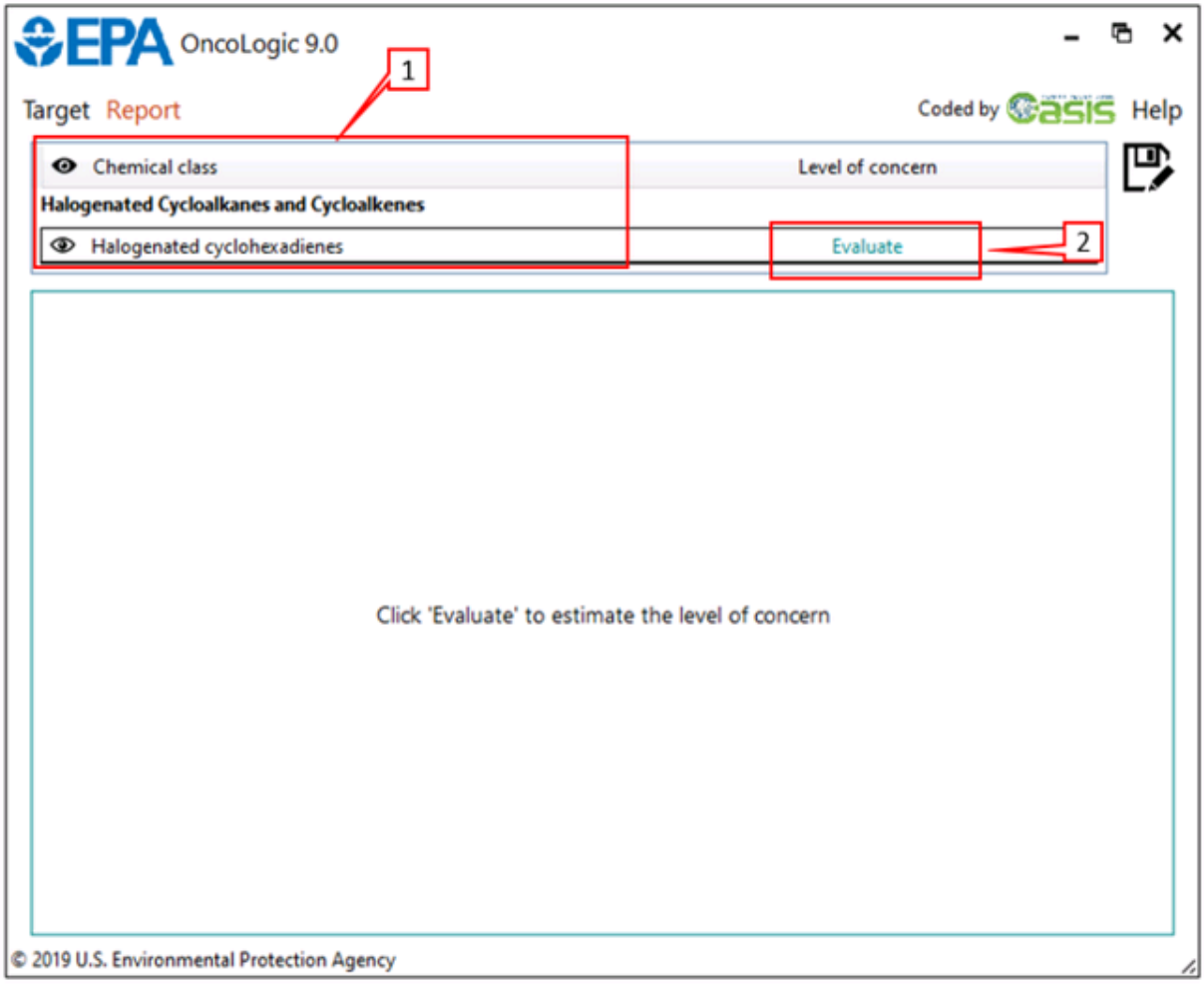

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

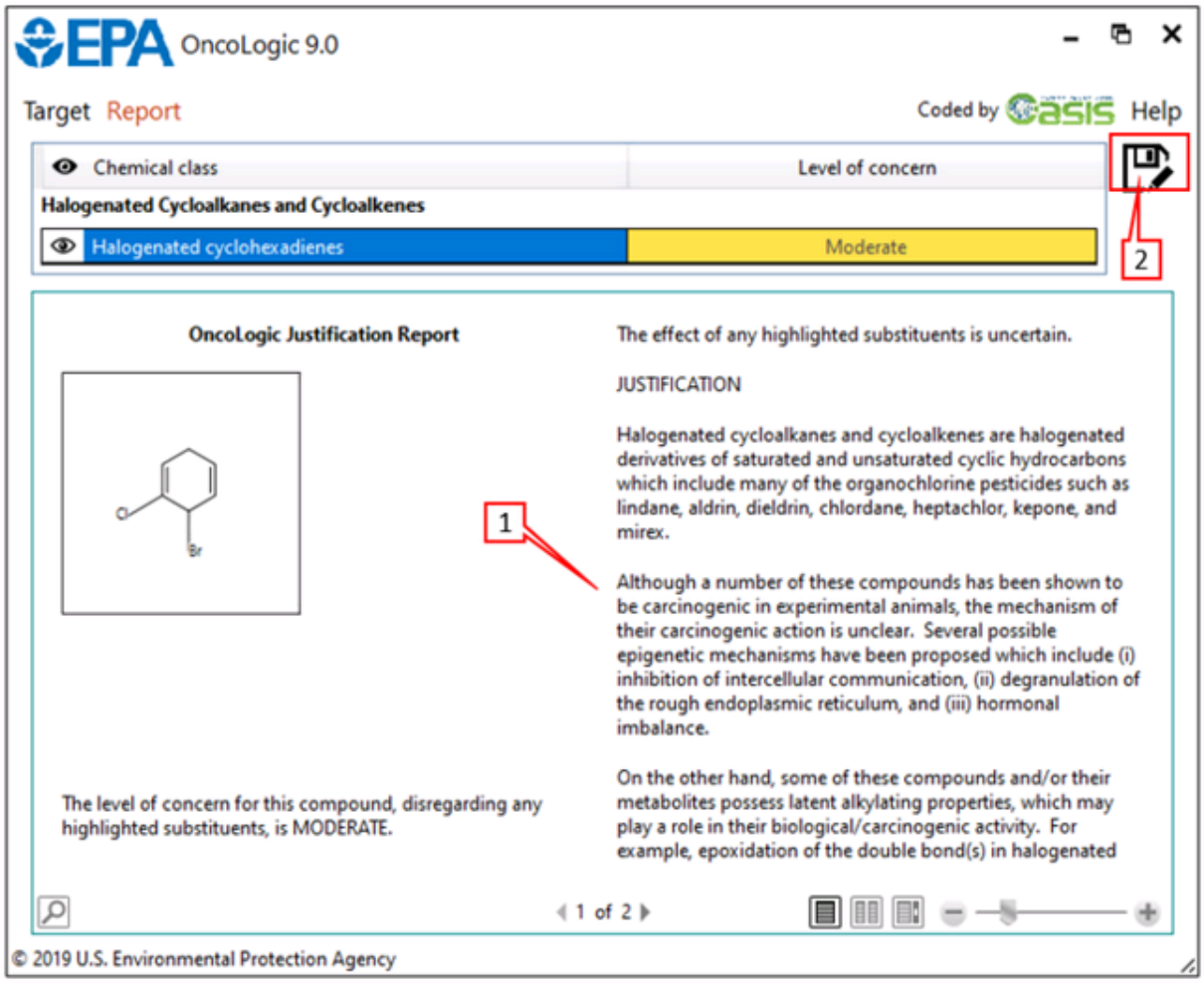
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Halogenated Cycloalkanes and Cycloalkenes
Halogenated cyclohexadienes
Moderate
2
OncoLogic Justification Report
1
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
Halogenated cycloalkanes and cycloalkenes are halogenated derivatives of saturated and unsaturated cyclic hydrocarbons which include many of the organochlorine pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, kepone, and mirex.
Although a number of these compounds has been shown to be carcinogenic in experimental animals, the mechanism of their carcinogenic action is unclear. Several possible epigenetic mechanisms have been proposed which include (i) inhibition of intercellular communication, (ii) degranulation of the rough endoplasmic reticulum, and (iii) hormonal imbalance.
On the other hand, some of these compounds and/or their metabolites possess latent alkylating properties, which may play a role in their biological/carcinogenic activity. For example, epoxidation of the double bond(s) in halogenated
The level of concern for this compound, disregarding any highlighted substituents, is MODERATE.
1 of 2
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Figure 4

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5.7 Halogenated Linear Aliphatics

-o-

5.7.1 Haloethylenes

1. Input a target chemical (1) and click OK (2) (Figure 1).

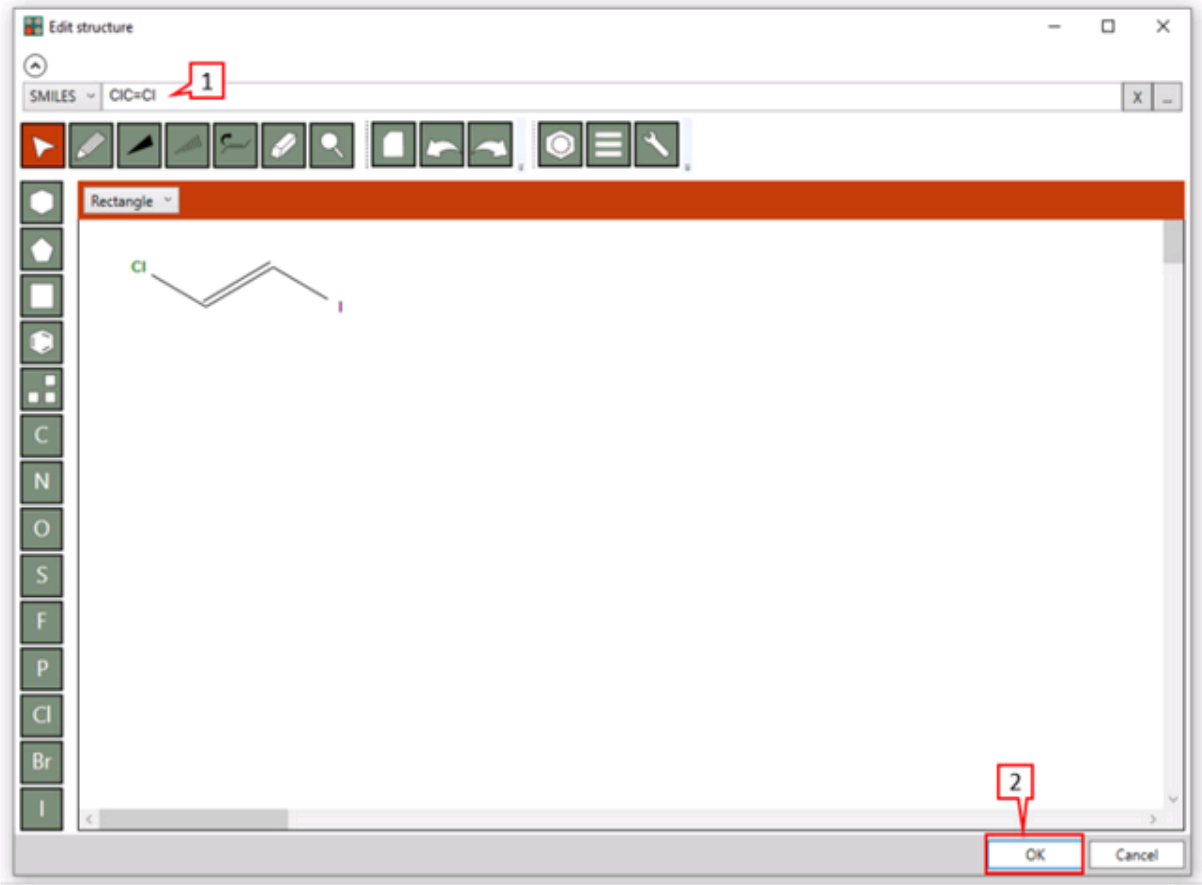

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

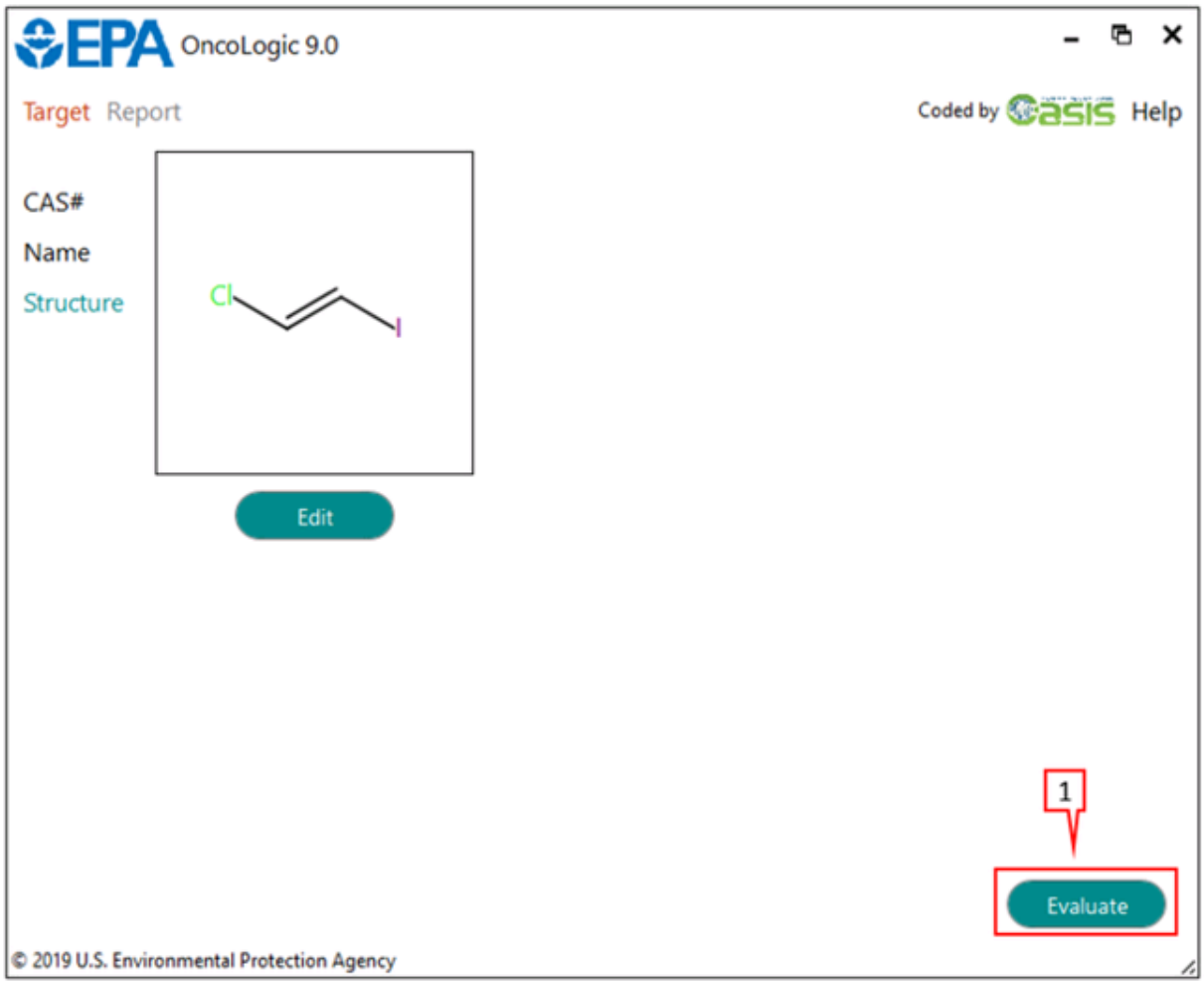

Figure 2

3. After the target chemical has been profiled as *Halogenated Linear Aliphatics/ Haloethylenes* (1), click on Evaluate (2) (Figure 3).

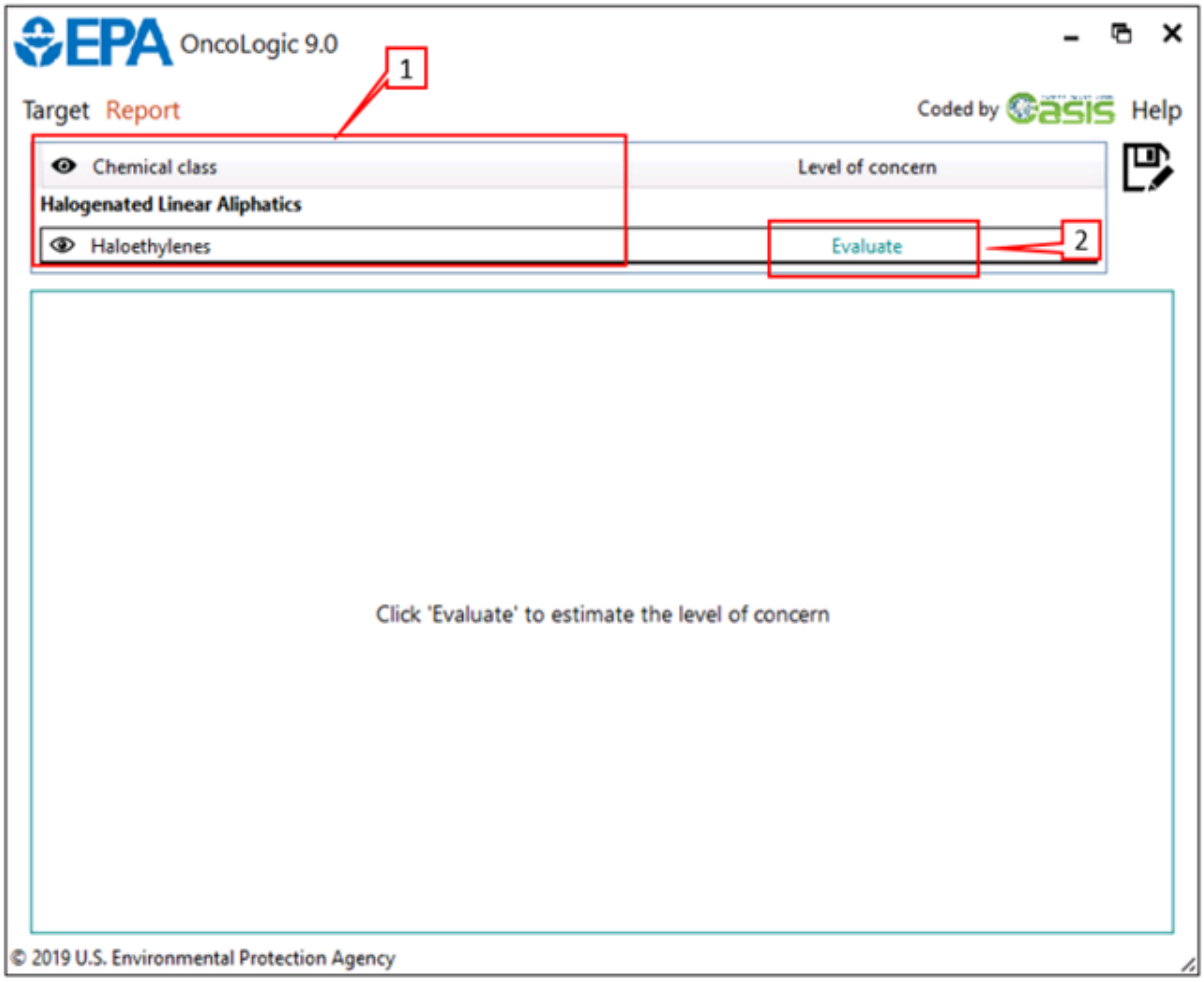

Figure 3

4. There is a specific question for this current chemical class that ask the user if the compound is predominantly a cys configuration. The concern is assigned accordingly.
If the configuration is predominantly cys, click on Yes (1) (Figure 4).

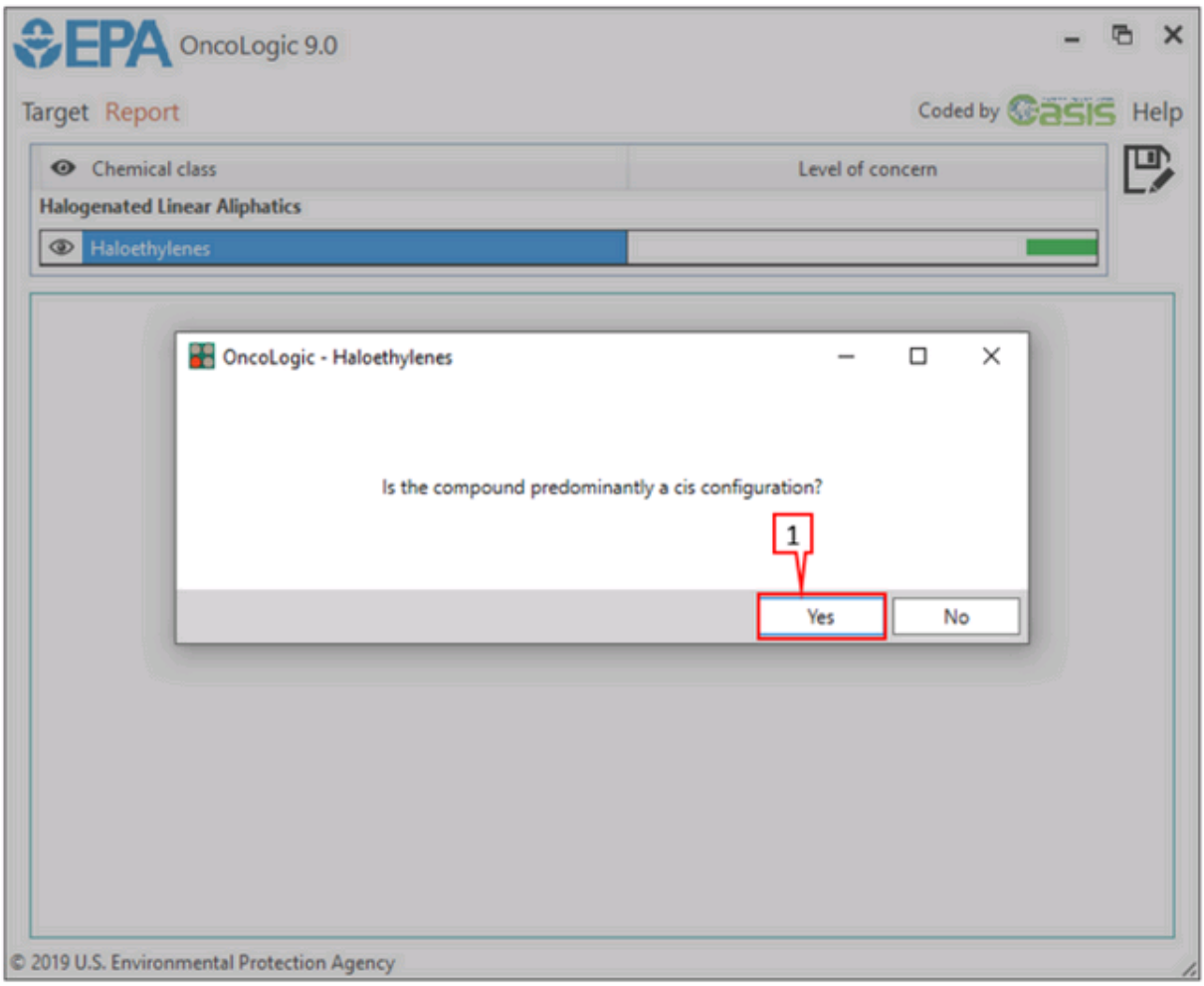

Figure 4

5. The report has been generated (1) and it could be saved (2) (Figure 5).

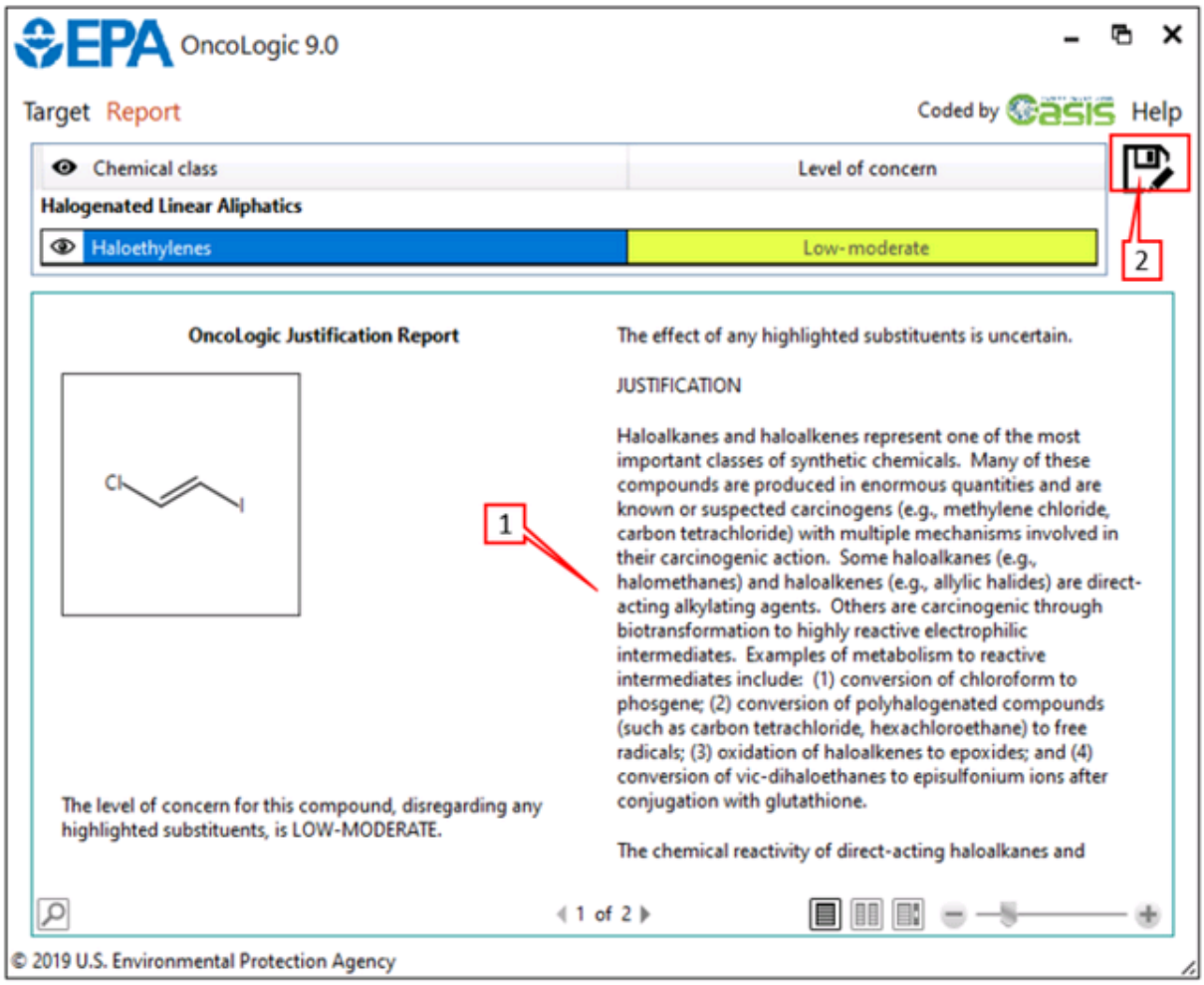

Figure 5

6. If the configuration is not predominantly cys, click on No (1) (Figure 4).

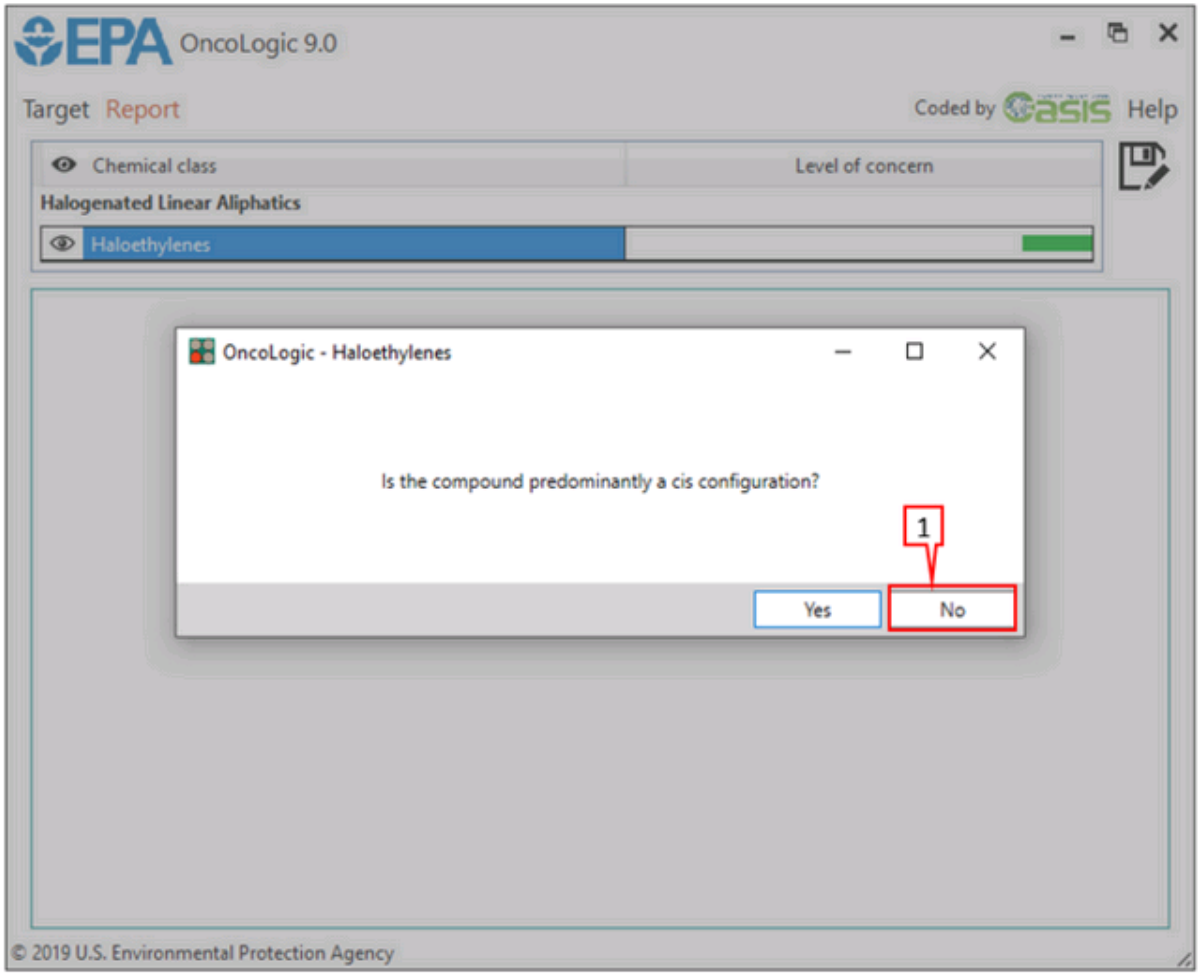

Figure 6

7. The report has been generated (1) and it could be saved (2) (Figure 7).

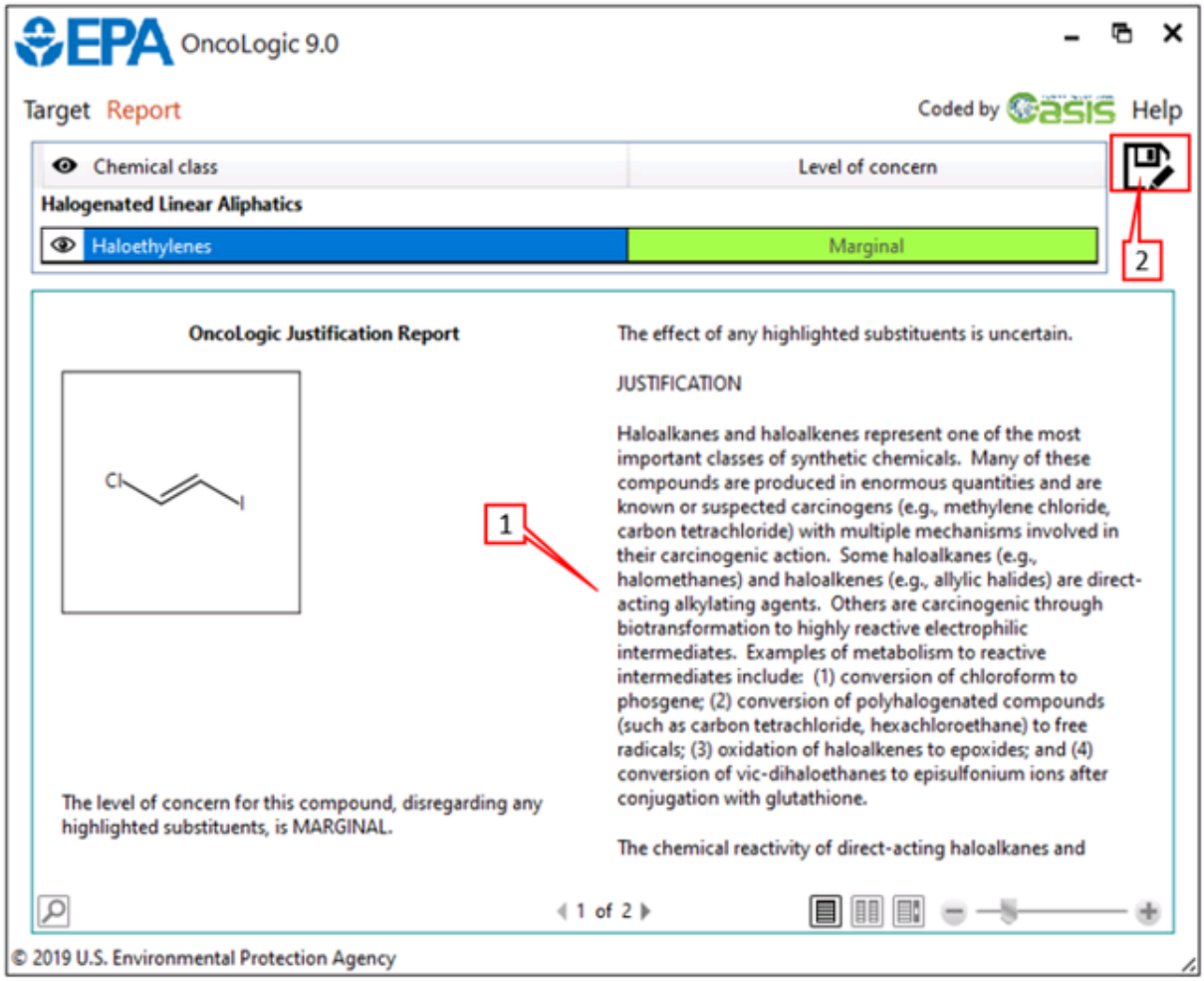
EPA OncoLogic 9.0
Target Report
Coded by oasis Help
Chemical class
Level of concern
Halogenated Linear Aliphatics
Haloethylenes
Marginal
2
OncoLogic Justification Report
Cl
I
1
The level of concern for this compound, disregarding any highlighted substituents, is MARGINAL.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.
The chemical reactivity of direct-acting haloalkanes and
1 of 2
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Figure 7

-o-

5.8 Hydrazo Compounds

-o-

5.8.1 Hydrazines, hydrazides and hydrazones

1. Input a target chemical (1) and click OK (2) (Figure 1).

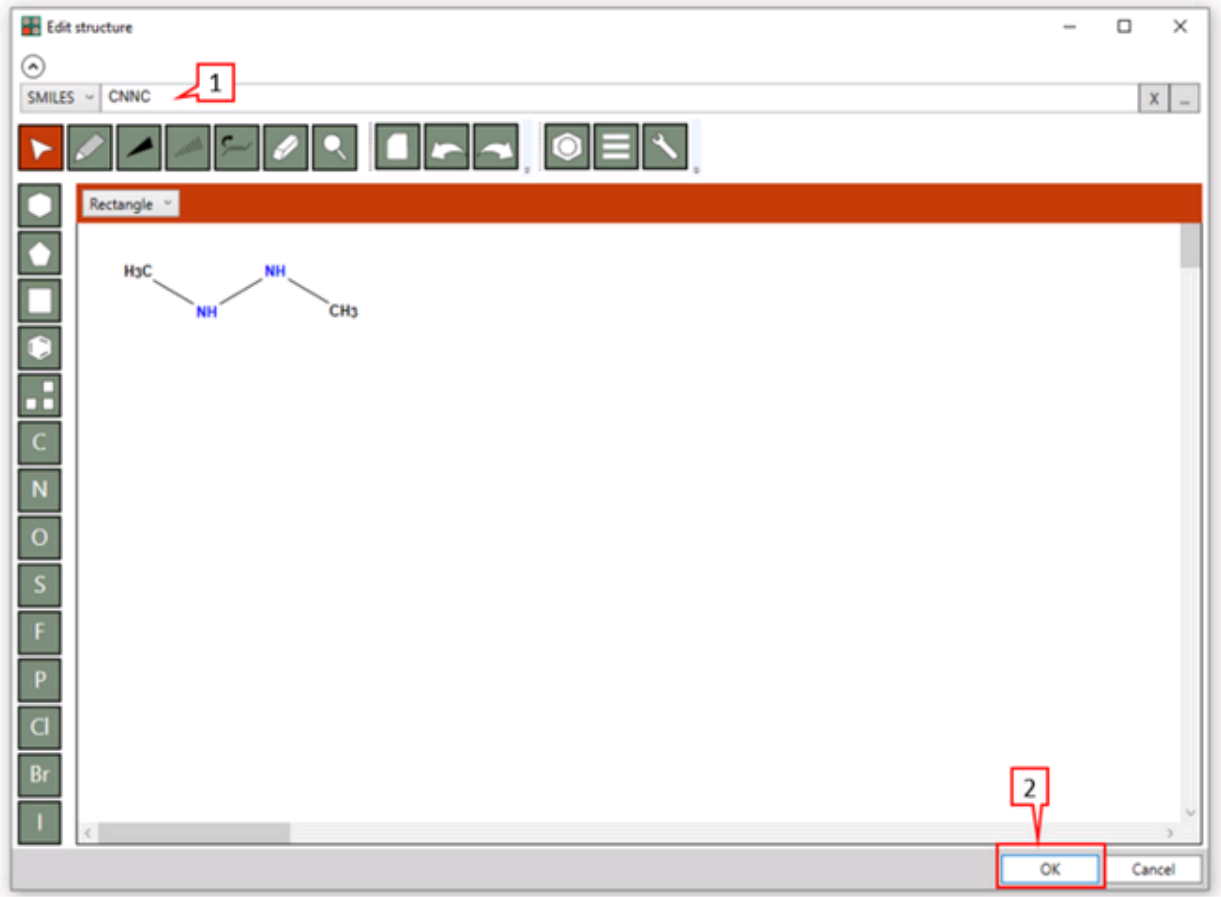

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

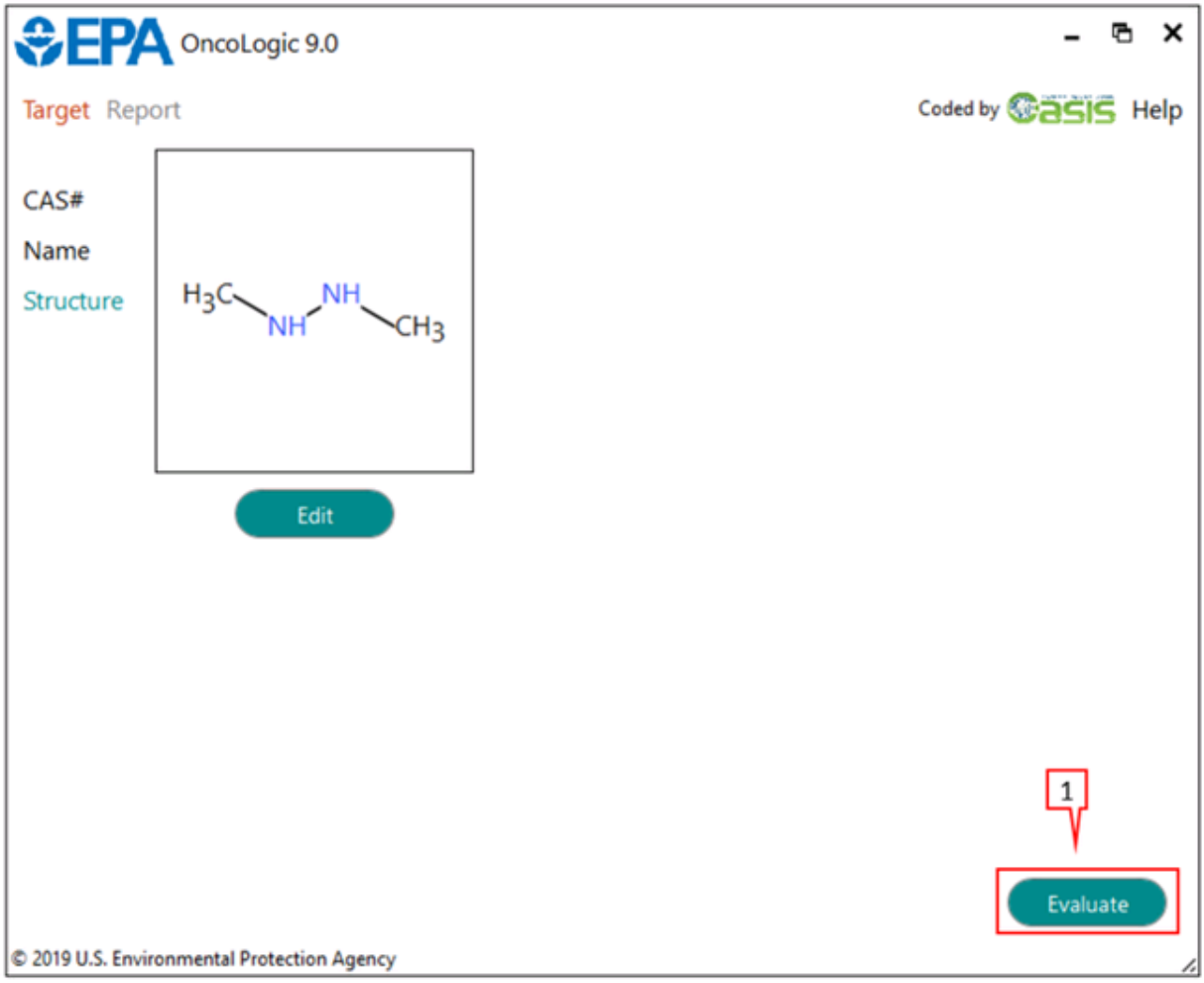

Figure 2

3. After the target chemical has been profiled as *Hydrazo Compounds/ Hydrazines, hydrazides and hydrazones* (1), click on Evaluate (2) (Figure 3).

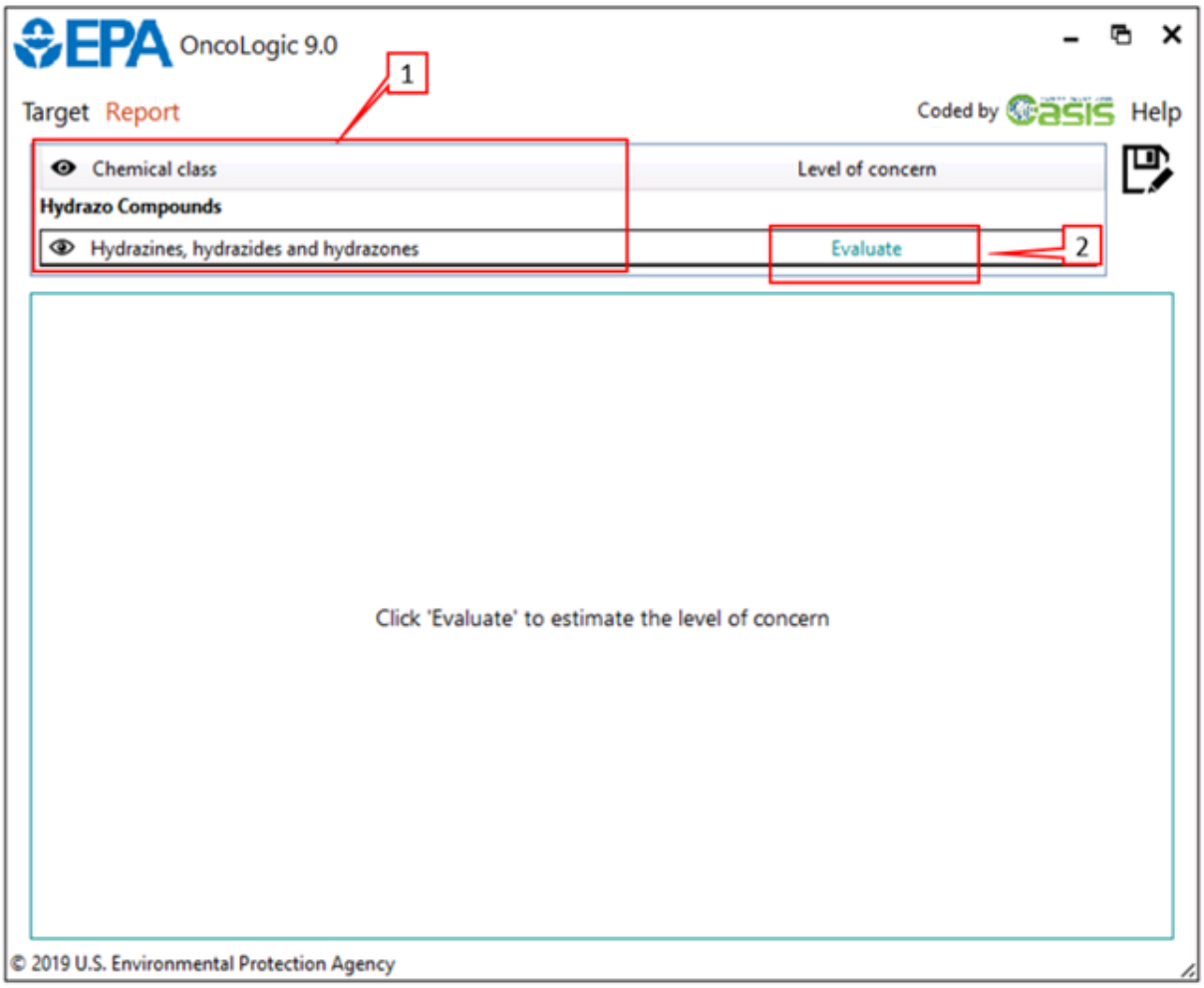

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

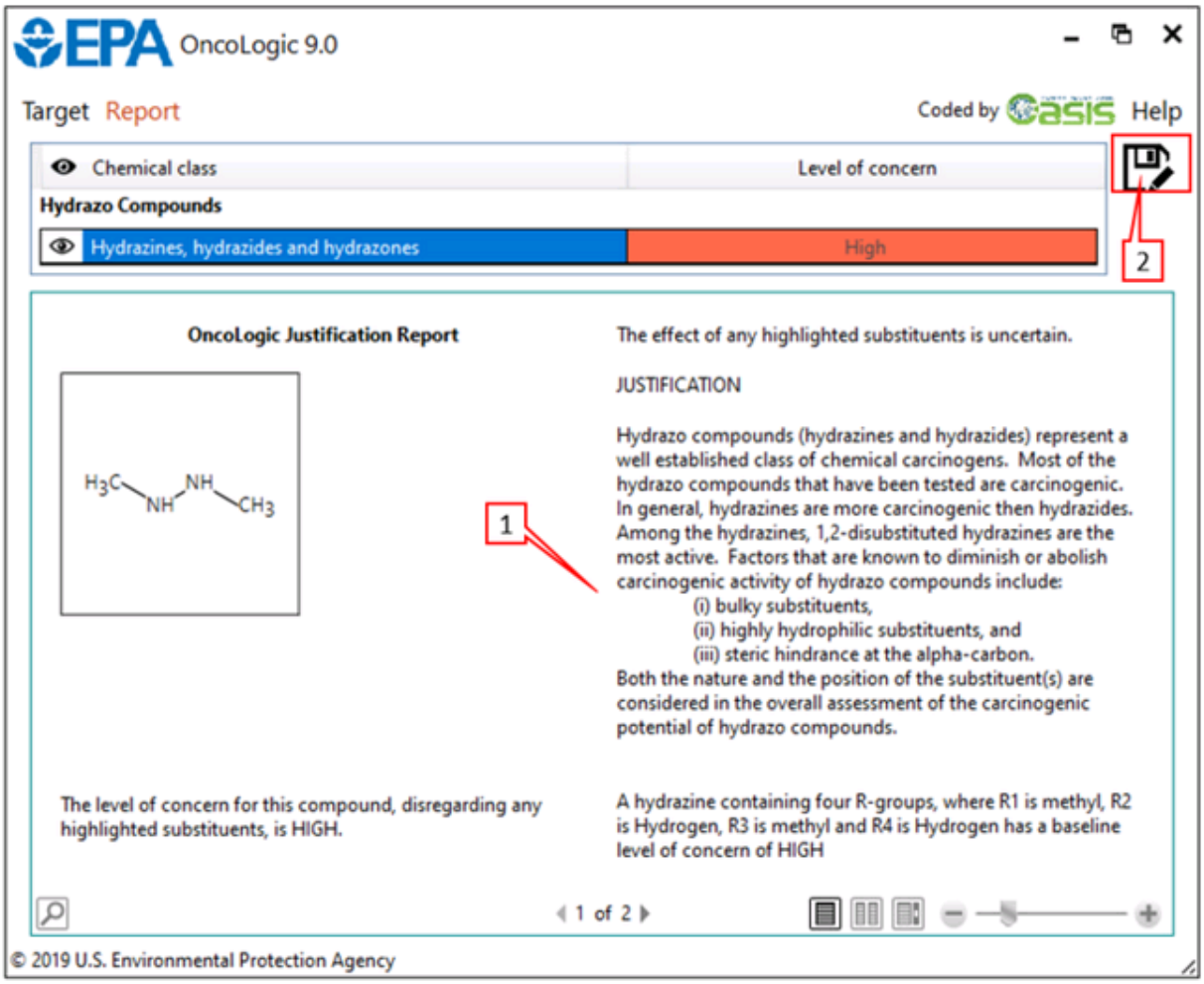
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Hydrazo Compounds
Hydrazines, hydrazides and hydrazones
High
2
OncoLogic Justification Report
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
Hydrazo compounds (hydrazines and hydrazides) represent a well established class of chemical carcinogens. Most of the hydrazo compounds that have been tested are carcinogenic. In general, hydrazines are more carcinogenic then hydrazides. Among the hydrazines, 1,2-disubstituted hydrazines are the most active. Factors that are known to diminish or abolish carcinogenic activity of hydrazo compounds include:
(i) bulky substituents,
(ii) highly hydrophilic substituents, and
(iii) steric hindrance at the alpha-carbon.
Both the nature and the position of the substituent(s) are considered in the overall assessment of the carcinogenic potential of hydrazo compounds.
1
The level of concern for this compound, disregarding any highlighted substituents, is HIGH.
A hydrazine containing four R-groups, where R1 is methyl, R2 is Hydrogen, R3 is methyl and R4 is Hydrogen has a baseline level of concern of HIGH
1 of 2
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Figure 4

-o-

5.9 Nitroso Compounds

-o-

5.9.1 C-Nitroso Compounds and Oximes

Since C-Nitroso compounds can tautomerize to oximes and the carcinogenic action of alkyl ketoximes appears to be due to oxidation to nitroalkanes, aliphatic C-Nitroso compounds and oximes are evaluated assuming their conversion to nitroalkanes and are, here after, referred to as Nitroalkane/Nitroalkene.

-o-

5.9.1.1 Nitroalkanes

1. Input a target chemical (1) and click OK (2) (Figure 1).

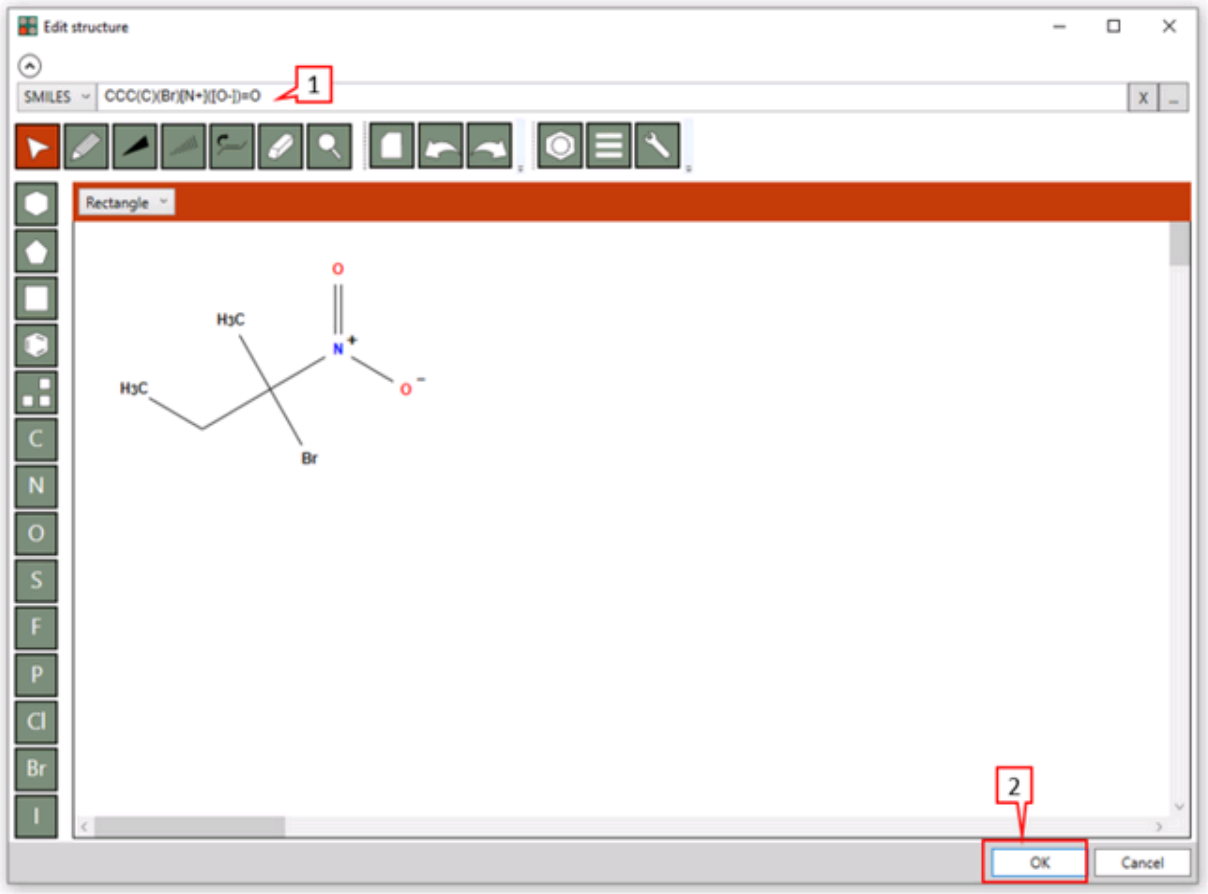

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

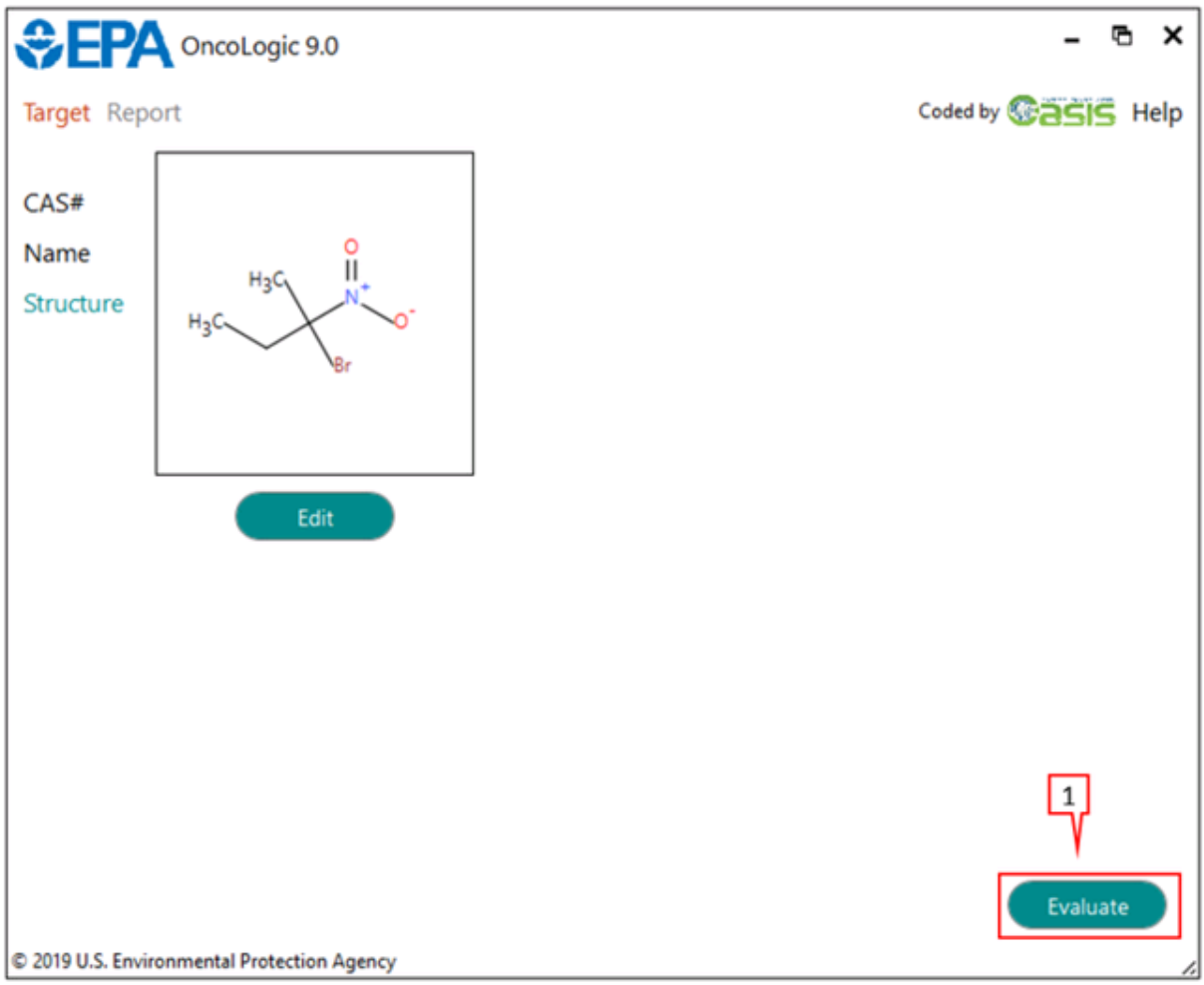

Figure 2

3. After the target chemical has been profiled as *Nitroso Compounds/ C-Nitroso Compounds and Oximes* (1), click on Evaluate (2) (Figure 3).

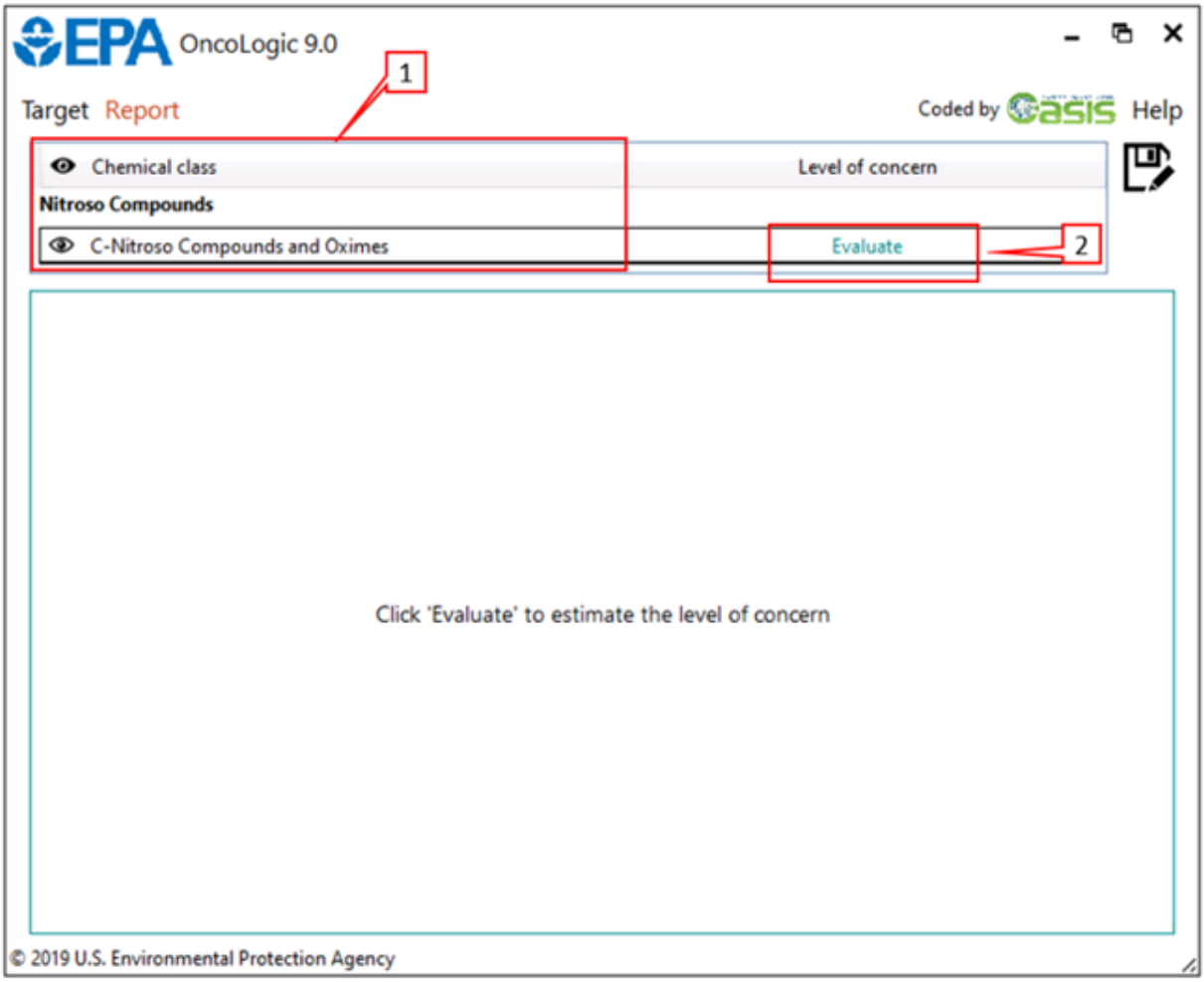

Figure 3

4. For the current chemical class, the oral exposure is taken into account. Tertiary nitroalkanes bearing a chloro, bromo, or iodo group on the carbon alpha to the nitro group are of concern by oral exposure since under acidic condition in the stomach, the nitro group is expected to be a leaving group yielding a reactive carbonium ion. Hence, the final concern depends on the either there is oral exposure or not.
If the oral exposure is expected, click on yes (1) (Figure 4).

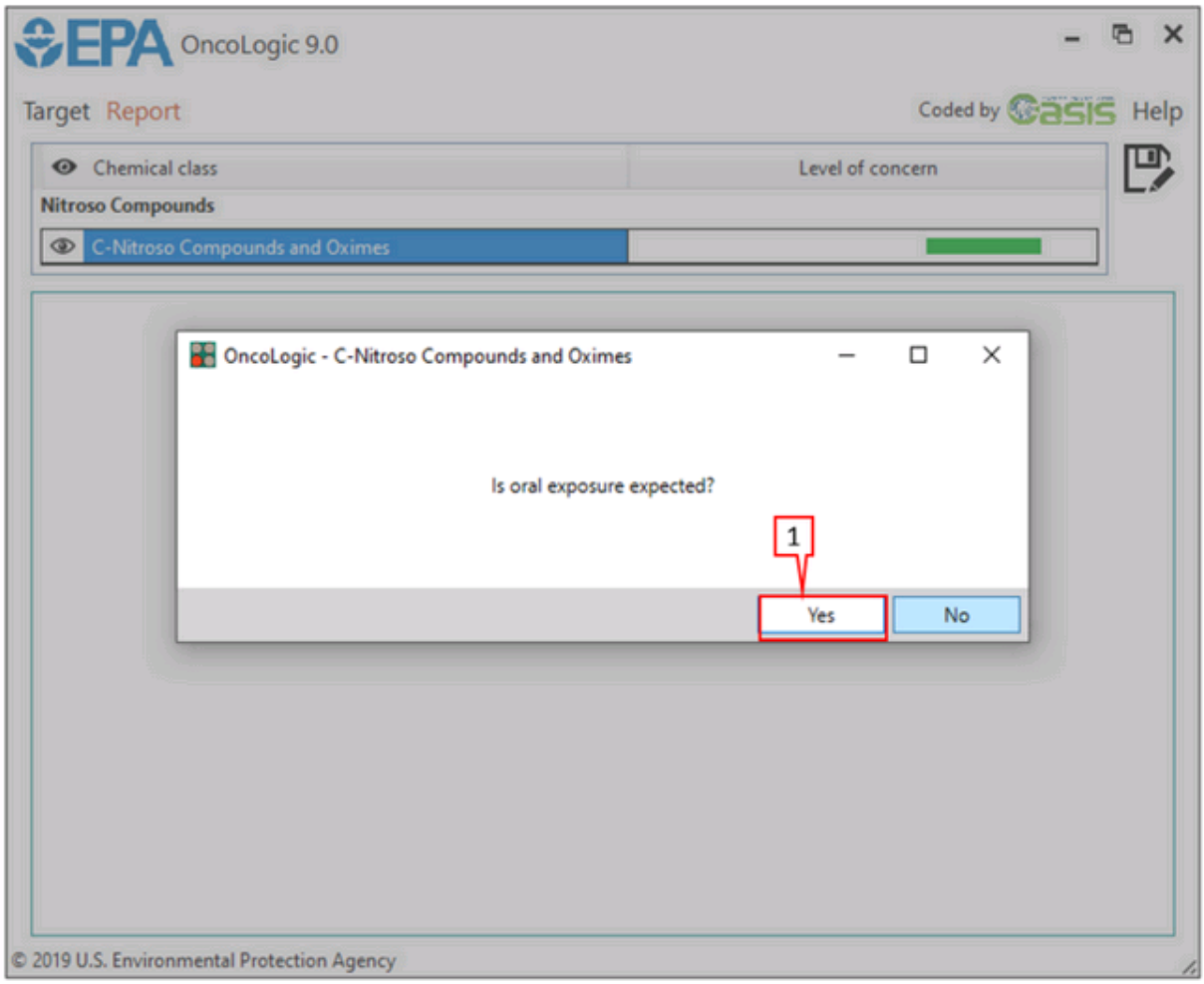

Figure 4

5. The report has been generated (1) and it could be saved (2) (Figure 5).

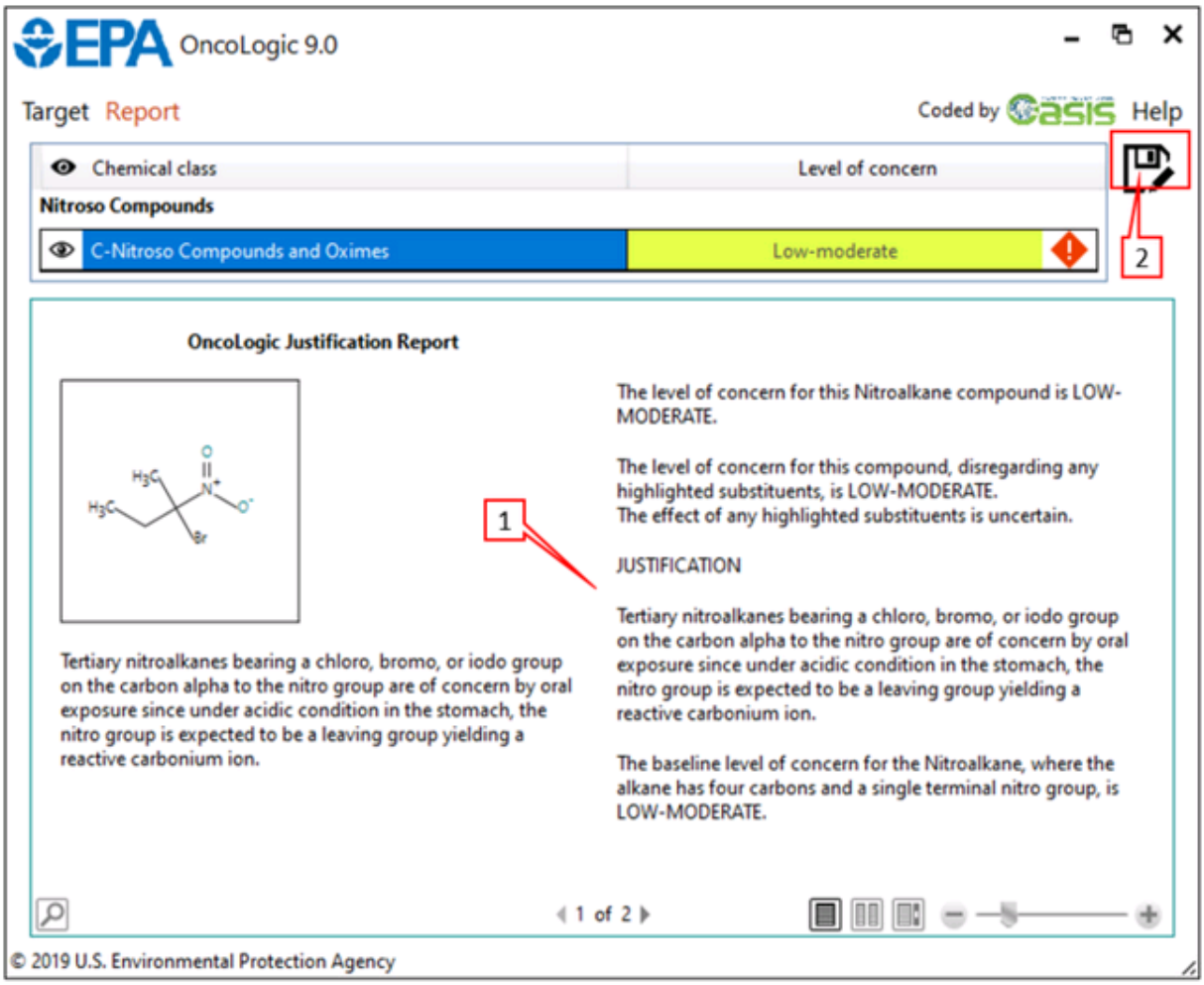

Figure 5

6. If the oral exposure is not expected, click on No (1) (Figure 6).

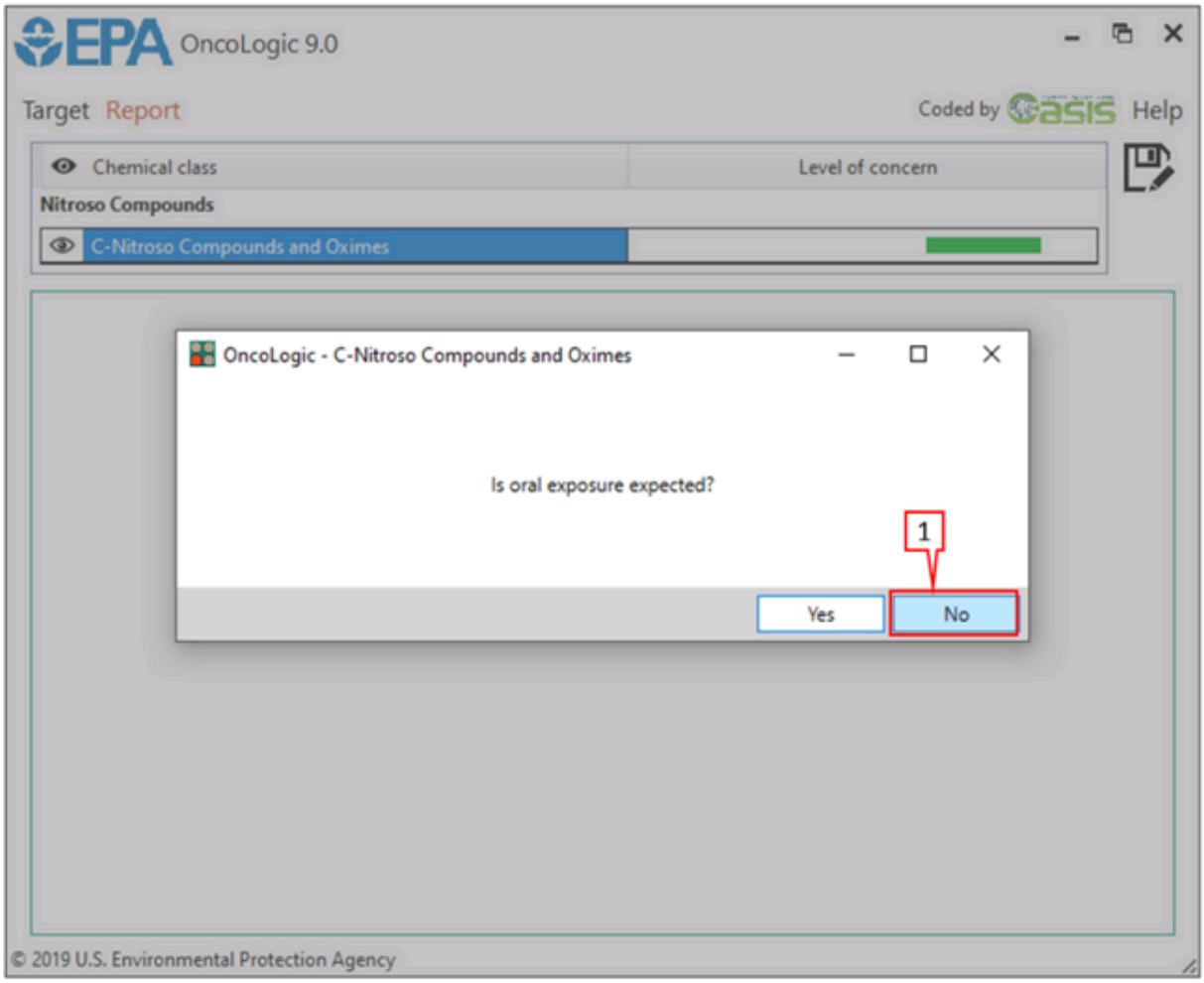

Figure 6

7. The report has been generated (1) and it could be saved (2) (Figure 7). In this case the concern can't be determined.

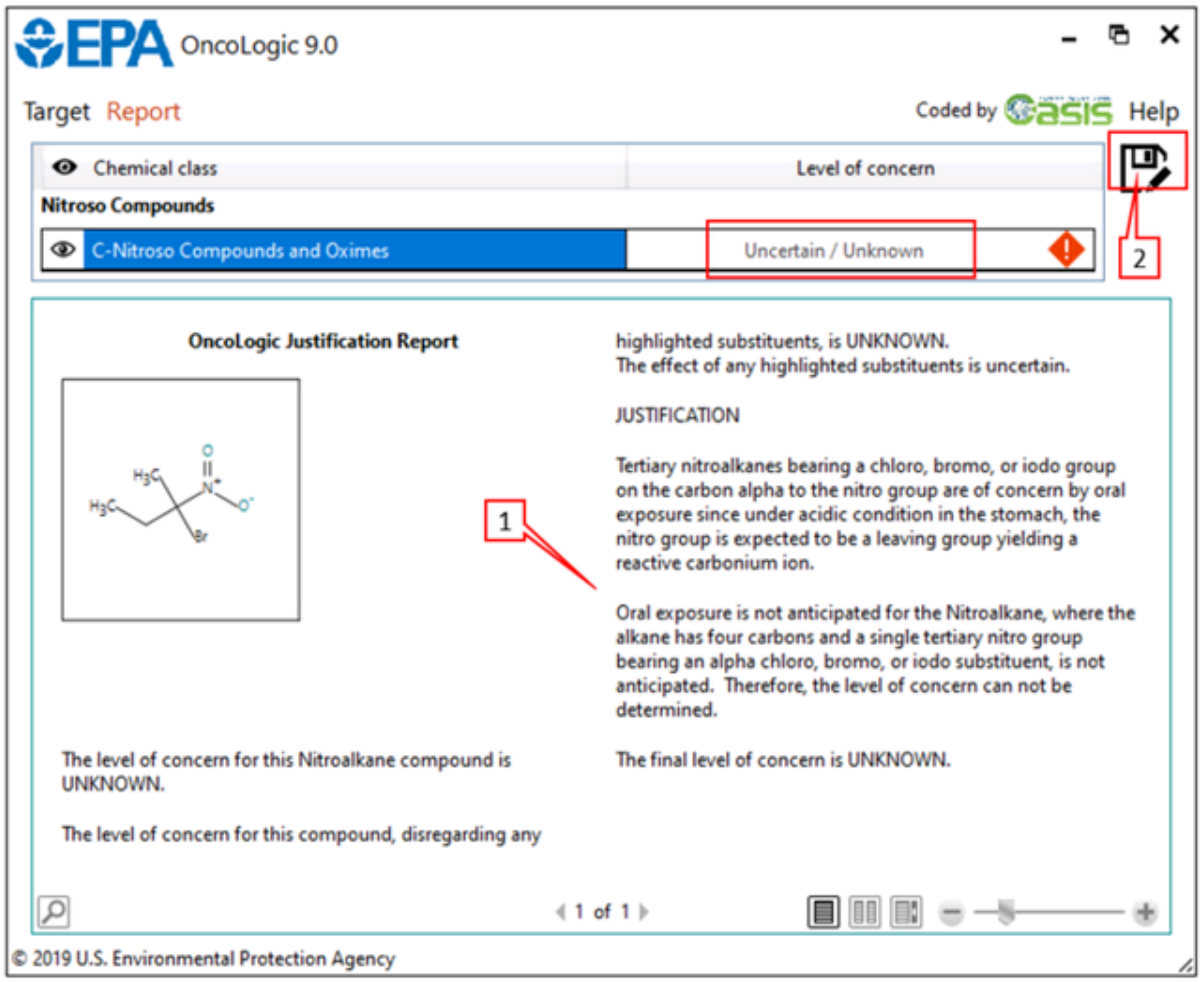
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Nitroso Compounds
C-Nitroso Compounds and Oximes
Uncertain / Unknown
2
OncoLogic Justification Report
1
highlighted substituents, is UNKNOWN.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
Tertiary nitroalkanes bearing a chloro, bromo, or iodo group on the carbon alpha to the nitro group are of concern by oral exposure since under acidic condition in the stomach, the nitro group is expected to be a leaving group yielding a reactive carbonium ion.
Oral exposure is not anticipated for the Nitroalkane, where the alkane has four carbons and a single tertiary nitro group bearing an alpha chloro, bromo, or iodo substituent, is not anticipated. Therefore, the level of concern can not be determined.
The level of concern for this Nitroalkane compound is UNKNOWN.
The final level of concern is UNKNOWN.
The level of concern for this compound, disregarding any
1 of 1
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Figure 7

-o-

5.9.1.2 C-Nitroso/Oxime compound

1. Input a target chemical (1) and click OK (2) (Figure 1).

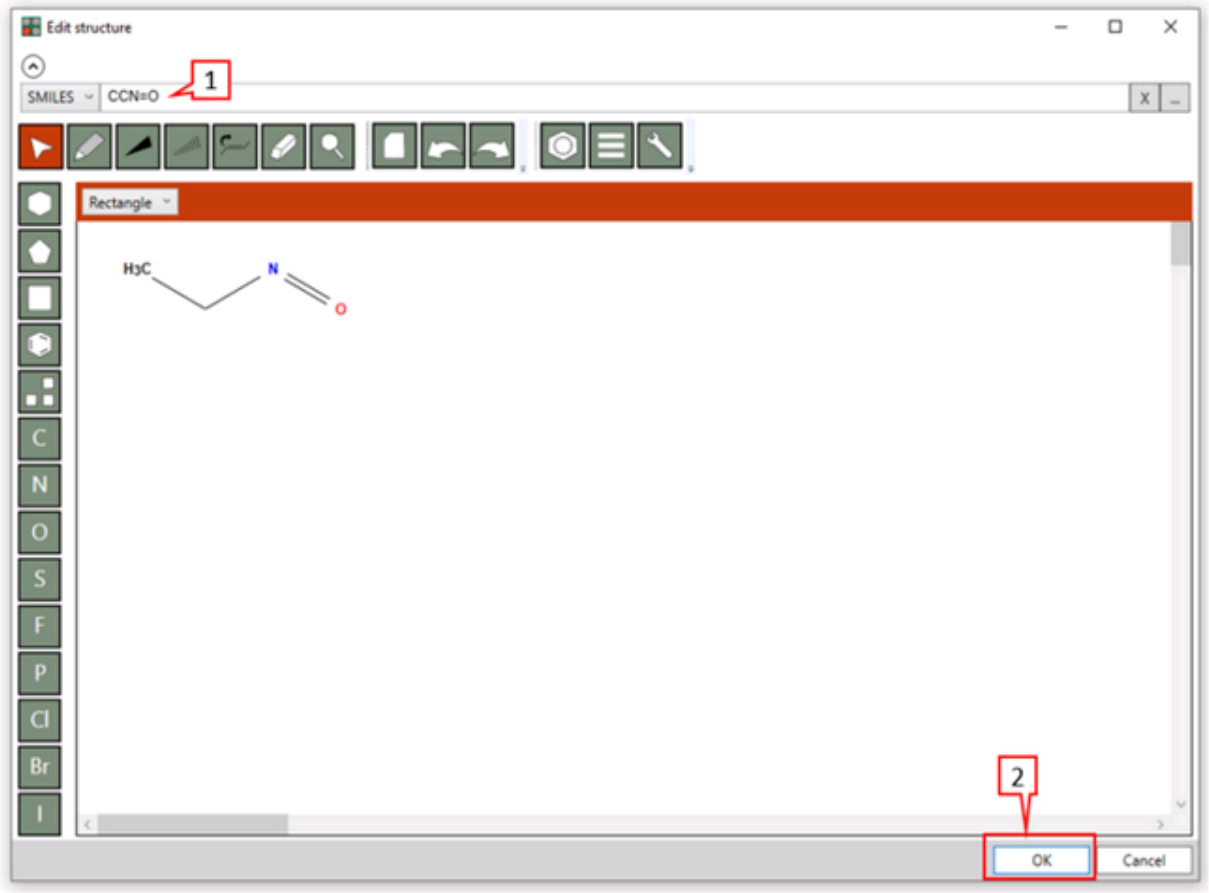

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

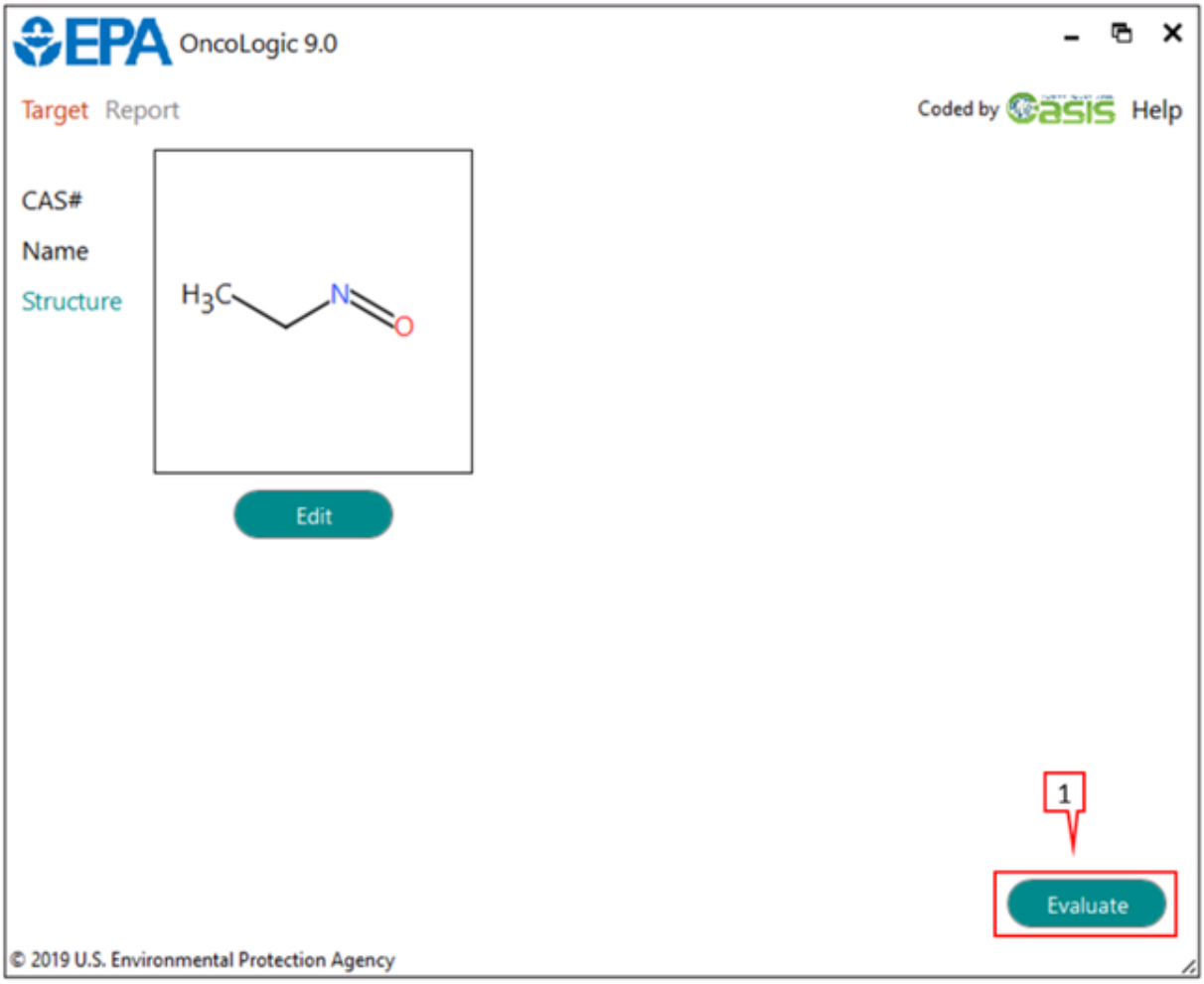

Figure 2

3. After the target chemical has been profiled as *C-Nitroso Compounds and Oximes/ C-Nitroso/Oxime compound* (1), click on Evaluate (2) (Figure 3).

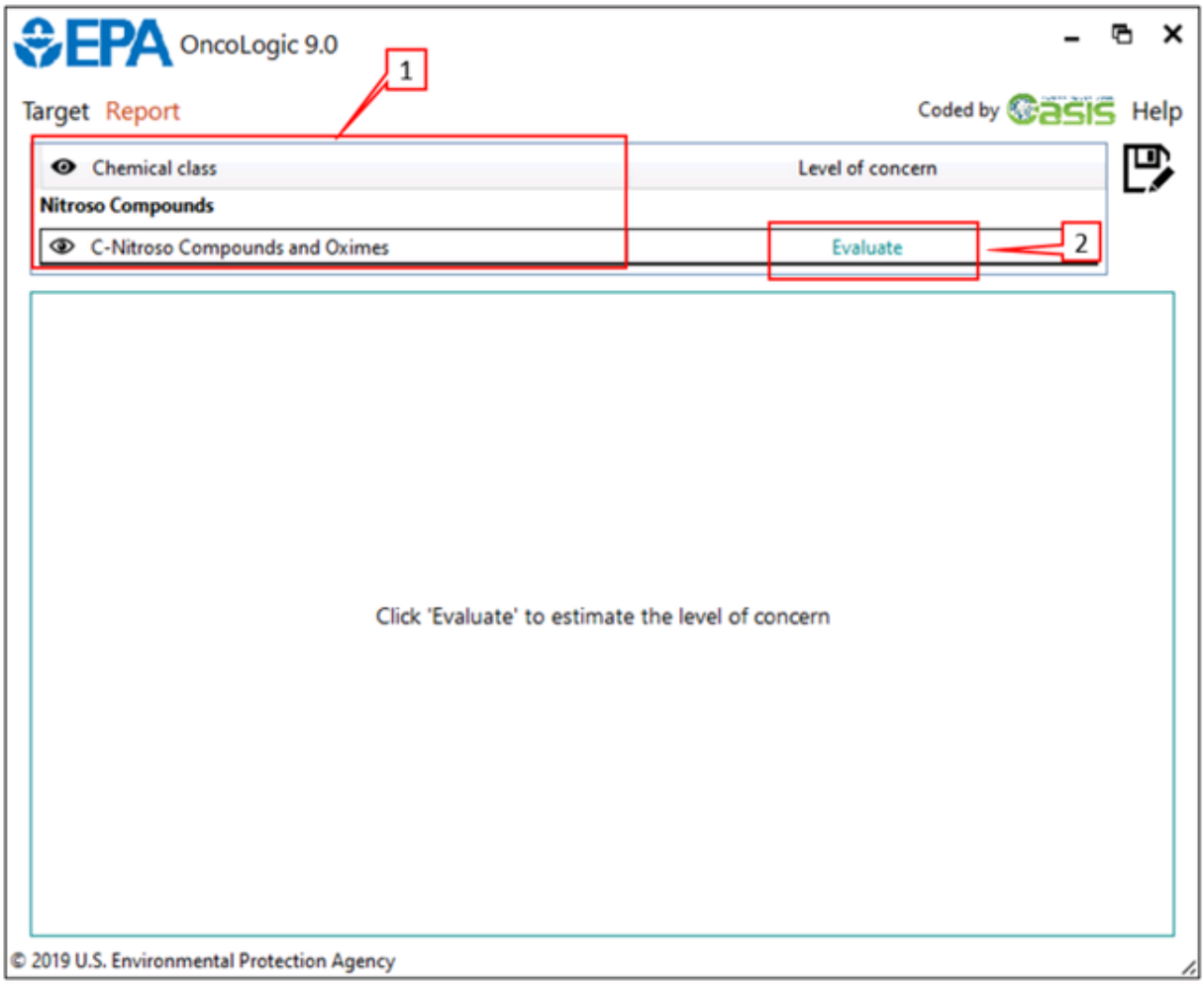

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

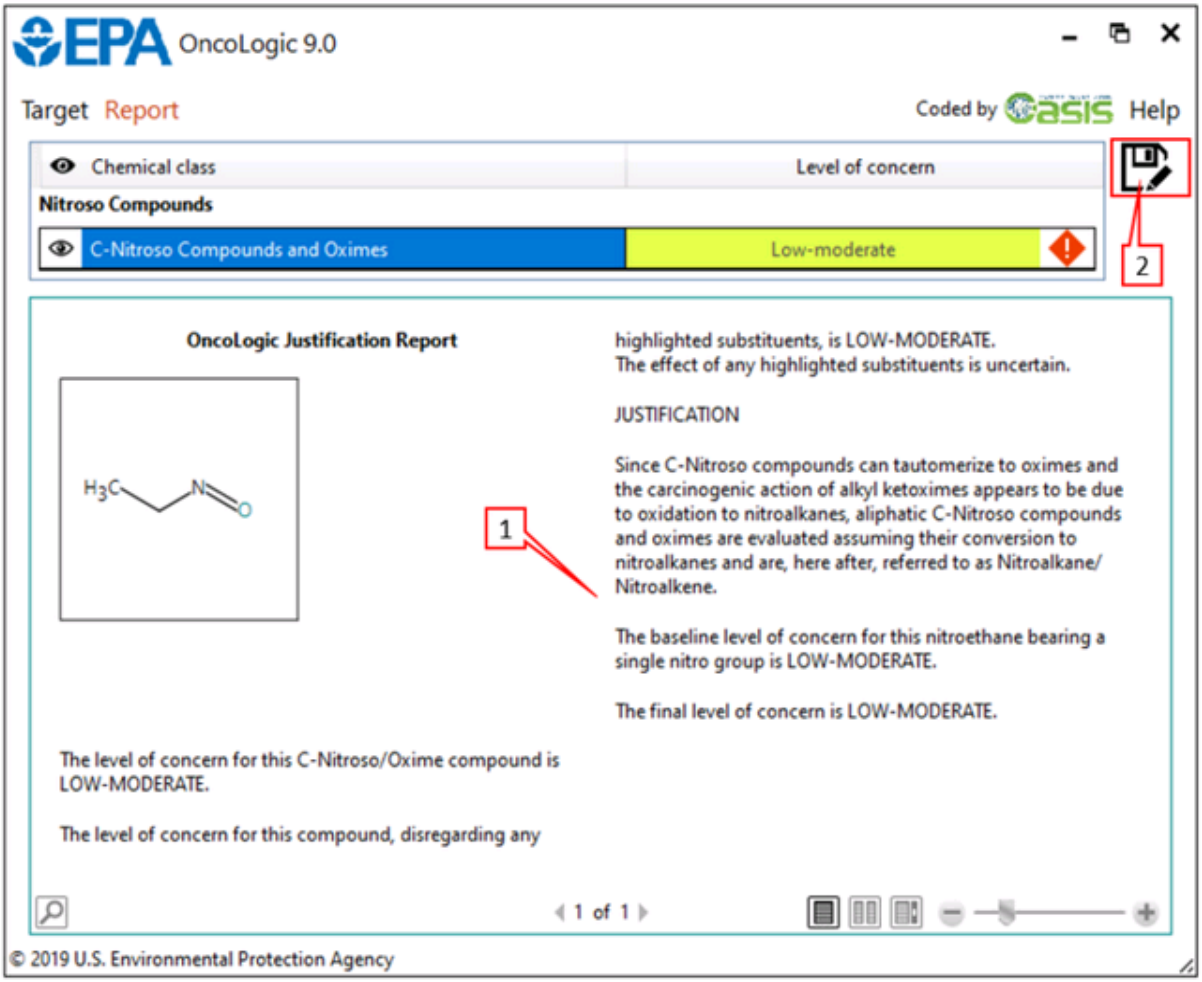
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Nitroso Compounds
C-Nitroso Compounds and Oximes
Low-moderate
2
OncoLogic Justification Report
highlighted substituents, is LOW-MODERATE.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
Since C-Nitroso compounds can tautomerize to oximes and the carcinogenic action of alkyl ketoximes appears to be due to oxidation to nitroalkanes, aliphatic C-Nitroso compounds and oximes are evaluated assuming their conversion to nitroalkanes and are, here after, referred to as Nitroalkane/ Nitroalkene.
1
The baseline level of concern for this nitroethane bearing a single nitro group is LOW-MODERATE.
The final level of concern is LOW-MODERATE.
The level of concern for this C-Nitroso/Oxime compound is LOW-MODERATE.
The level of concern for this compound, disregarding any
1 of 1
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Figure 4

-o-

5.10 N-Nitroamide Compounds

-o-

5.10.1 N-nitrosocarbamate

1. Input a target chemical (1) and click OK (2) (Figure 1).

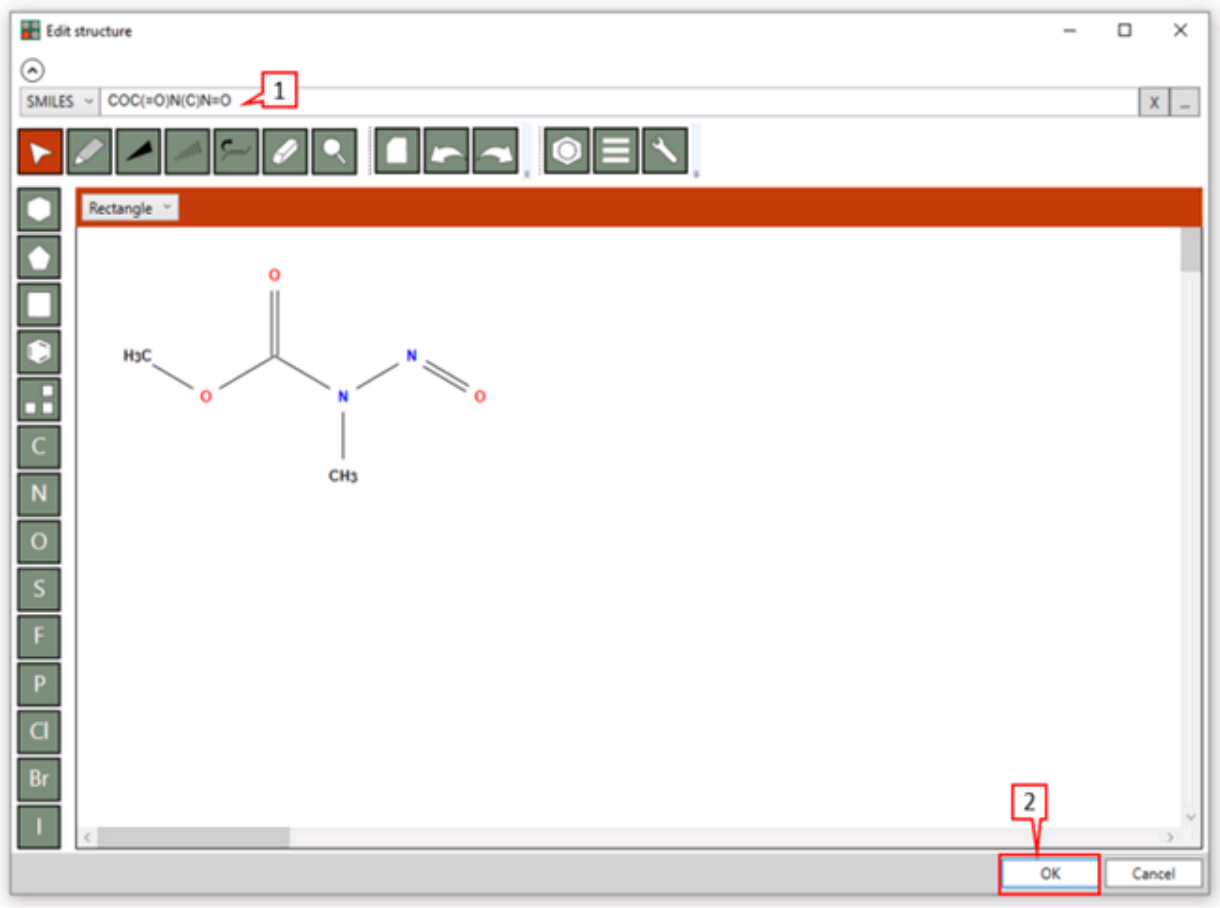

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

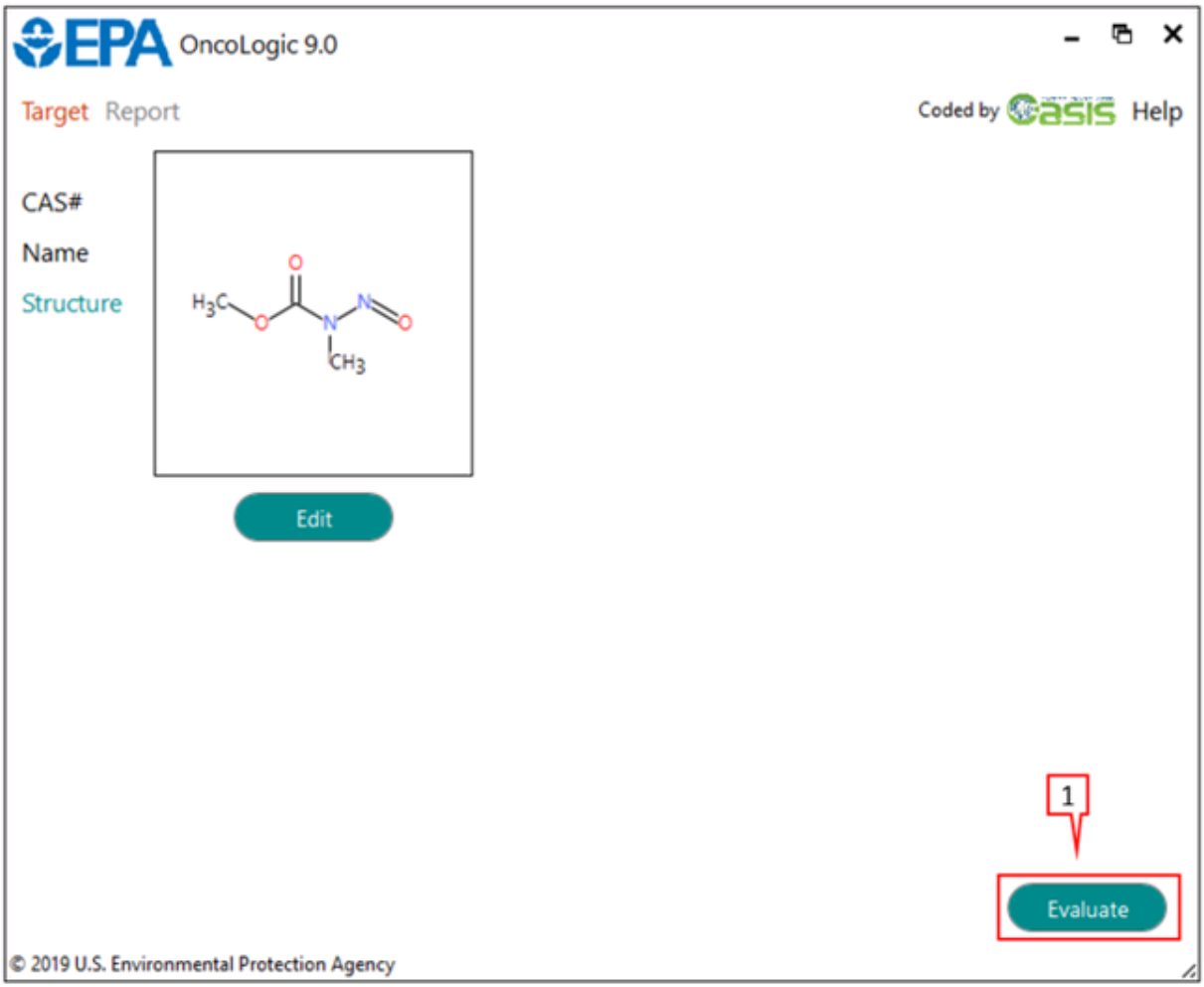

Figure 2

3. This target falss in two chemical classes - *N-Nitrosoamide Compounds and Carbamates* and *thiocarbamates*. Click on *N-nitrosocarbamate* (1) and *Evaluate* (2) (Figure 3).

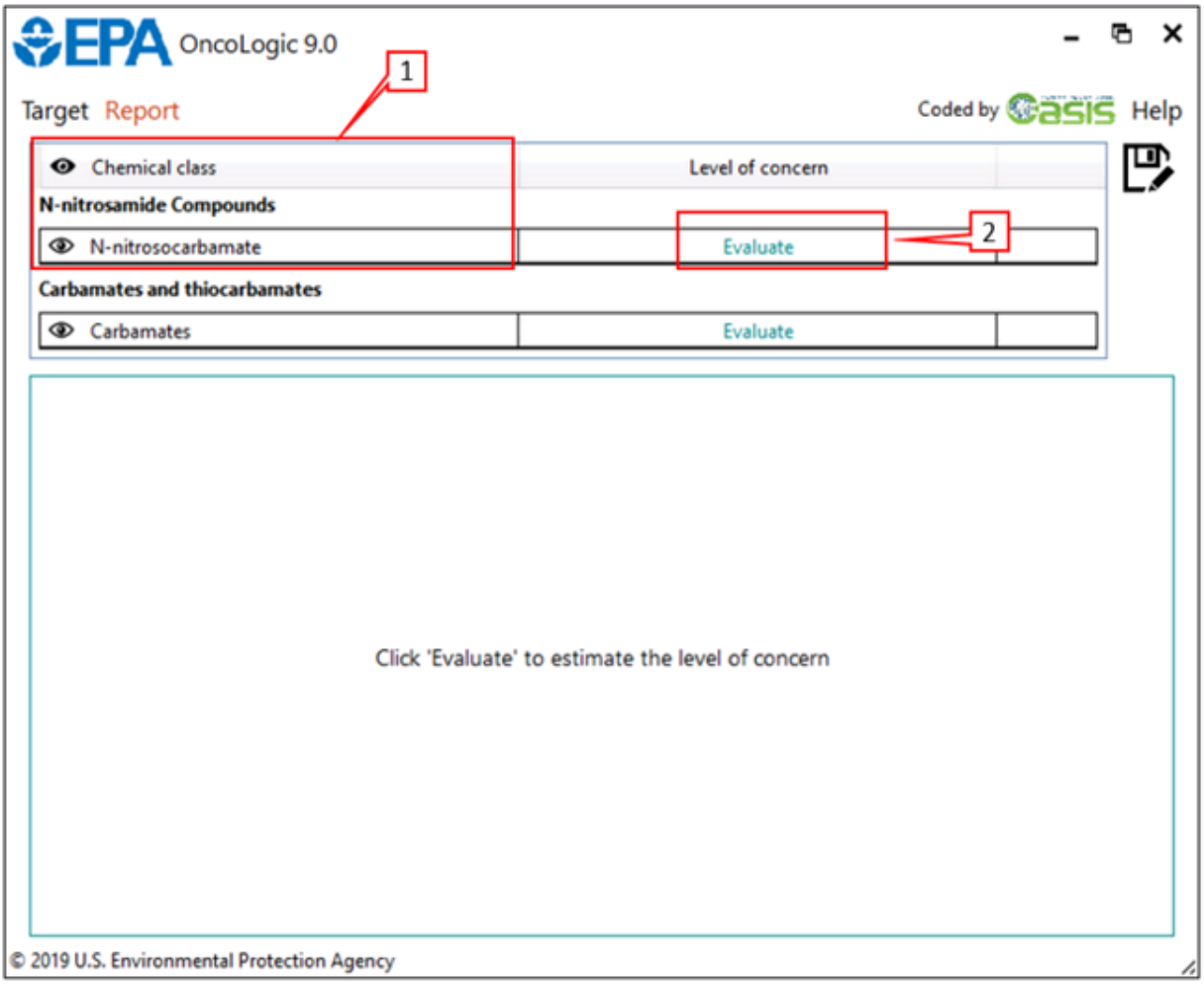

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

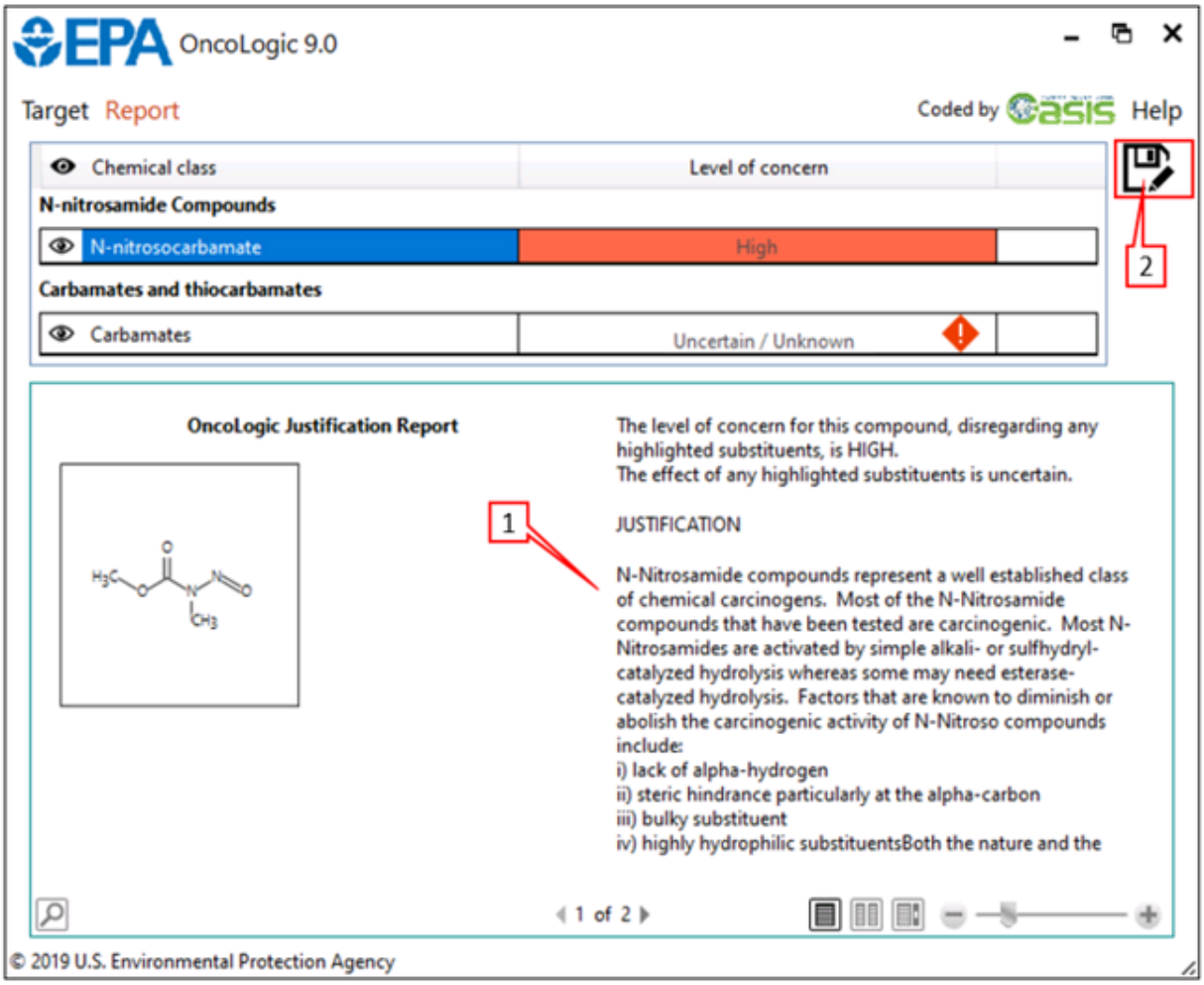
EPA OncoLogic 9.0
Target Report
Coded by oasis Help
Chemical class
Level of concern
N-nitrosamide Compounds
N-nitrosocarbamate
High
Carbamates and thiocarbamates
Carbamates
Uncertain / Unknown
2
OncoLogic Justification Report
1
The level of concern for this compound, disregarding any highlighted substituents, is HIGH.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
N-Nitrosamide compounds represent a well established class of chemical carcinogens. Most of the N-Nitrosamide compounds that have been tested are carcinogenic. Most N-Nitrosamides are activated by simple alkali- or sulfhydryl-catalyzed hydrolysis whereas some may need esterase-catalyzed hydrolysis. Factors that are known to diminish or abolish the carcinogenic activity of N-Nitroso compounds include:
i) lack of alpha-hydrogen
ii) steric hindrance particularly at the alpha-carbon
iii) bulky substituent
iv) highly hydrophilic substituentsBoth the nature and the
1 of 2
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Figure 4

-o-

5.11 N-nitrosamine Compounds

-o-

5.11.1 N-nitrosamine (acyclic)

1. Input a target chemical (1) and click OK (2) (Figure 1).

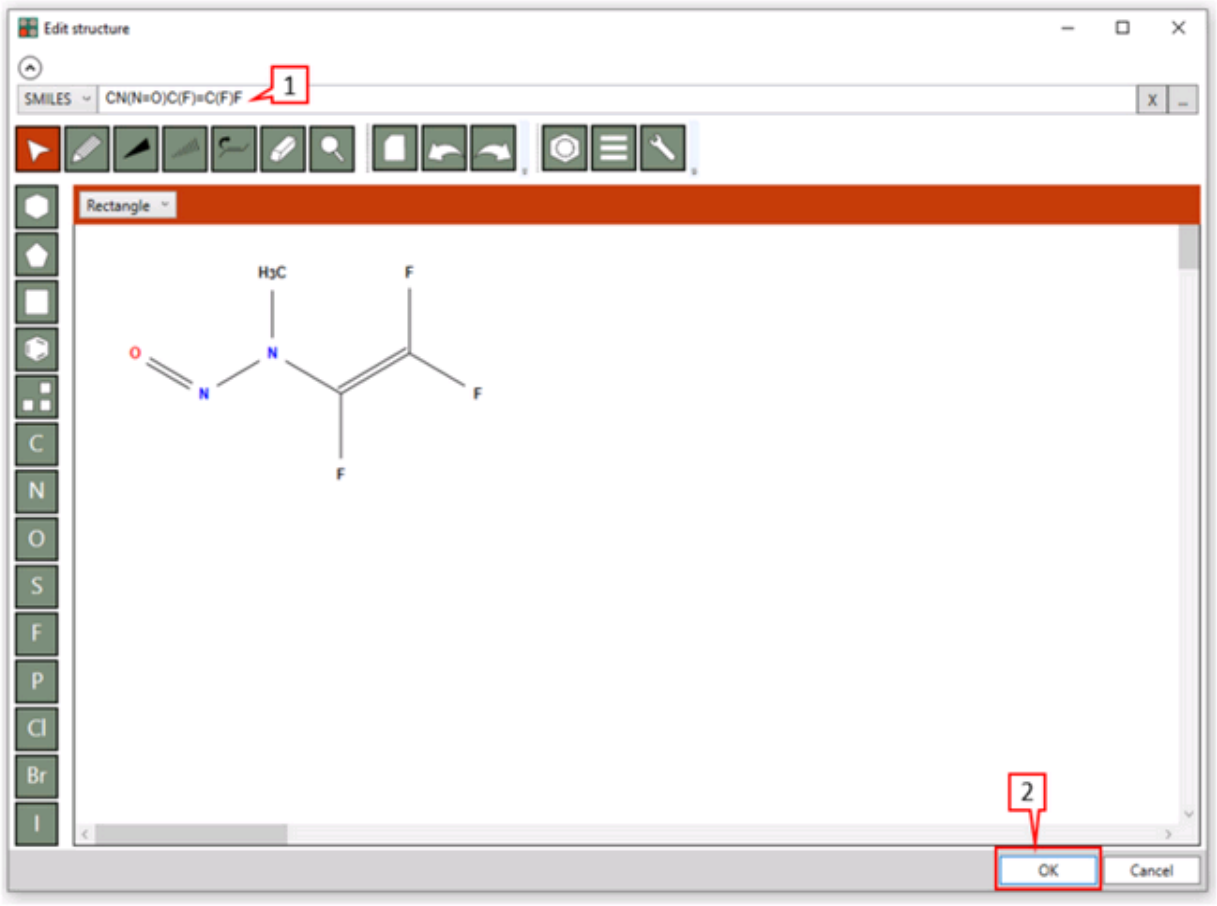

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

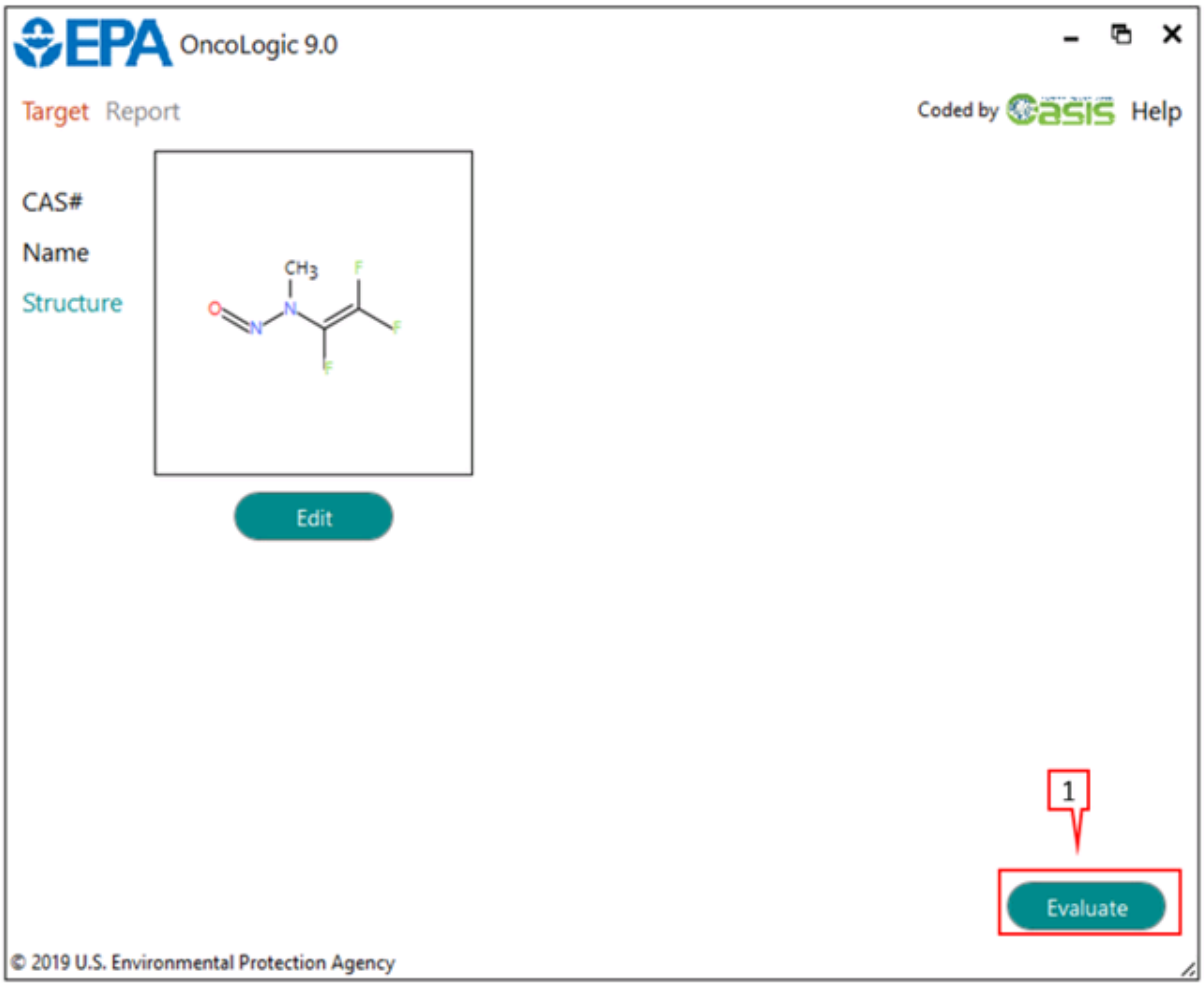

Figure 2

3. After the target chemical has been profiled as *N-nitrosamine compounds/ N-nitroasmine (acyclic)* (1), click on Evaluate (2) (Figure 3).

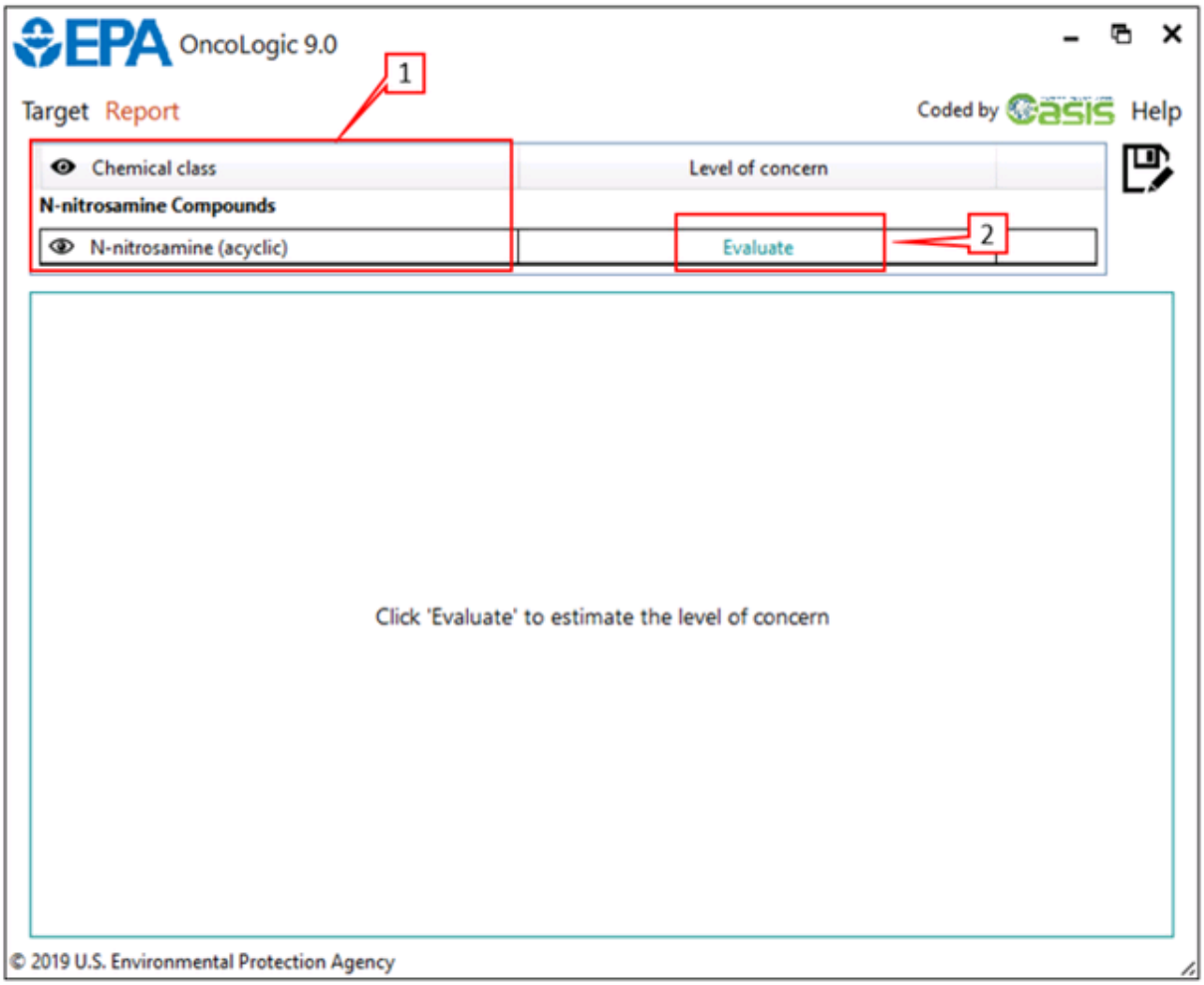

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

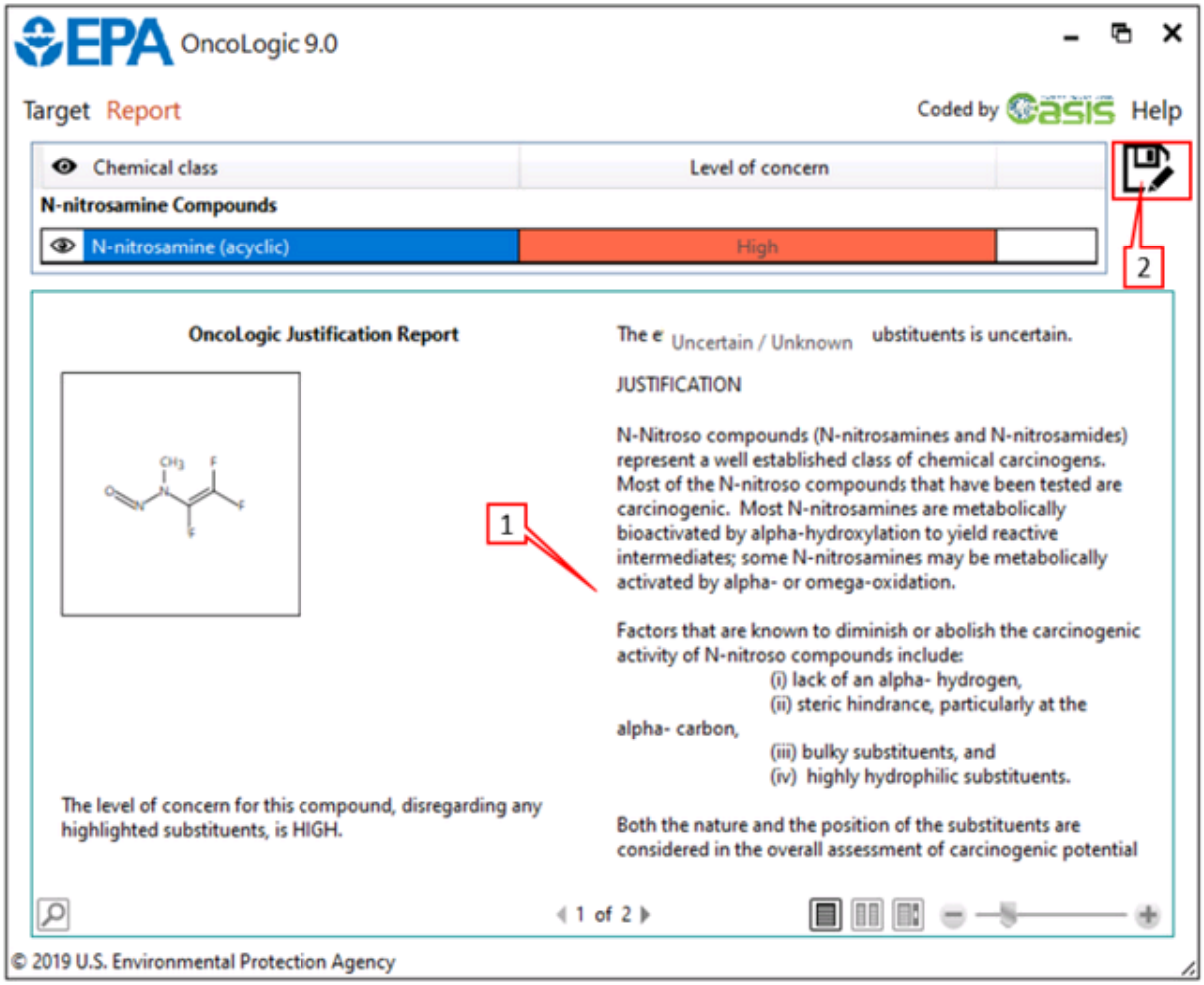
EPA OncoLogic 9.0
Target Report
Coded by oasis Help
Chemical class
Level of concern
N-nitrosamine Compounds
N-nitrosamine (acyclic)
High
2
OncoLogic Justification Report
The e Uncertain / Unknown ubstituents is uncertain.
JUSTIFICATION
N-Nitroso compounds (N-nitrosamines and N-nitrosamides) represent a well established class of chemical carcinogens. Most of the N-nitroso compounds that have been tested are carcinogenic. Most N-nitrosamines are metabolically bioactivated by alpha-hydroxylation to yield reactive intermediates; some N-nitrosamines may be metabolically activated by alpha- or omega-oxidation.
1
Factors that are known to diminish or abolish the carcinogenic activity of N-nitroso compounds include:
(i) lack of an alpha- hydrogen,
(ii) steric hindrance, particularly at the alpha- carbon,
(iii) bulky substituents, and
(iv) highly hydrophilic substituents.
The level of concern for this compound, disregarding any highlighted substituents, is HIGH.
Both the nature and the position of the substituents are considered in the overall assessment of carcinogenic potential
1 of 2
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Figure 4

-o-

5.12 Organophosphorus Compounds

-o-

5.12.1 (Thio)phosphoramides

1. Input a target chemical (1) and click OK (2) (Figure 1).

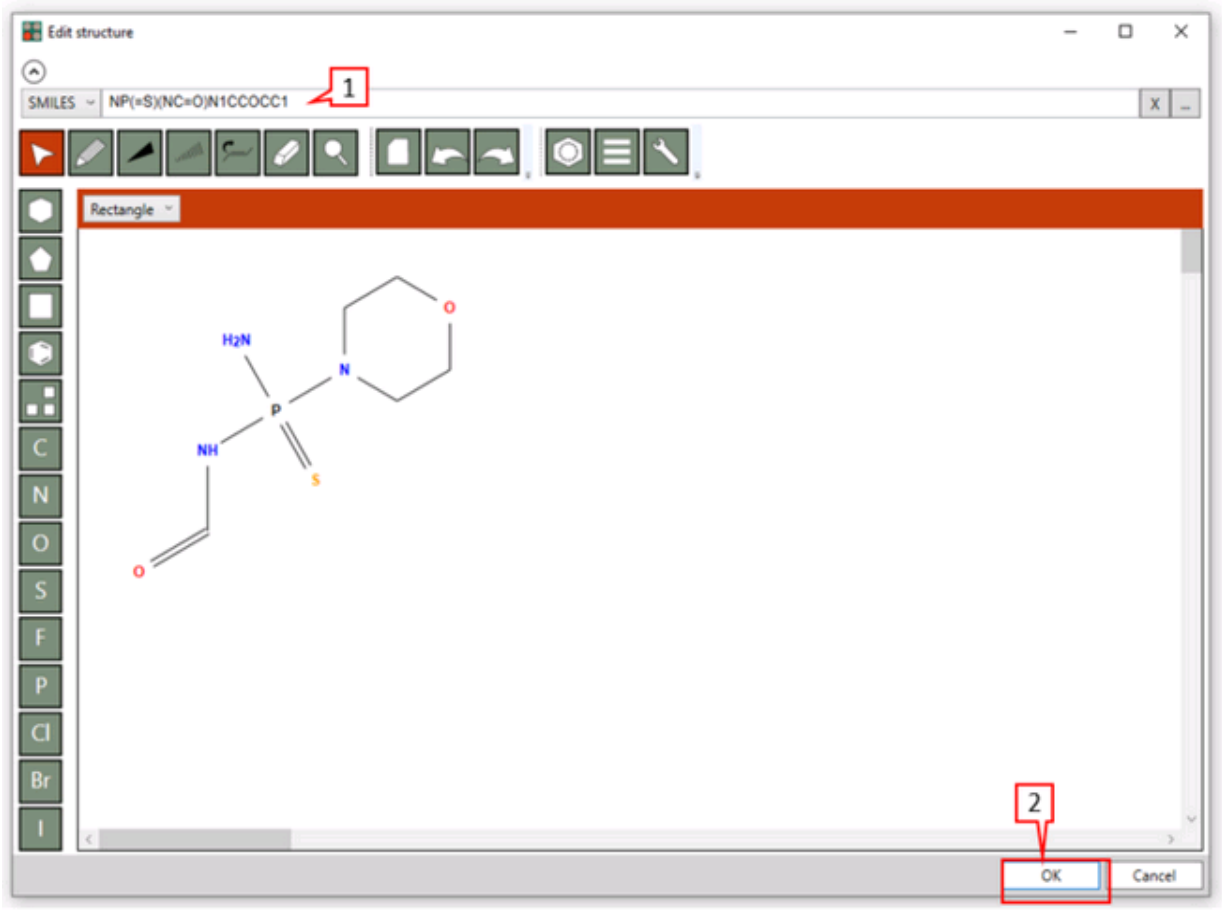

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

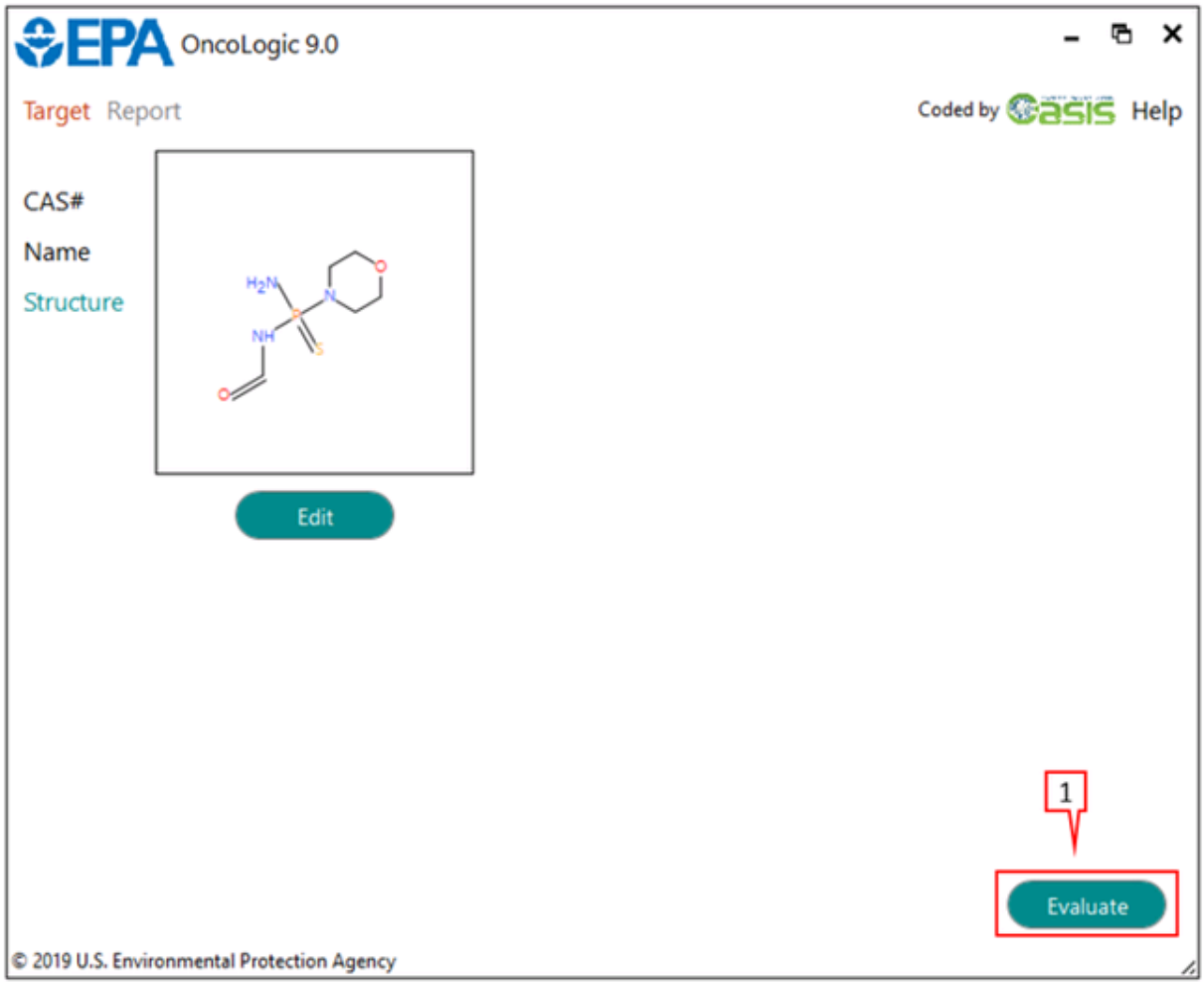

Figure 2

3. After the target chemical has been profiled as *Organophosphorus Compounds/ (Thio)phosphoramides* (1), click on Evaluate (2) (Figure 3).

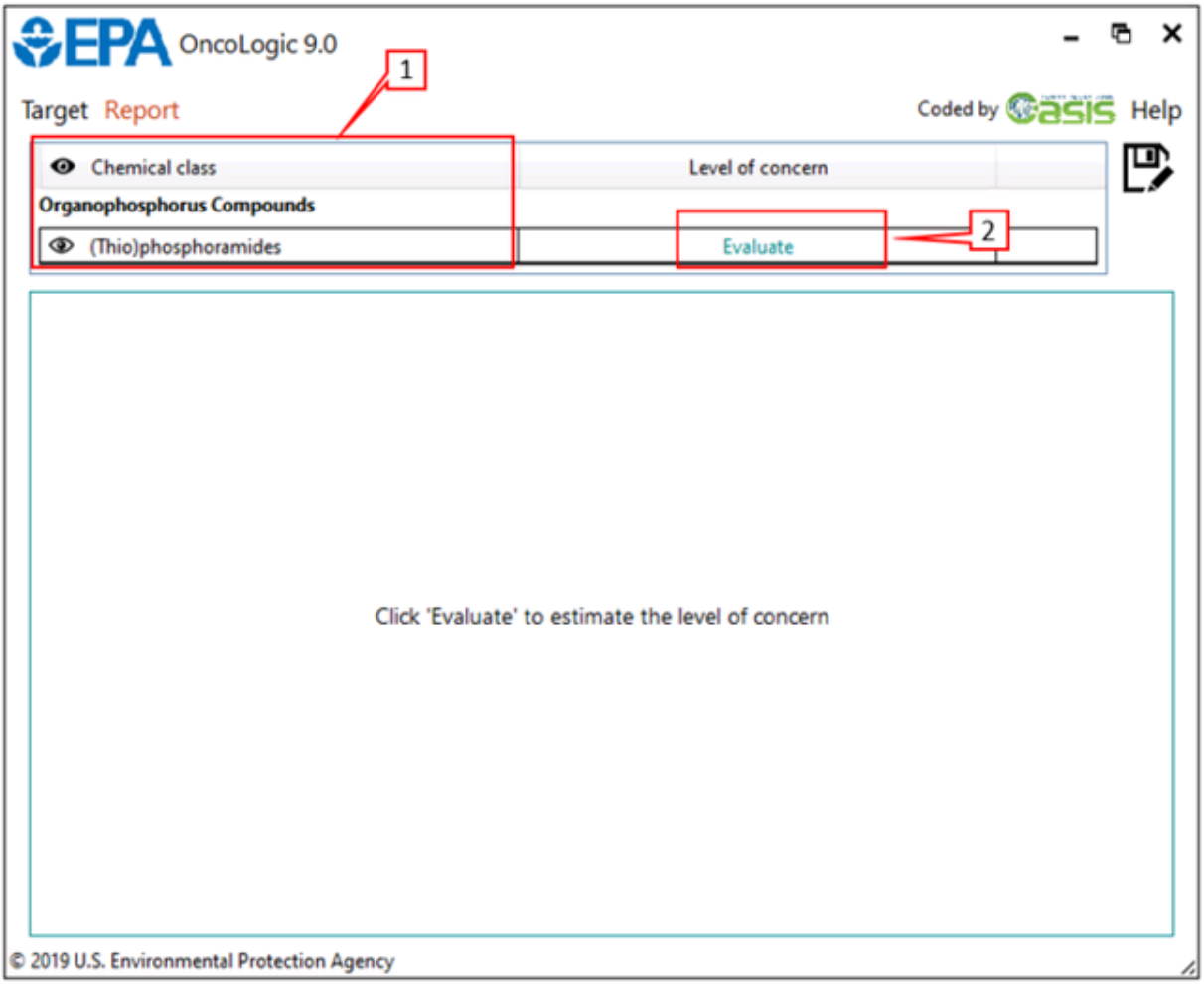

Figure 3

4. The concern for the Organophosphorus compounds depends on the outcome from the list with question related to the genotoxic data for the target chemical, or other type of question. For this example the questions are as depicted in Figures 4-6.

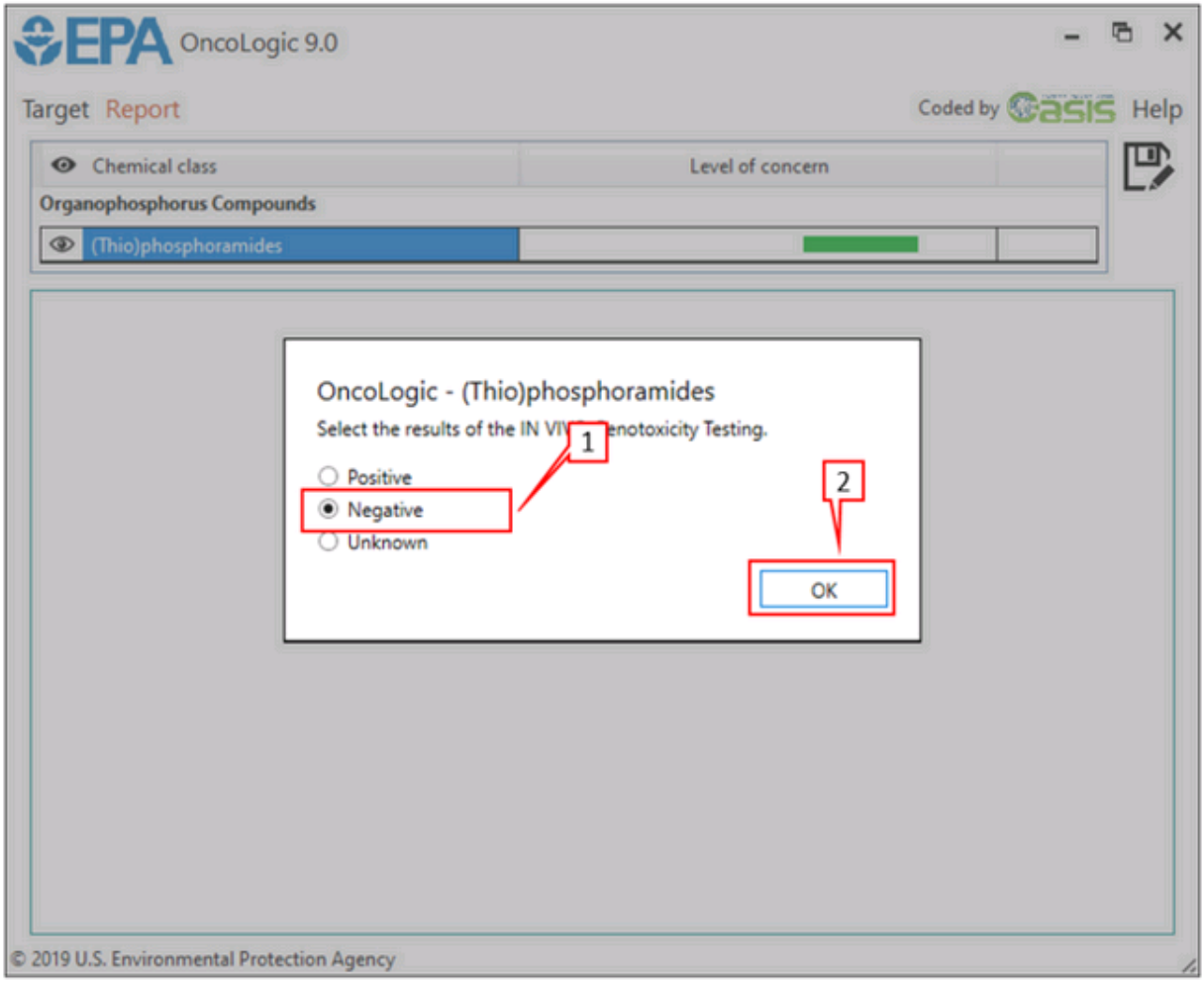
EPA OncoLogic 9.0
Target Report
Coded by Help
Chemical class
Level of concern
Organophosphorus Compounds
(Thio)phosphoramides
OncoLogic - (Thio)phosphoramides
Select the results of the IN VI notoxicity Testing.
1
Positive
Negative
Unknown
2
OK
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Figure 4

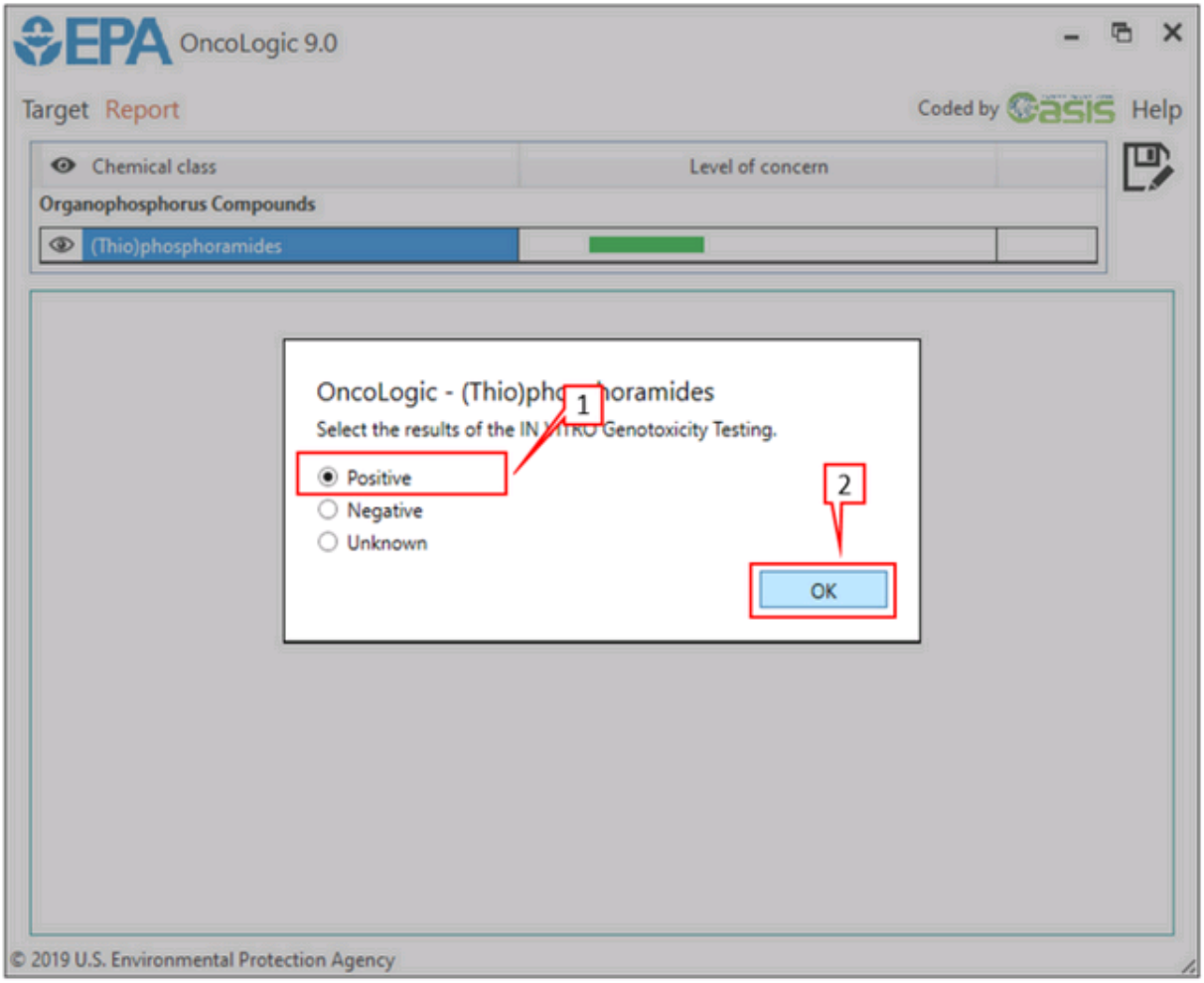
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Organophosphorus Compounds
(Thio)phosphoramides
OncoLogic - (Thio)phosphoramides
Select the results of the IN VITRO Genotoxicity Testing.
Positive
Negative
Unknown
1
2
OK
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Figure 5

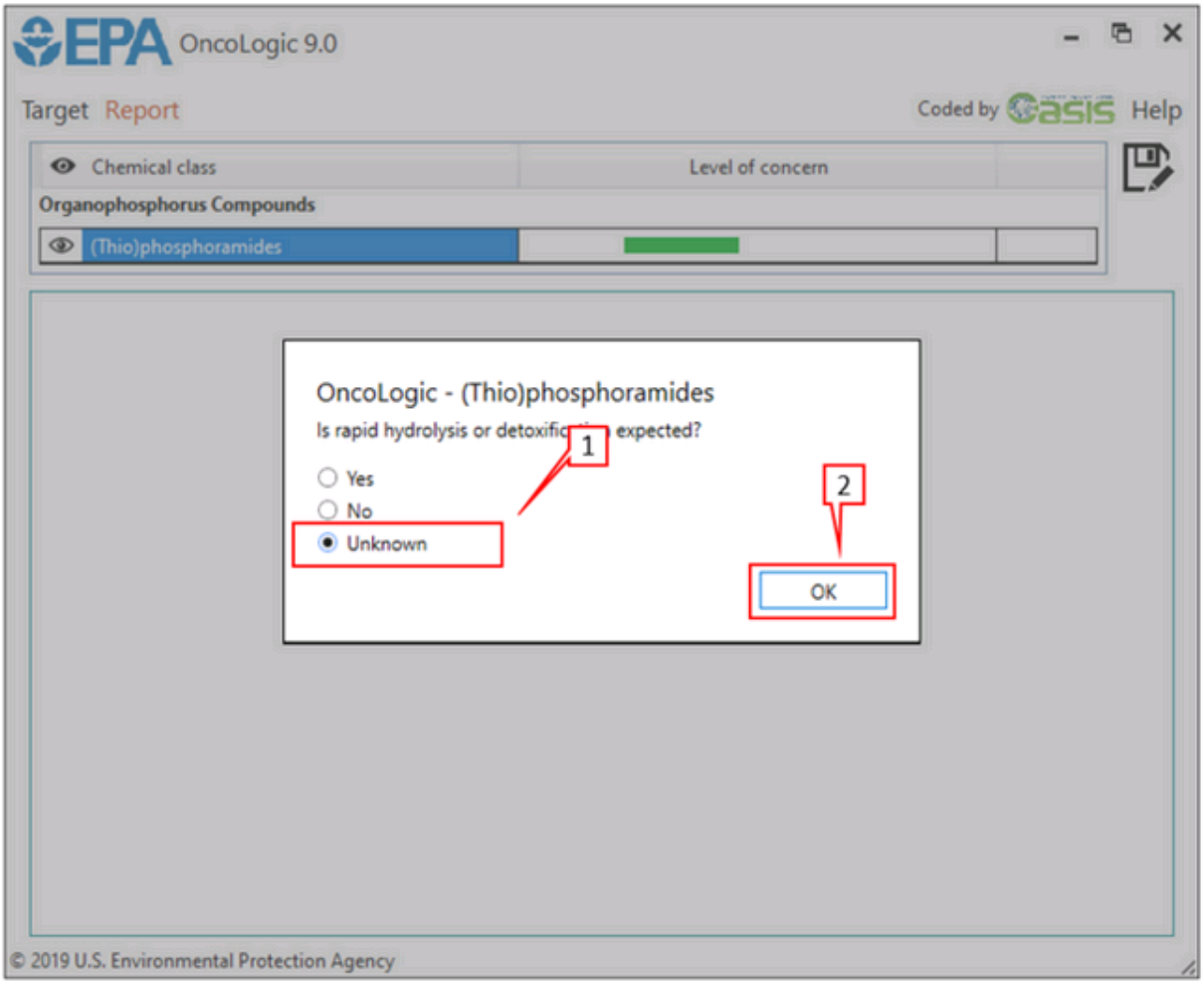

Figure 6

5. The report has been generated (1) and it could be saved (2) (Figure 7).

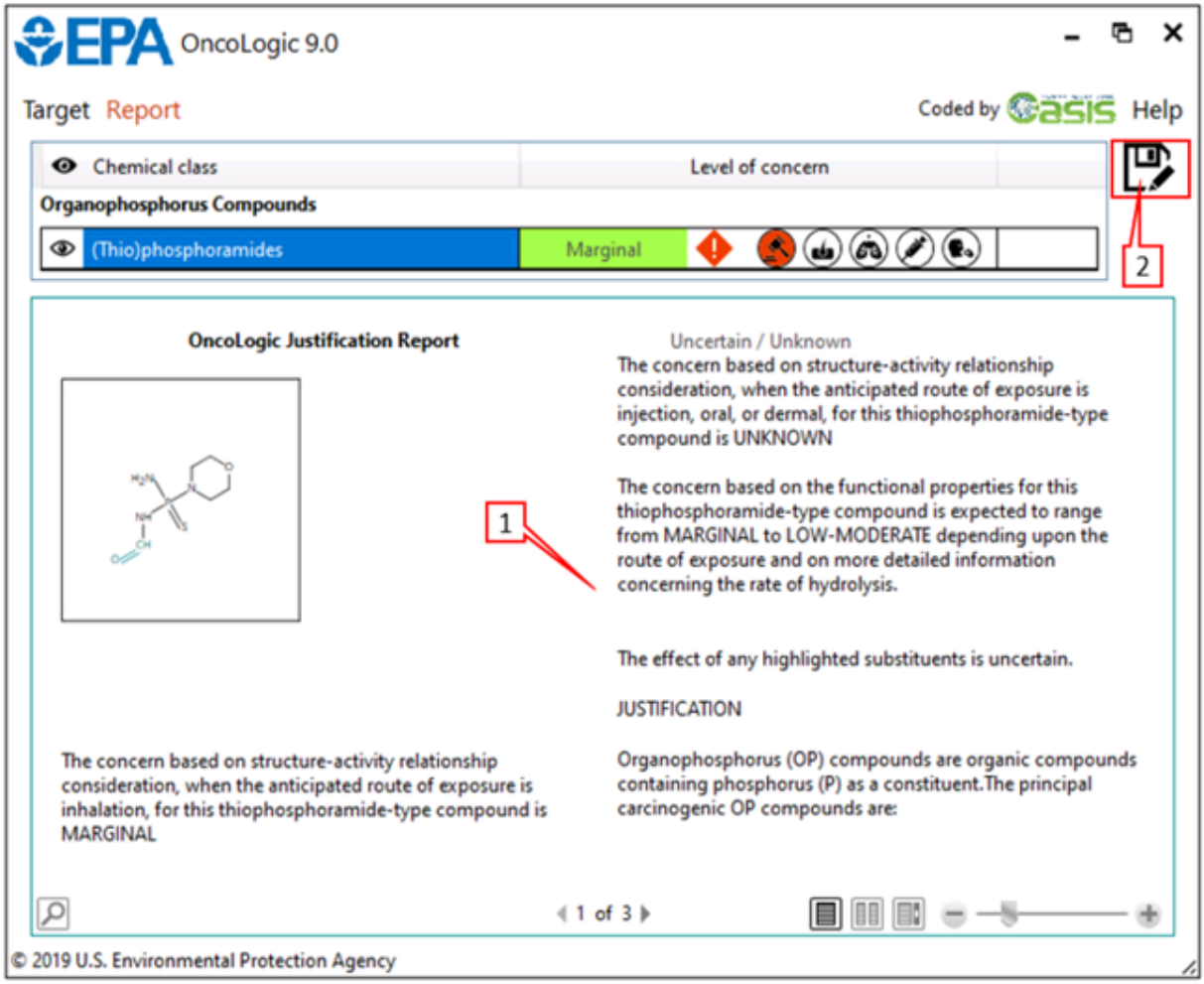
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Organophosphorus Compounds
(Thio)phosphoramides
Marginal
2
OncoLogic Justification Report
Uncertain / Unknown
The concern based on structure-activity relationship consideration, when the anticipated route of exposure is injection, oral, or dermal, for this thiophosphoramide-type compound is UNKNOWN
1
The concern based on the functional properties for this thiophosphoramide-type compound is expected to range from MARGINAL to LOW-MODERATE depending upon the route of exposure and on more detailed information concerning the rate of hydrolysis.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
The concern based on structure-activity relationship consideration, when the anticipated route of exposure is inhalation, for this thiophosphoramide-type compound is MARGINAL
Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent.The principal carcinogenic OP compounds are:
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Figure 7

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5.12.2 Trialkyl (thio)phosphates

1. Input a target chemical (1) and click OK (2) (Figure 1).

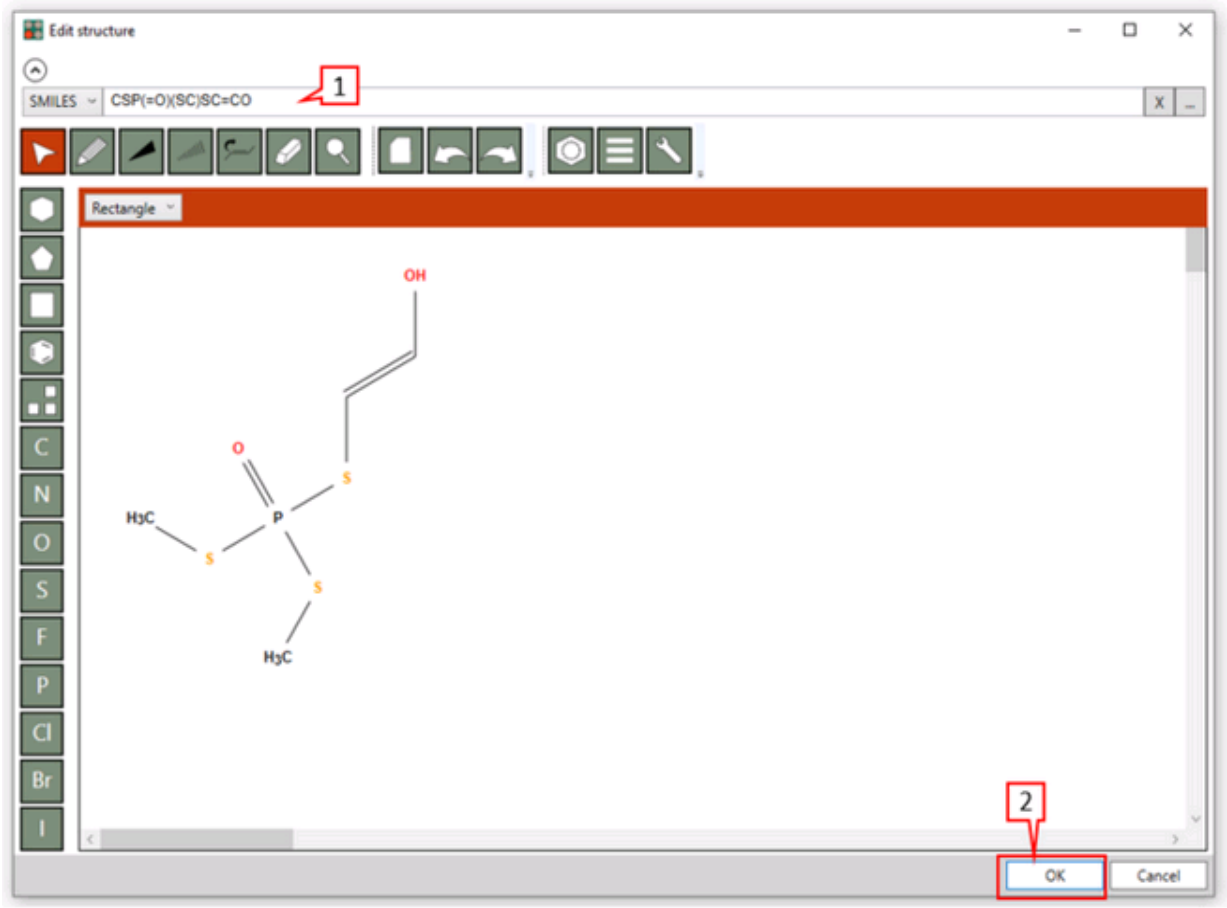

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

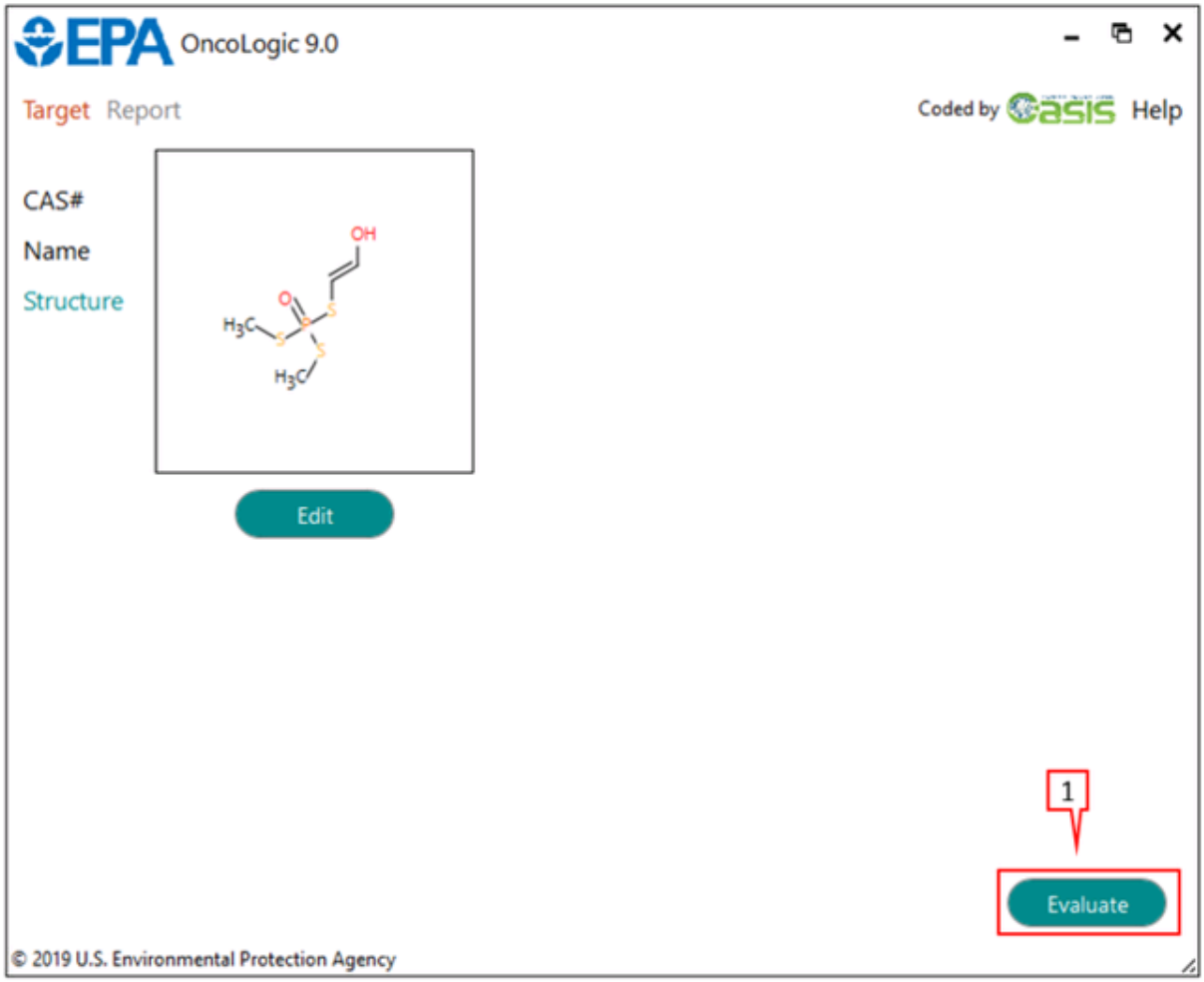

Figure 2

3. After the target chemical has been profiled as *Organophosphorus Compounds/ Trialkyl(thio)phosphates* (1), click on Evaluate (2) (Figure 3).

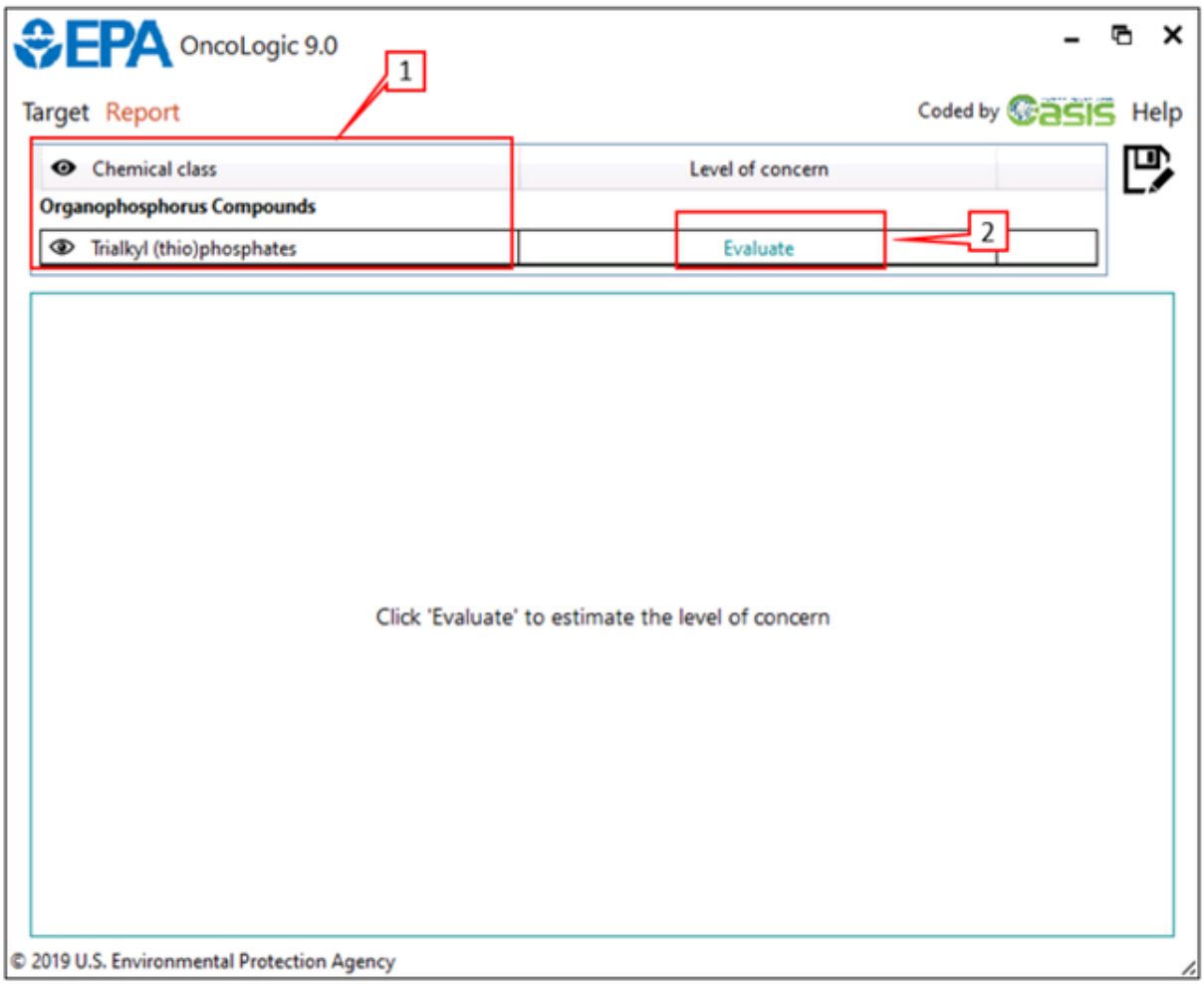

Figure 3

4. The concern for the Organophosphorus compounds depends on the outcome from the list with question related to the genotoxic data for the target chemical, or other type of question. For this example the questions are as depicted in Figures 4-8.

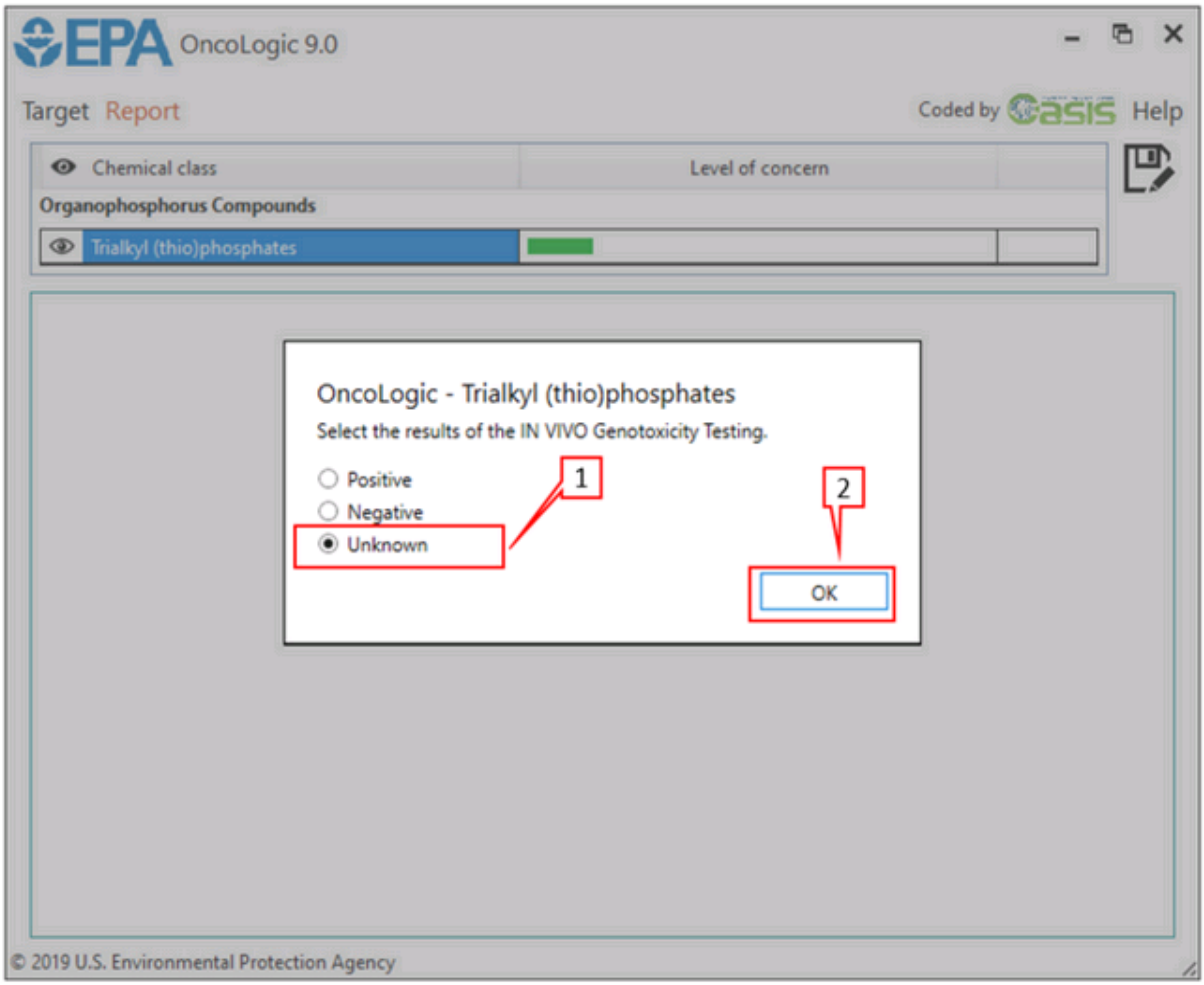
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Organophosphorus Compounds
Trialkyl (thio)phosphates
OncoLogic - Trialkyl (thio)phosphates
Select the results of the IN VIVO Genotoxicity Testing.
Positive
Negative
Unknown
1
2
OK
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Figure 4

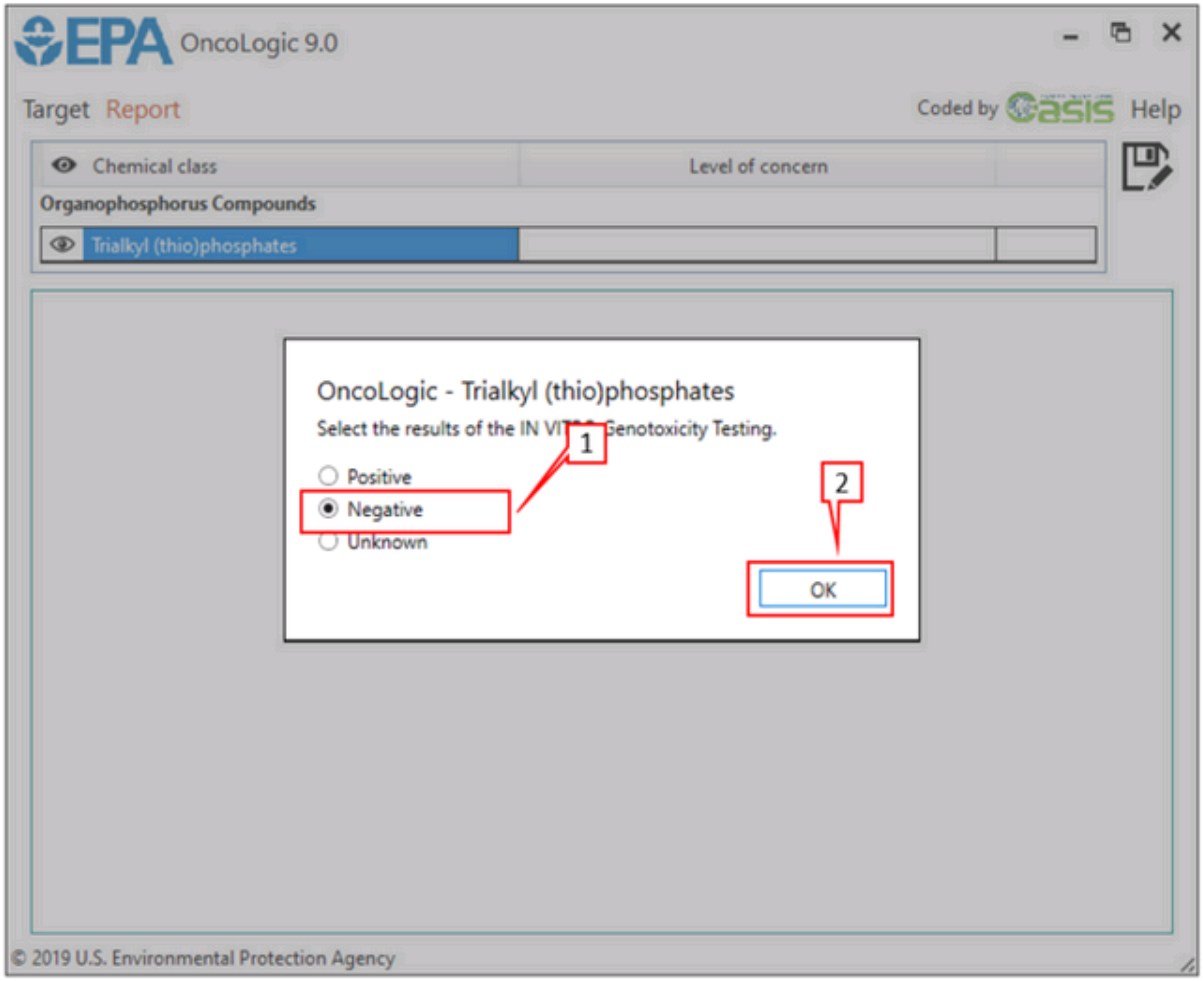
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Organophosphorus Compounds
Trialkyl (thio)phosphates
OncoLogic - Trialkyl (thio)phosphates
Select the results of the IN VI Genotoxicity Testing.
Positive
Negative
Unknown
1
2
OK
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Figure 5

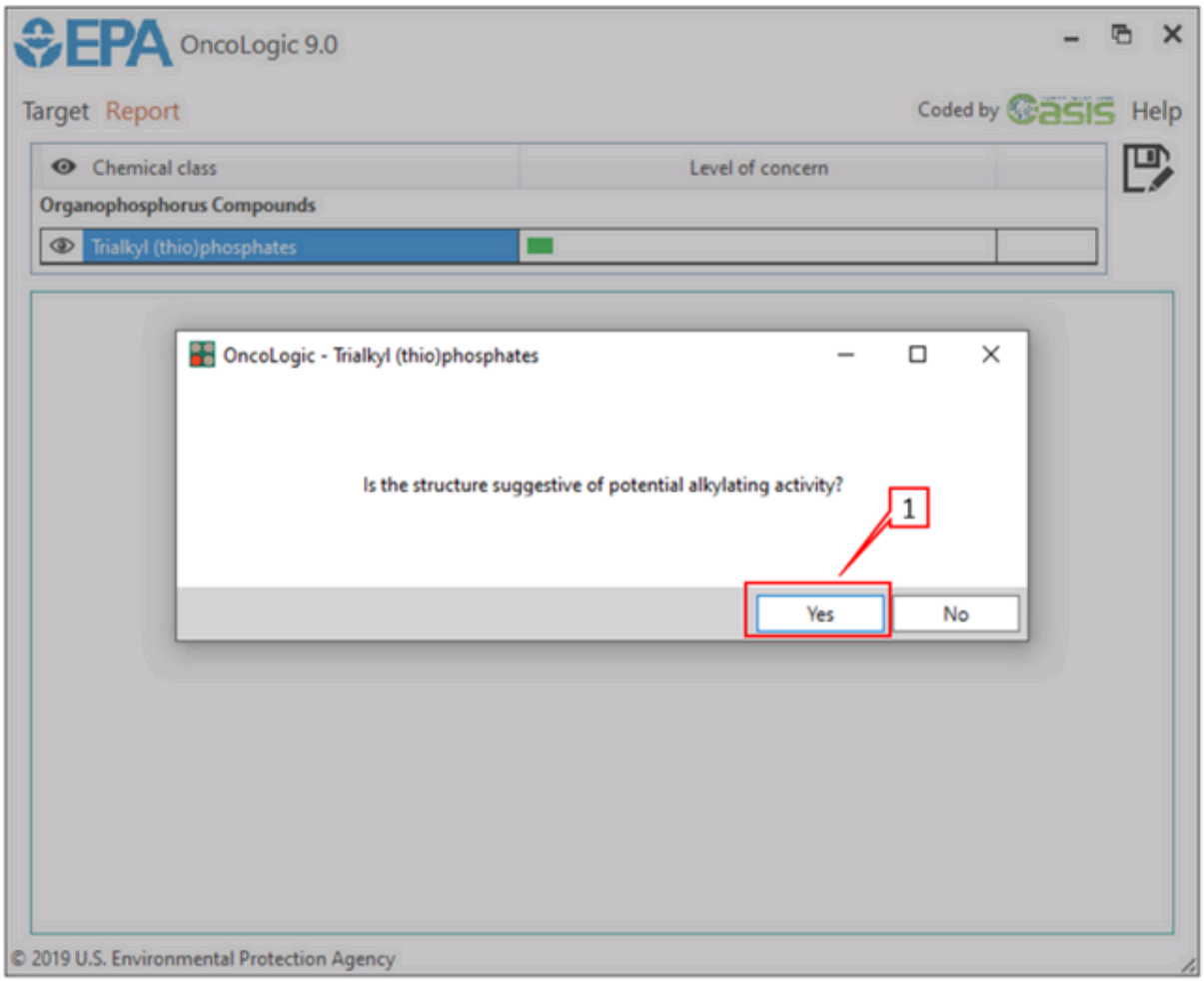
EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Organophosphorus Compounds
Trialkyl (thio)phosphates
OncoLogic - Trialkyl (thio)phosphates
Is the structure suggestive of potential alkylating activity?
1
Yes
No
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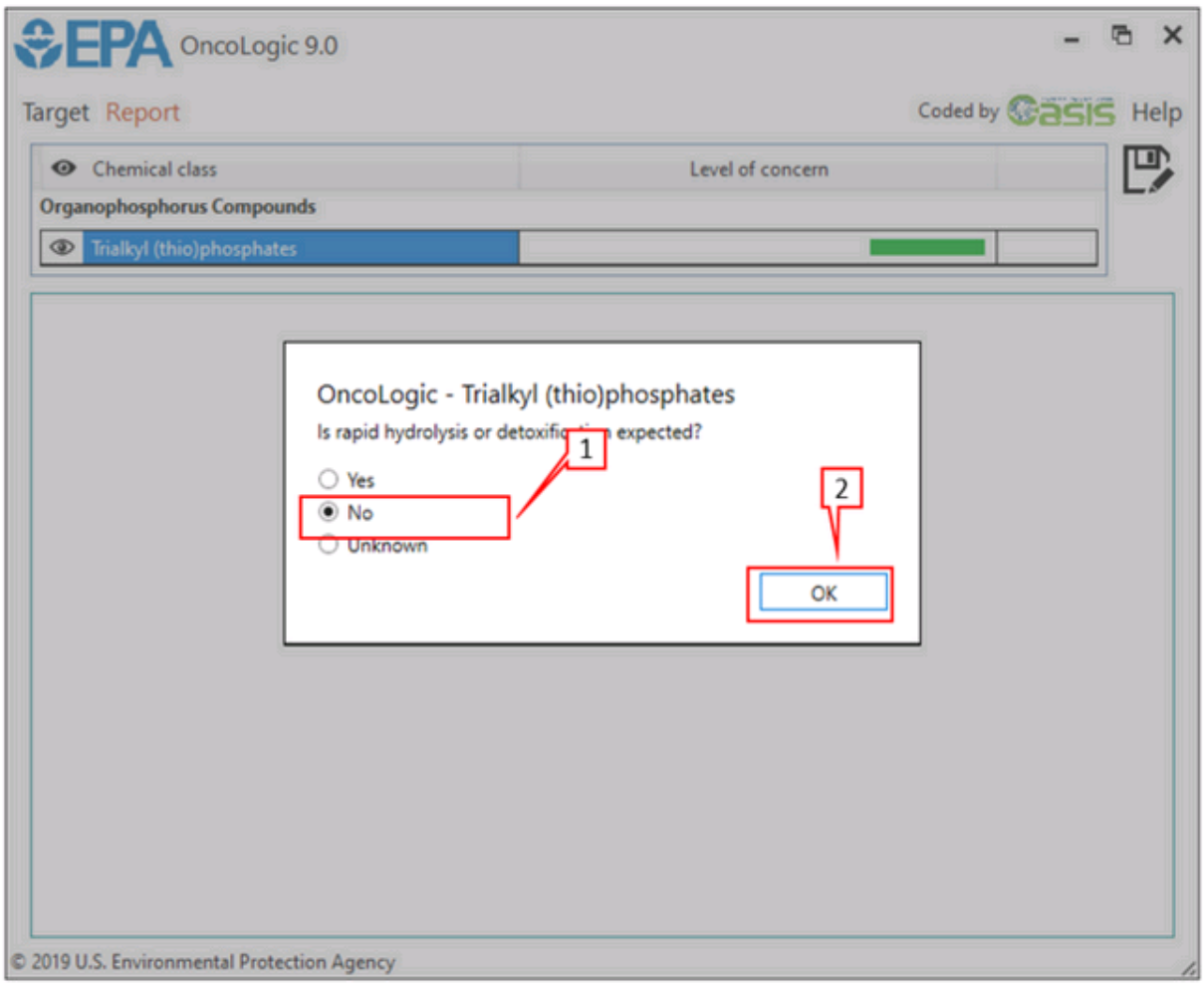
Figure 6


EPA OncoLogic 9.0
Target Report
Coded by Oasis Help
Chemical class
Level of concern
Organophosphorus Compounds
Trialkyl (thio)phosphates
OncoLogic - Trialkyl (thio)phosphates
Is rapid hydrolysis or detoxification expected?
Yes
No
Unknown
1
2
OK
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Fugure 7

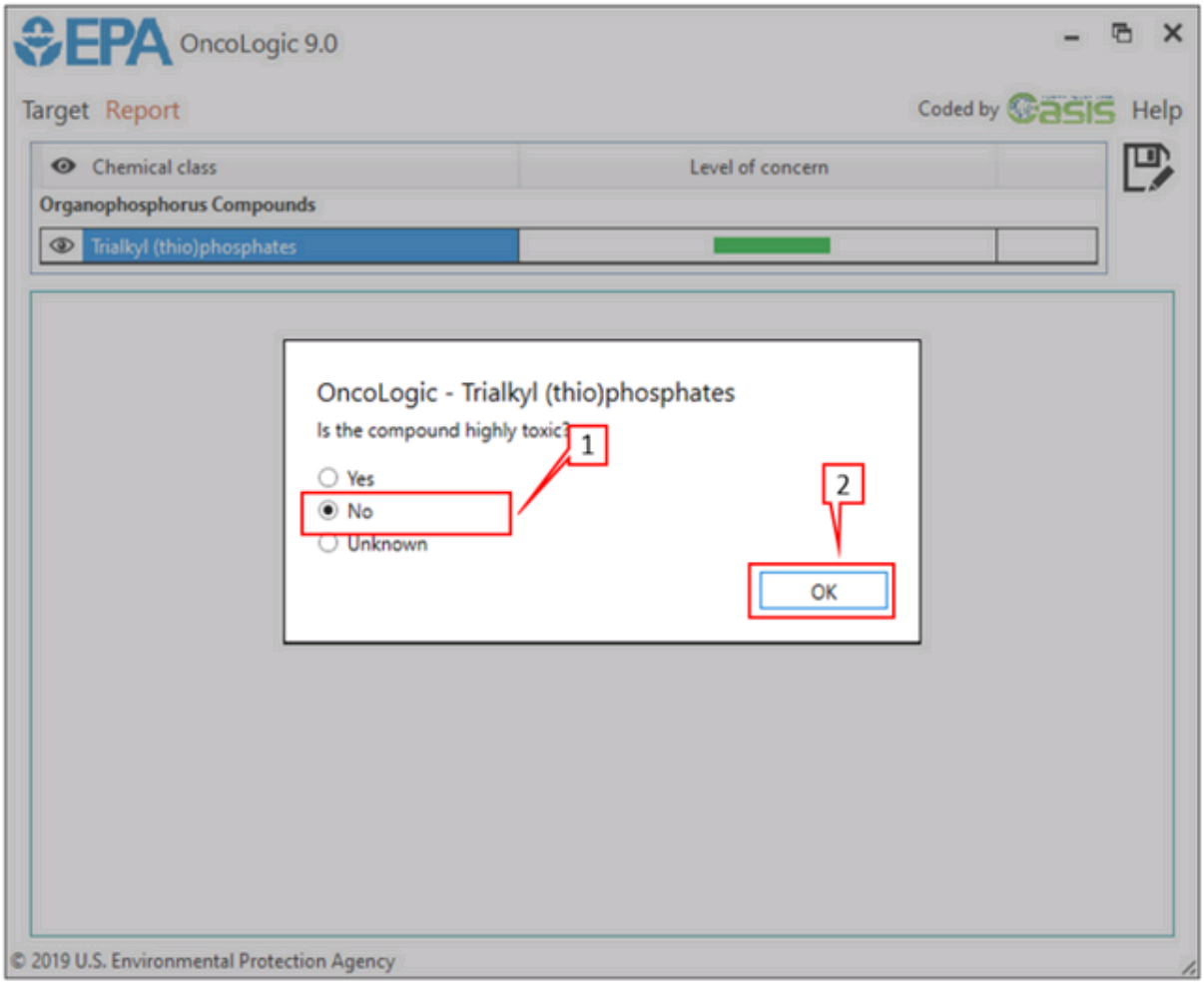

Figure 8

5. The report has been generated (1) and it could be saved (2) (Figure 9).

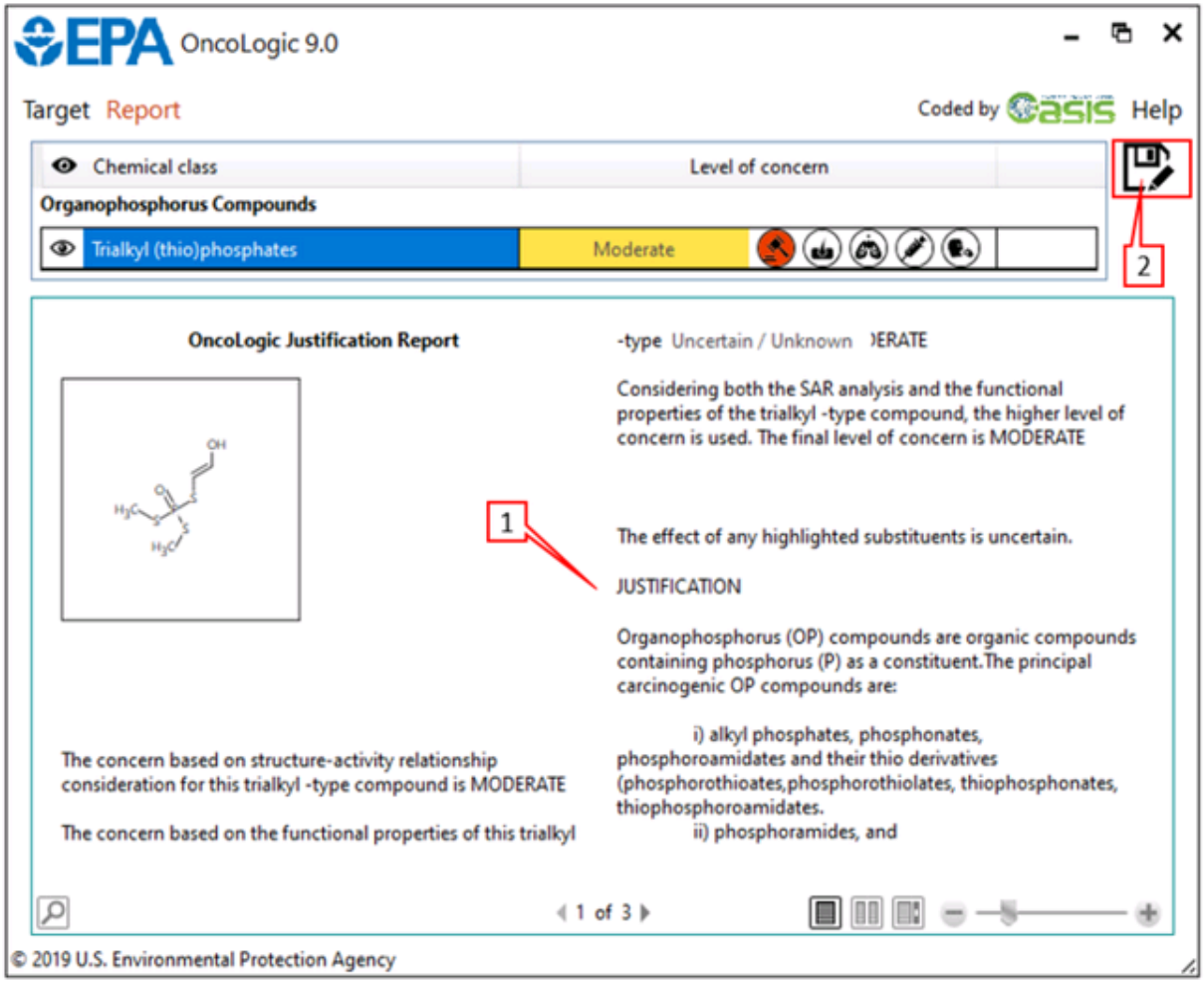
EPA OncoLogic 9.0
Target Report
Coded by oasis Help
Chemical class
Level of concern
Organophosphorus Compounds
Trialkyl (thio)phosphates
Moderate
2
OncoLogic Justification Report
-type Uncertain / Unknown)ERATE
Considering both the SAR analysis and the functional properties of the trialkyl -type compound, the higher level of concern is used. The final level of concern is MODERATE
1
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent.The principal carcinogenic OP compounds are:
i) alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates, thiophosphonates, thiophosphoroamidates.
ii) phosphoramides, and
The concern based on structure-activity relationship consideration for this trialkyl -type compound is MODERATE
The concern based on the functional properties of this trialkyl
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Figure 9

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5.13 PAH

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5.13.1 Homocyclic Polyaromatic Hydrocarbons

1. Input a target chemical (1) and click OK (2) (Figure 1).

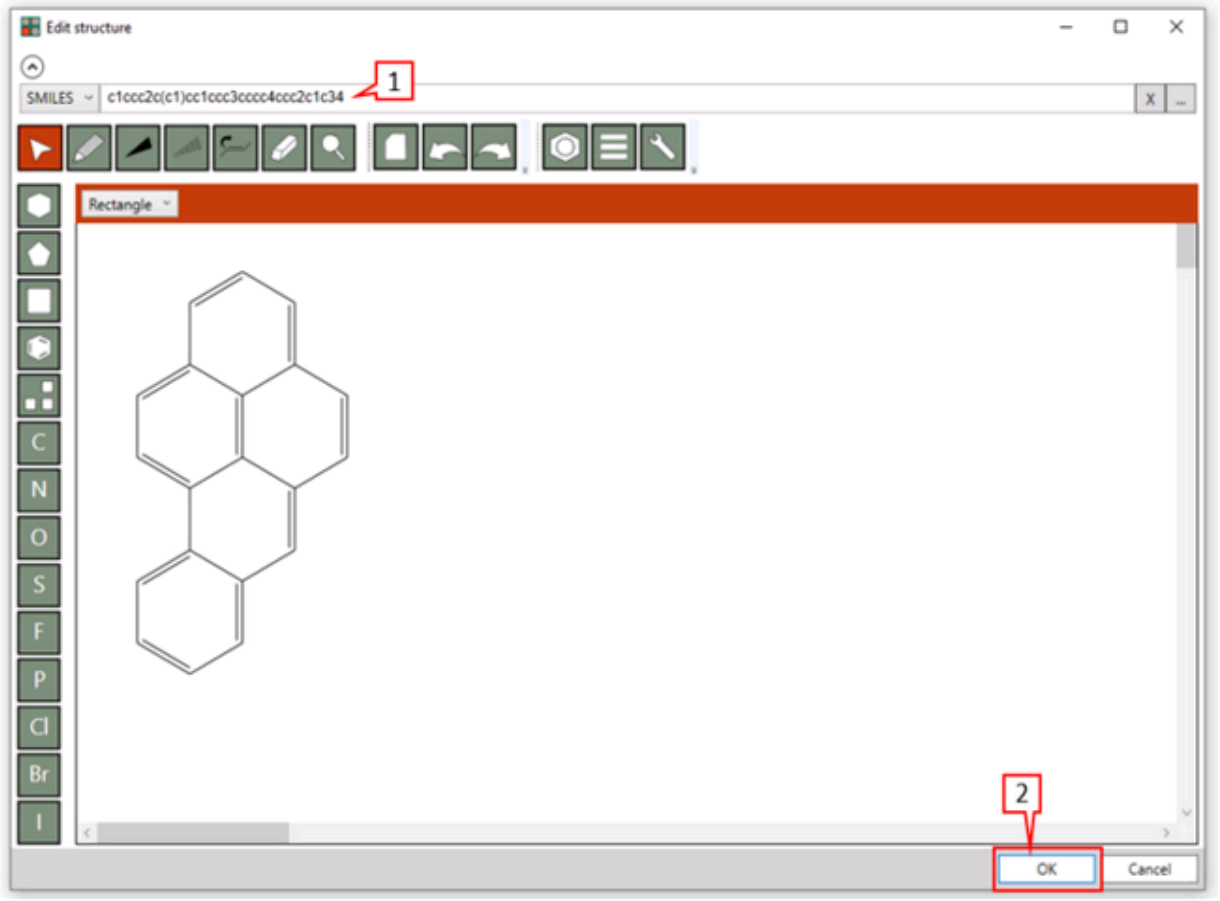

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

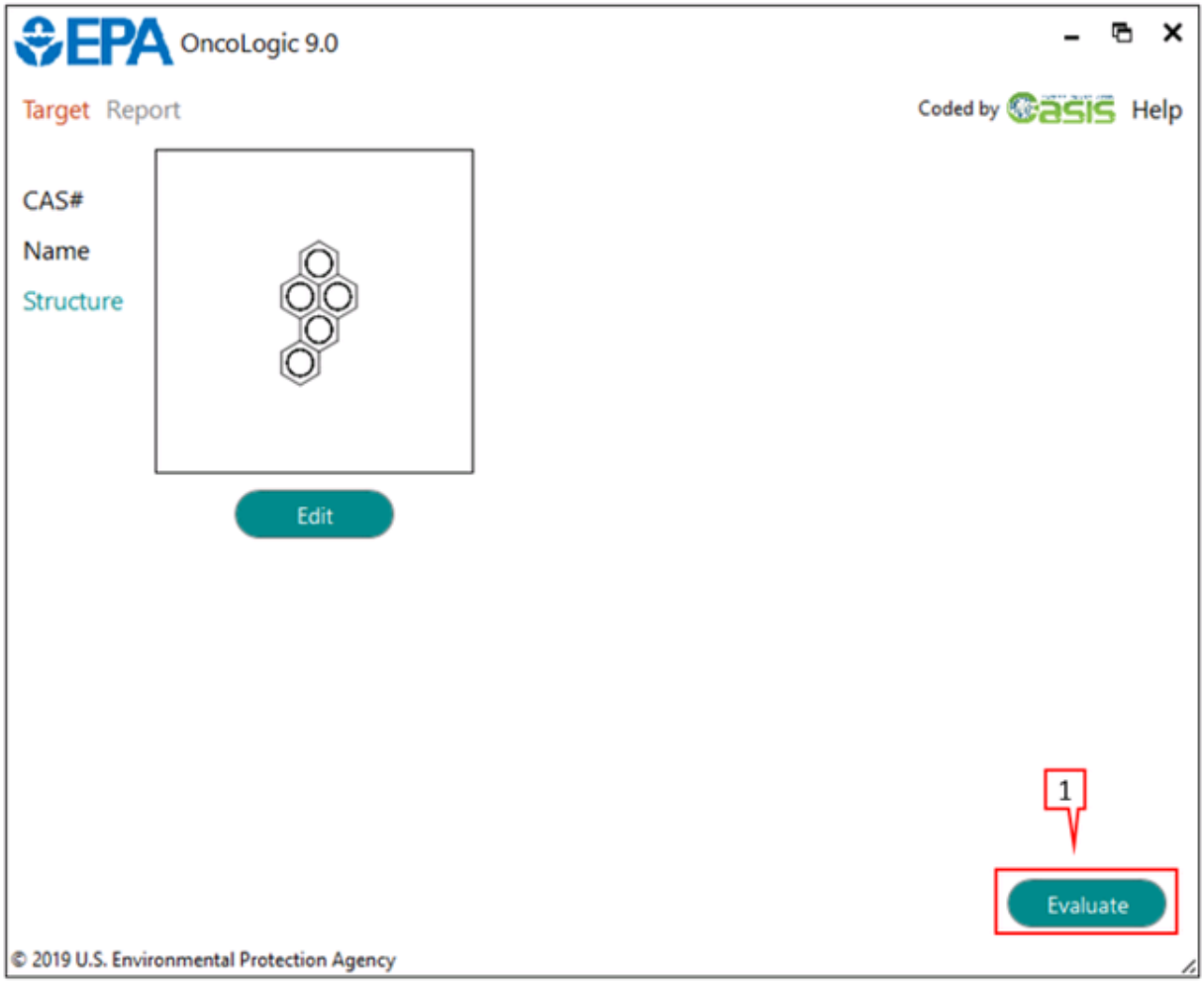

Figure 2

3. After the target chemical has been profiled as *PAH/ Homocyclic Polyaromatic Hydrocarbons* (1), click on Evaluate (2) (Figure 3).

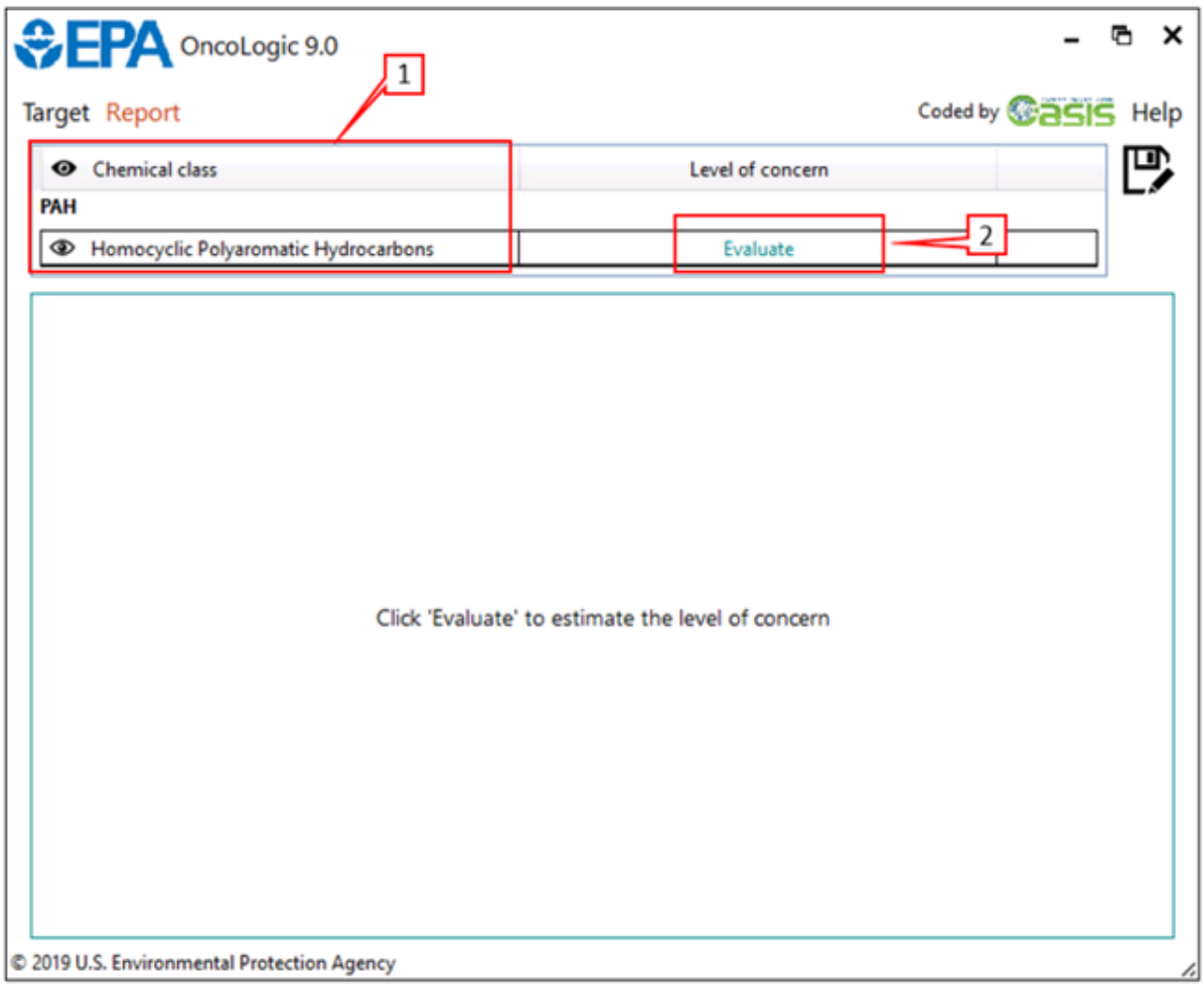

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

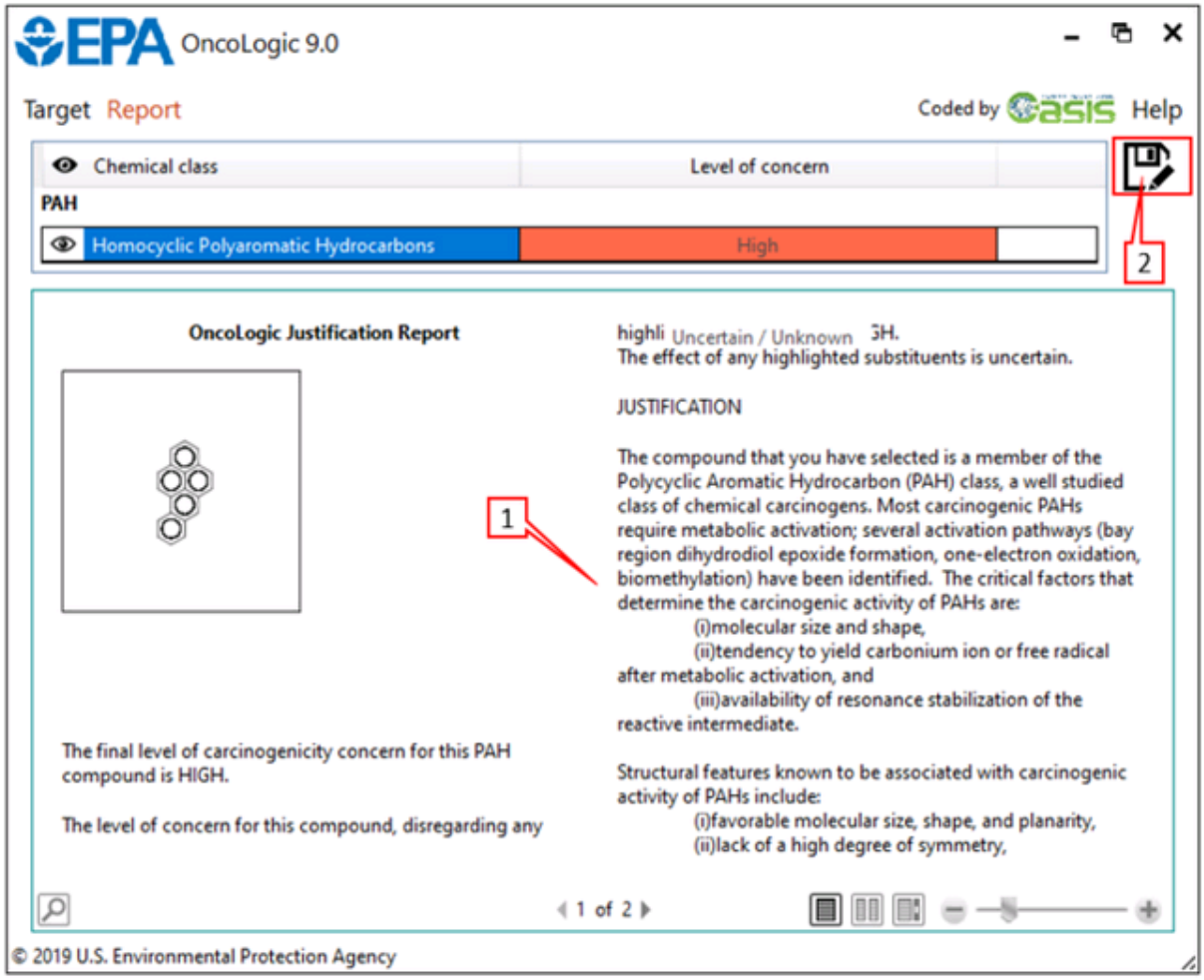
EPA OncoLogic 9.0
Target Report
Coded by oasis Help
Chemical class
Level of concern
PAH
Homocyclic Polyaromatic Hydrocarbons
High
2
OncoLogic Justification Report
highli Uncertain / Unknown 3H.
The effect of any highlighted substituents is uncertain.
JUSTIFICATION
1
The compound that you have selected is a member of the Polycyclic Aromatic Hydrocarbon (PAH) class, a well studied class of chemical carcinogens. Most carcinogenic PAHs require metabolic activation; several activation pathways (bay region dihydrodiol epoxide formation, one-electron oxidation, biomethylation) have been identified. The critical factors that determine the carcinogenic activity of PAHs are:
(i)molecular size and shape,
(ii)tendency to yield carbonium ion or free radical after metabolic activation, and
(iii)availability of resonance stabilization of the reactive intermediate.
The final level of carcinogenicity concern for this PAH compound is HIGH.
Structural features known to be associated with carcinogenic activity of PAHs include:
(i)favorable molecular size, shape, and planarity,
(ii)lack of a high degree of symmetry,
The level of concern for this compound, disregarding any
1 of 2
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Figure 4

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5.14 Thiocarbonyls

1. Input a target chemical (1) and click *OK* (2) (Figure 1).

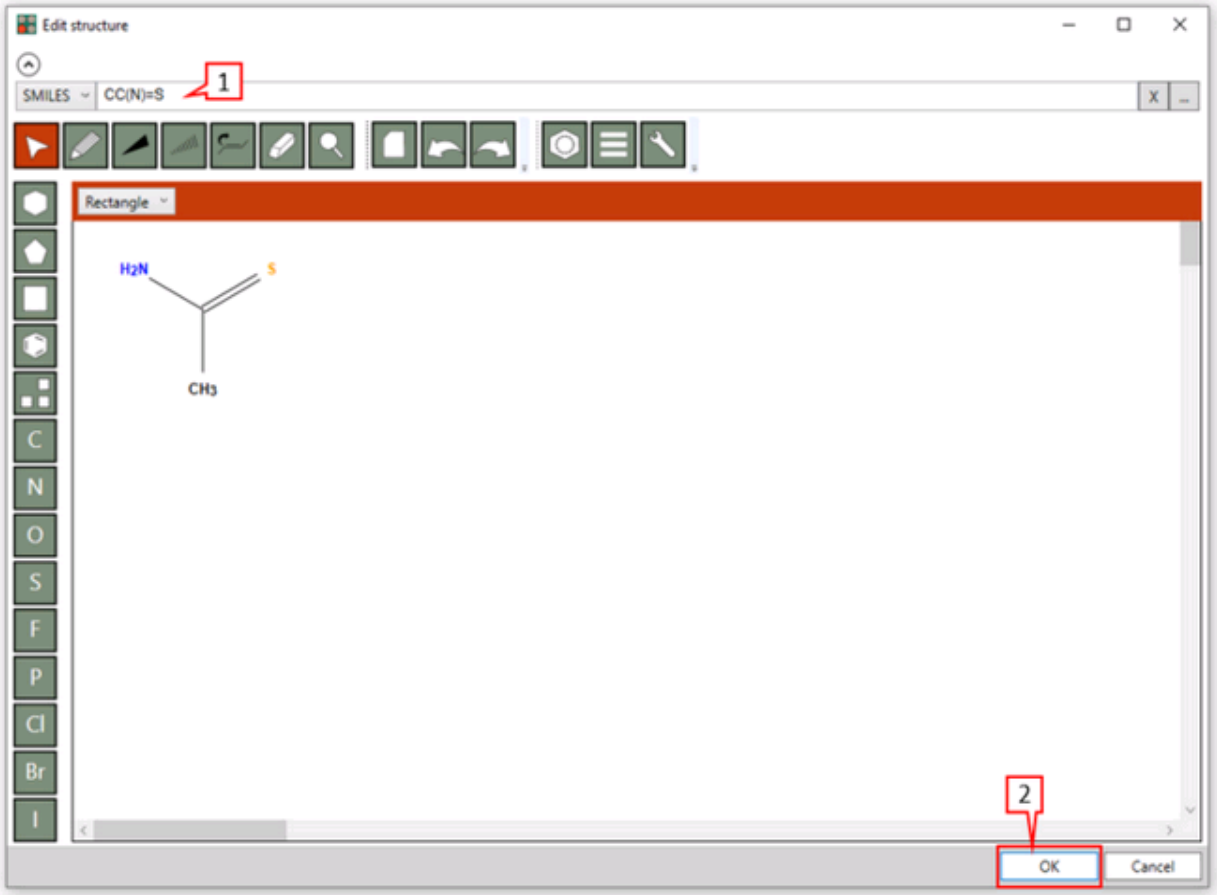

Figure 1

2. Click on *Evaluate* (1) (Figure 2).

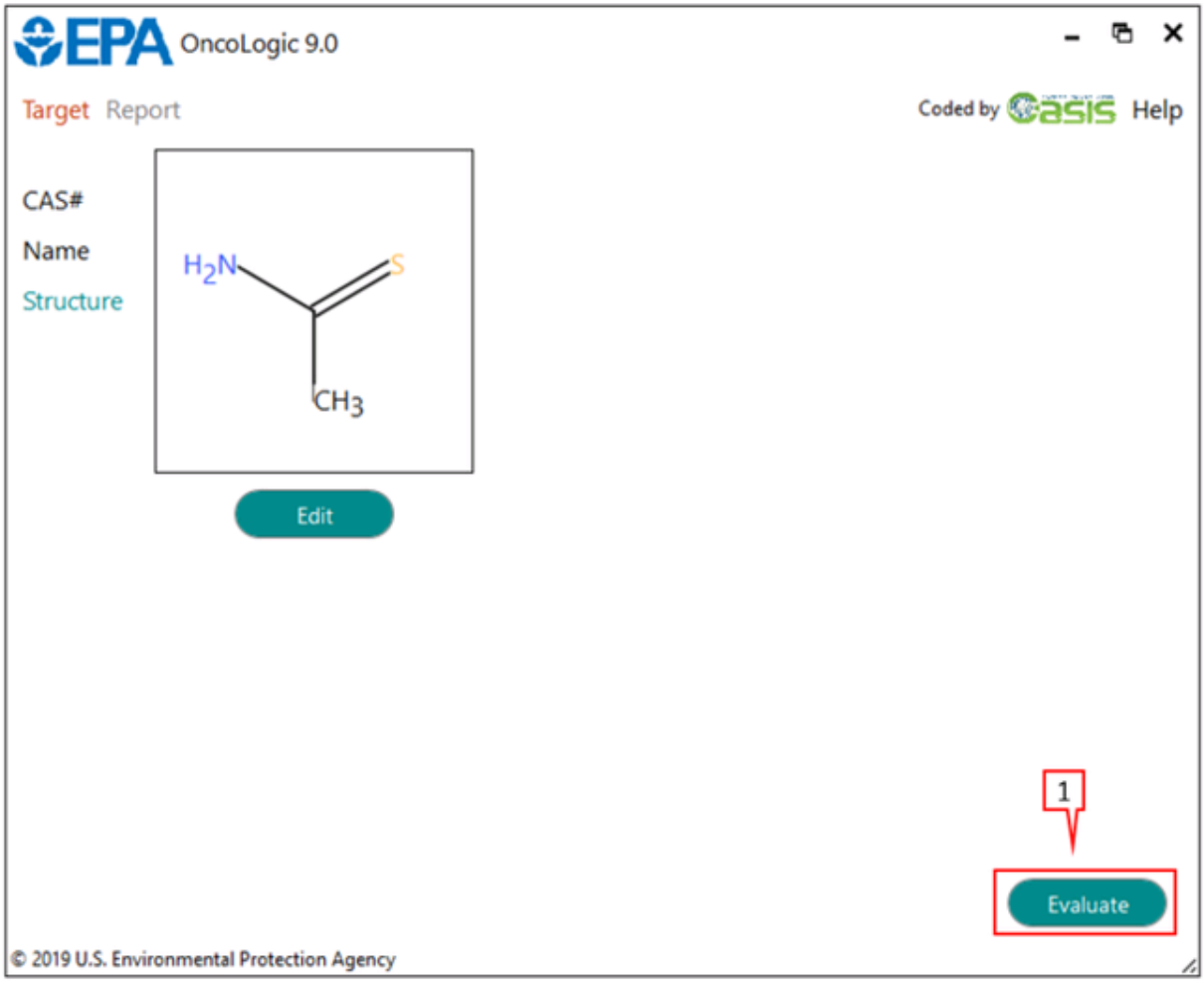

Figure 2

3. After the target chemical has been profiled as *Thiocarbonyls/ Thioamide* (1), click on *Evaluate* (2) (Figure 3).

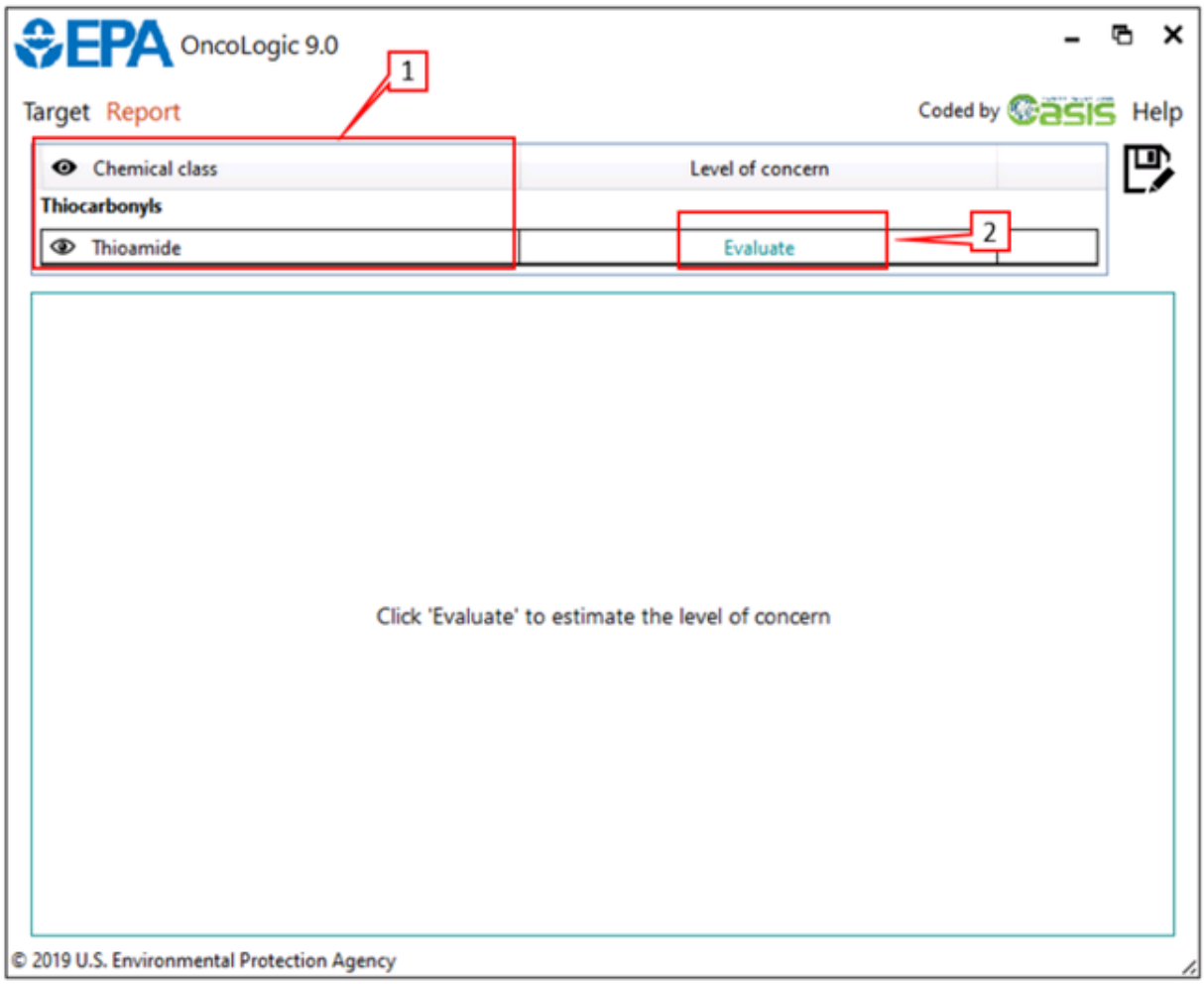

Figure 3

4. The report has been generated (1) and it could be saved (2) (Figure 4).

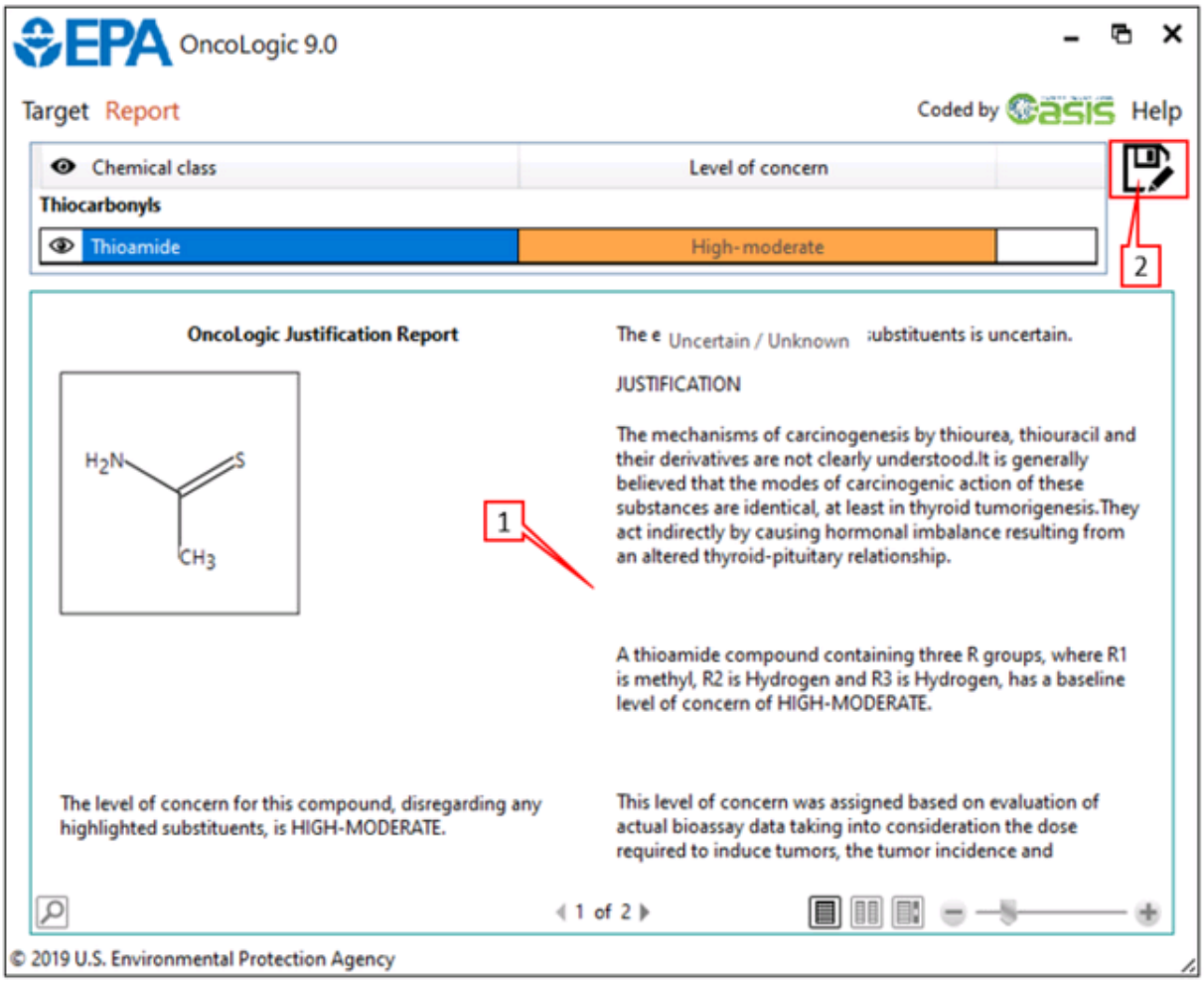
EPA OncoLogic 9.0
Target Report
Coded by oasis Help
Chemical class
Level of concern
Thiocarbonyls
Thioamide
High-moderate
2
OncoLogic Justification Report
The e Uncertain / Unknown substituents is uncertain.
JUSTIFICATION
The mechanisms of carcinogenesis by thiourea, thiouracil and their derivatives are not clearly understood.It is generally believed that the modes of carcinogenic action of these substances are identical, at least in thyroid tumorigenesis.They act indirectly by causing hormonal imbalance resulting from an altered thyroid-pituitary relationship.
1
A thioamide compound containing three R groups, where R1 is methyl, R2 is Hydrogen and R3 is Hydrogen, has a baseline level of concern of HIGH-MODERATE.
The level of concern for this compound, disregarding any highlighted substituents, is HIGH-MODERATE.
This level of concern was assigned based on evaluation of actual bioassay data taking into consideration the dose required to induce tumors, the tumor incidence and
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Figure 4

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6. Glossary

Glossary

C# - C-Sharp is a programming language developed by Microsoft that runs on the .NET Framework. C# is used to develop web apps, desktop apps, mobile apps, games and much more.
CAS - A CAS Registry Number, also referred to as CASRN or CAS Number, is a unique numerical identifier assigned by the Chemical Abstracts Service
DNA - Deoxyribonucleic acid
EPA - Environmental Protection Agency's
IARC - International Agency for Research on Cancer
.NET platform - The .NET framework is a software development framework from Microsoft. It provides a controlled programming environment where software can be developed, installed and executed on Windows-based operating systems
NTP - National Toxicology Program
NCI - National Cancer Institute
OECD - Organization for Economic Co-operation and Development
QSAR - Quantitative structure–activity relationship
OP - Organophosphorus
PAH - Polycyclic Aromatic Hydrocarbon
PHS - Public Health service
PMN - Pre-Manufacture Notification
SMILES - Simplified Molecular-input Line-entry System
SAR - Structure Activity Relationship
SAT - Structure Activity Team
TCDD - 2,3,7,8-tetrachlorodibenzo-p-dioxin

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