Non-Cancer Human Health Hazard Assessment for Sustainable Futures

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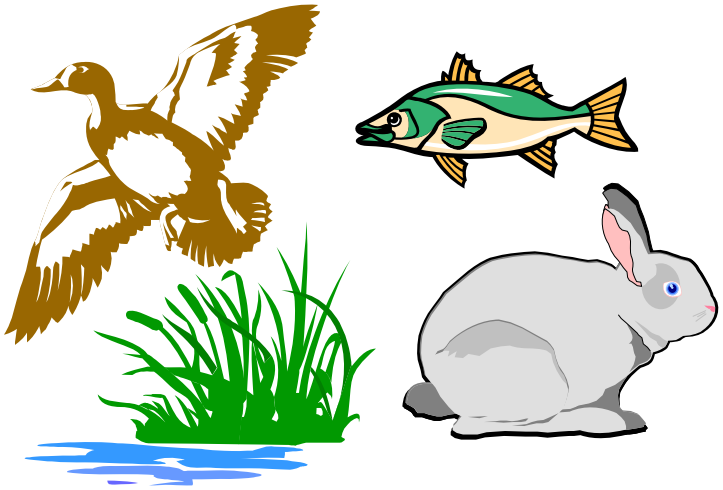
U.S. EPA



Non-Cancer Health Hazard Screen

- **Background**
  - **No computer models for assistance**
  - **Analysis based on available experimental data for the compound of interest and closely related analogs**
  - **Includes a broad range of acute, subchronic, and chronic endpoints**

Non-Cancer Health Hazard Endpoints

Endpoints generally used to assign hazard concern levels for PBT score and potential regulation of PMNs

- **Systemic toxicity (e.g., liver, kidney, or generalized toxicity)**
  - **Subchronic or chronic duration**
  - **Acute studies may offer evidence of potential health hazards if longer duration studies are not available**
- **Neurotoxicity**
  - **Behavioral evidence of neurotoxicity, brain pathology**
- **Reproductive toxicity**
  - **Effects on ability to reproduce (e.g., fertility)**

Non-Cancer Health Hazard Endpoints

Endpoints generally used to assign hazard concern levels for PBT score and potential regulation of PMNs (cont.)

- **Developmental toxicity**
  - **Effects on the developing fetus**
  - **Maternal toxicity may indicate greater sensitivity of pregnant animals with respect to systemic effects**
- **Immunotoxicity**
  - **Effects on immune system organs (spleen, thymus)**
  - **Immune suppression observed in immunotoxicity studies**

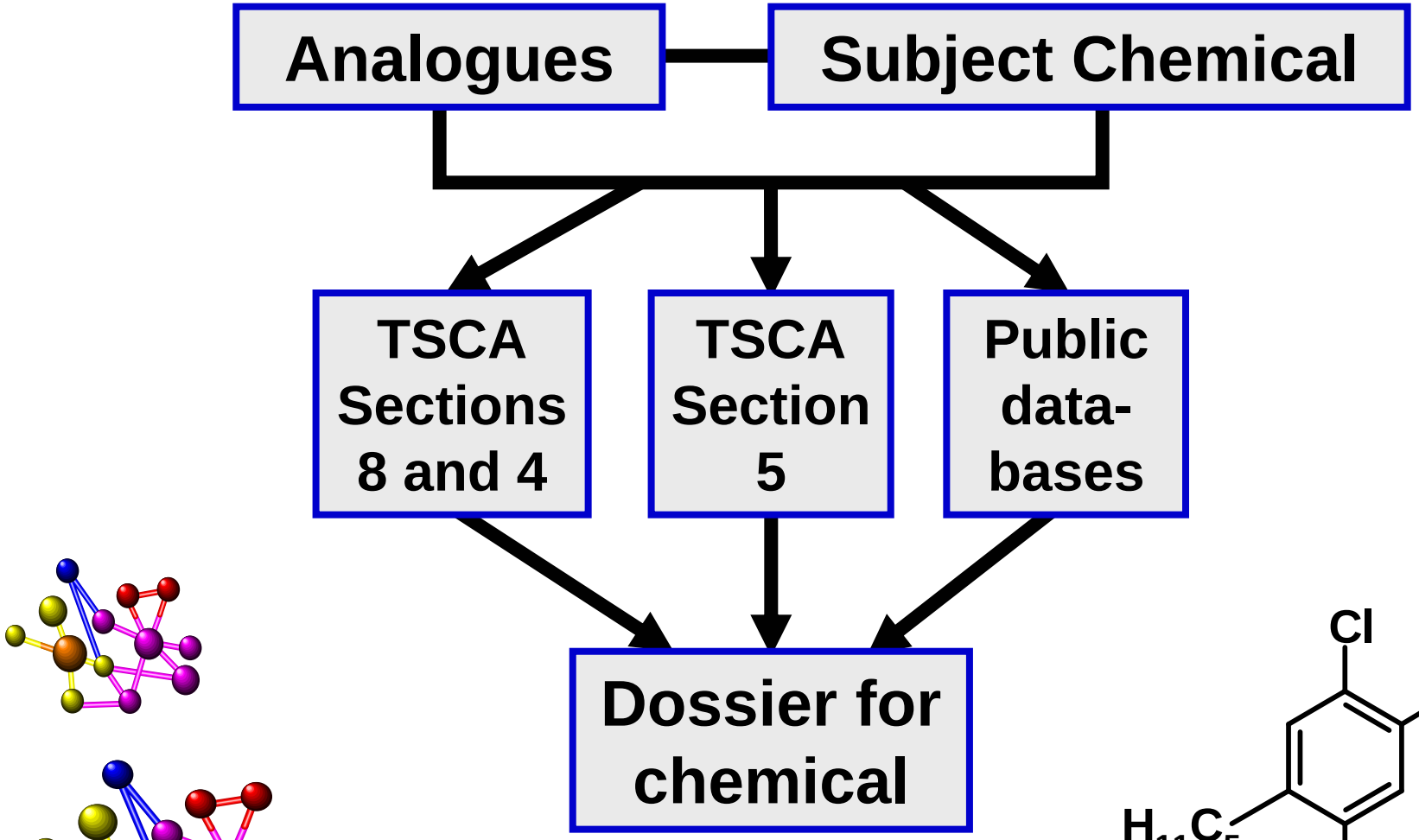
Non-Cancer Health Hazard Endpoints

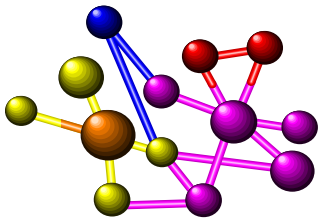
- Other hazard endpoints not considered for PBT score
  - Mutagenicity
  - Skin Sensitization
  - Irritation (eye, skin, respiratory)
- Not generally the sole basis for regulating a chemical or assigning the PBT score
  - These endpoints should be identified in the MSDS

Five Steps in Conducting a Non-Cancer Hazard Screen

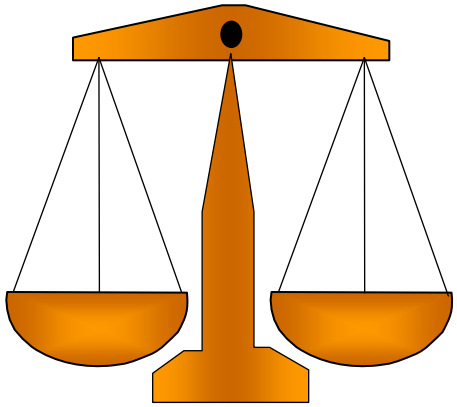
- **Step 1. Locate relevant information on substance (if available) and report information in SF summary assessment**
- **Step 2. Determine if chemical is a member of a category known to be associated with hazards**
- **Step 3. Identify appropriate analog(s) if available data on PMN chemical is not sufficient to allow for toxicity characterization**
- **Step 4. Locate measured toxicity data on analog(s)**
  - **Quality measured data on chemical substance supercedes analog data**
- **Step 5. Assign HAZARD concern level**

EPA Search Strategies

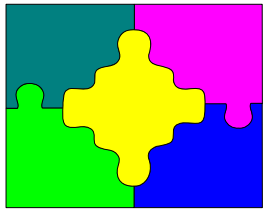




Factors in Health Hazard Assessment

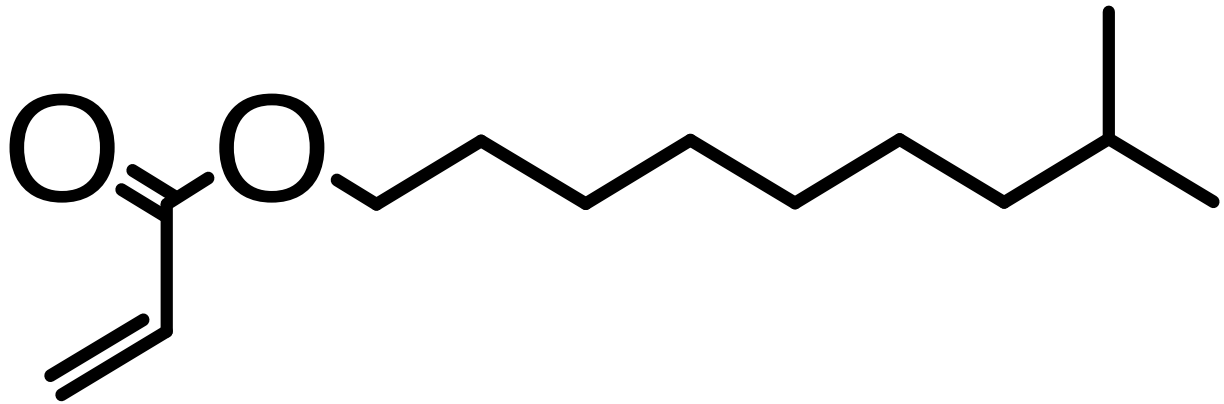


- Chemical toxicity data
- Analogue toxicity data
- Chemical Class toxicity data
- Mechanistic considerations
- Professional judgement



Step by Step Non-Cancer Hazard Assessment for Example Chemical

Example Chemical: Isodecyl acrylate



Step 1. Search for toxicity data on chemical

- **Where to search for chemical toxicity data**
  - **In-house data**
  - **TOXNET (toxnet.nlm.nih.gov)**
    - **HSDB, TOXLINE, CCRIS, GENETOX, DART/ETIC**
  - **IARC, IPCS, NTP, U.S. EPA HPV program, SIDS data sets, RTECS, TSCATS, and others (URLs included in attachment**
- **Other sources are available**

Step 1. Important Details to Record From Toxicity Data in SF Summary Assessment

- Hazard concern identified
- Type of study (e.g., 2-generation reproductive toxicity study, 28-day repeated-dose study)
- Study duration
- Animal species

Step 1. Important Details to Record From Toxicity Data in SF Summary Assessment (cont.)

- Exposure route (oral gavage, diet, dermal, inhalation)
- Effect Levels
  - No adverse effect levels (NOAEL) for each hazard identified
  - Lowest adverse effect levels (LOAEL) for each hazard identified
- Reference

Step 1. Important Factors in Evaluating Available Data

- No data is not equivalent to negative data
  - Hazard concerns based on scientific judgment
- If conflicting data exist, a weight of evidence approach should be used to support conclusions

Step 1. Other Factors to Consider

- **Absorption**
  - Absorption is necessary for some chemicals to be toxic
  - May vary by exposure route
  - May be estimated using measured data (chemical or analog) or by chemical and physical properties
    - Molecular weight, Kow, water solubility, physical state
  - Often need to extrapolate across exposure routes
    - Not appropriate for portal of entry effects

Step 1. Dermal Absorption

- Assessed on a case-by-case basis
- The following generally absorb well through the skin:
  - Liquid chemicals with log P values of 2 to 4
  - Liquid chemicals with MW <500
  - Formulated products with surfactants and detergents
  - Small molecular weight amines and carboxylic acids

Step 1. Dermal Absorption (cont.)

- **The following generally absorb poorly through the skin:**
  - **Solids**
    - **Solids may absorb better if the melting point is at approximately skin temperature**
  - **Chemicals with MW >500**
  - **Charged chemicals and salts**

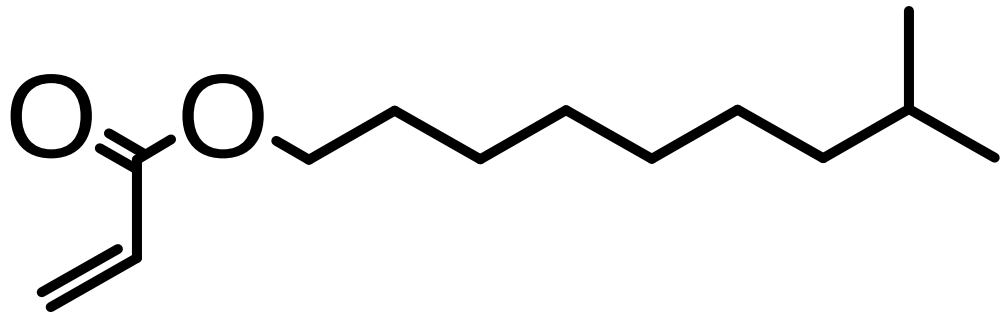
Step 1. Absorption (Other Exposure Routes)

- Assessed on a case-by-case basis
- Important chemical factors often include molecular weight, physical state, Kow, solubility, and ionization state

Step 1. Other Factors to Consider

- **Biological activity, metabolism, bioactivation, pharmacokinetics, distribution**
  - **Toxicity study on appropriate analog mitigates the need to consider these factors separately**

Step 1. Results for Example Chemical



- No relevant toxicity data on isodecyl acrylate were located in the data sources that were searched

- Analog data need to be identified

Step 2. Determine if Chemical Belongs to a Category of Concern

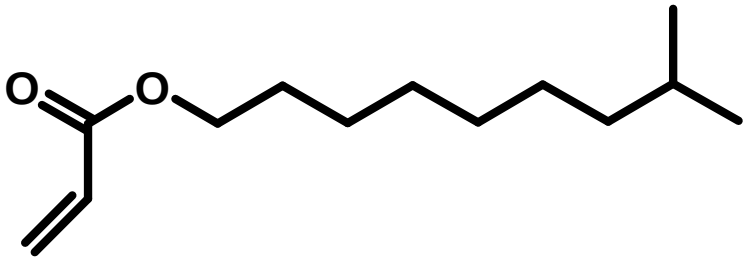
- U.S. EPA Category Statements
  - http://www.epa.gov/opptintr/newchems/pubs/chemcat.htm
  - 55 categories based on PMN data that have consistently been shown to induce toxic effects
  - Concern may exist for chemicals with structures that are not consistent with an EPA category
- Review articles

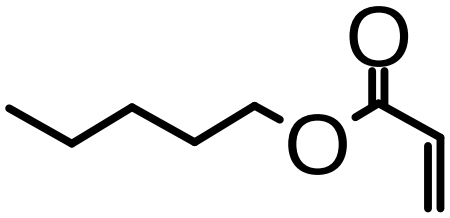
Step 2. Conclusions for Isodecyl Acrylate

- Acrylates are not regulated by U.S. EPA as a category
- Some acrylates may be biologically active

Step 3. Identifying Appropriate Analog(s)

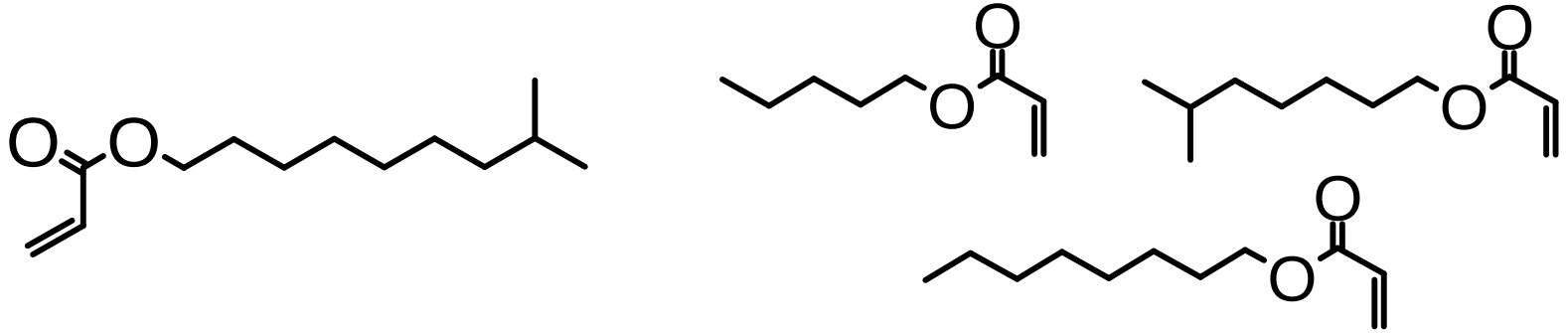
- **Substructure or similarity searches**
  - **Publicly available databases that allow substructure searches**
    - **CHEMID** http://chem.sis.nlm.nih.gov/chemidplus/
    - **CHEMFINDER** http://chemfinder.cambridgesoft.com/
    - **TSCATS** http://www.syrres.com/esc/tscats_info.htm
  - **Substructure searches may include**





Step 3. Identifying Appropriate Analog(s)

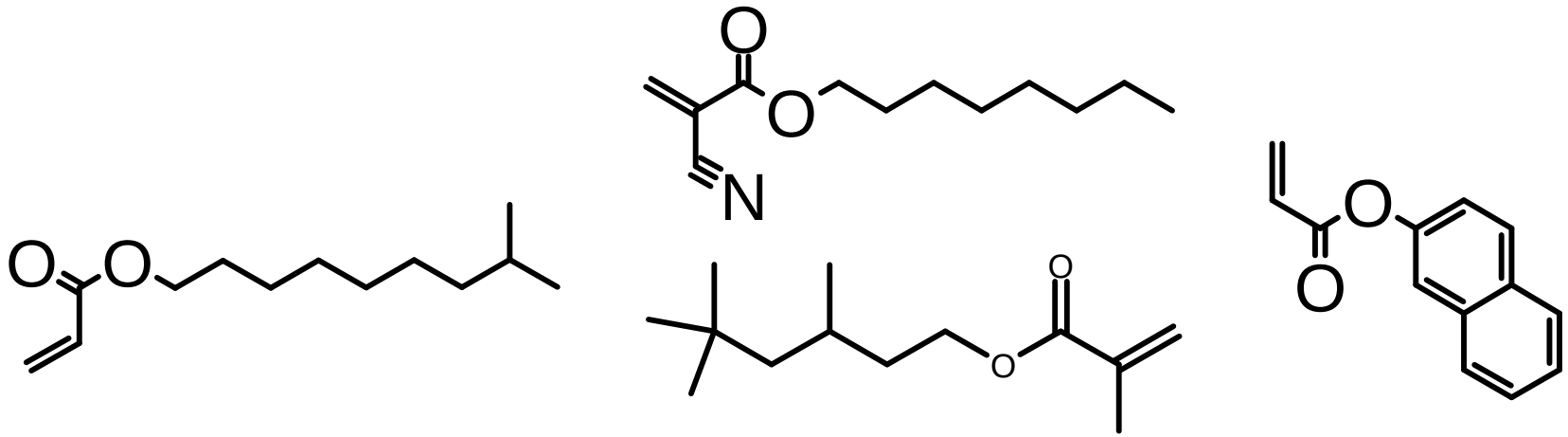
- **Characteristics of an appropriate analog**
  - **Size and functional groups are representative of chemical of interest**
  - **Does not contain biologically active groups that are NOT represented on chemical of interest**



Expect a similar mechanism of action for these chemicals.

Step 3. Identifying Appropriate Analogs(s)

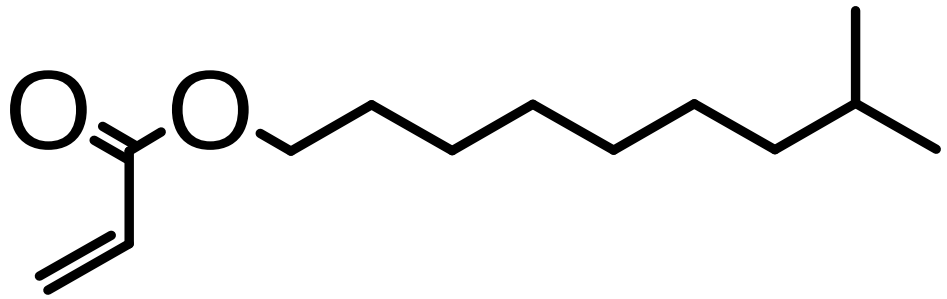
- **Characteristics of a poor analog**
  - **Size and functional groups are NOT representative of chemical of interest**
  - **Functional groups are present, but not expected to be representative of toxicity (e.g., steric hindrance)**



Different mechanistic pathways are expected for these chemicals.

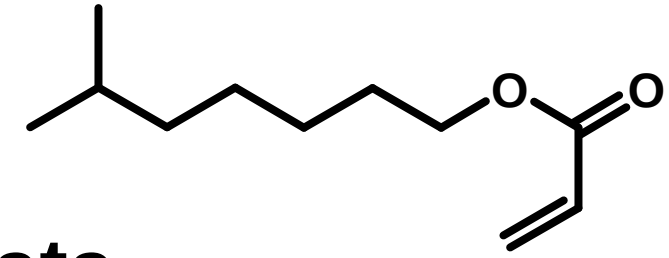
Step 4. Collection of Toxicity Data for Analog(s) Identified in Step 3

- Process is identical to that described in Step 1
- Results for example chemical



Step 4. Locate Measured Toxicity Data (Analog 1)

Analog:



- **Toxicity Data**
  - **Positive:**
    - **Developmental toxicity (oral): Induced skeletal variations in rats gavaged at 1000 mg/kg (the only dose tested)**
    - **Dermal irritation: Induced marked irritation in rats**

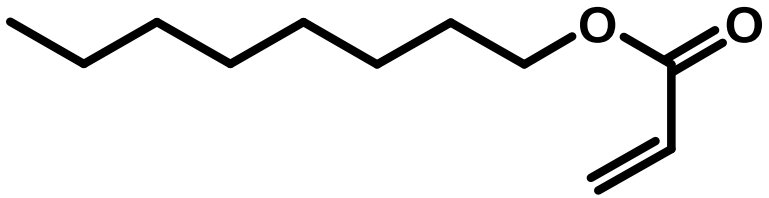
Step 4. Locate Measured Toxicity Data (Analog 1, cont.)

Toxicity Data (cont.)

- **Negative Data:**
  - **Developmental toxicity: Negative in rats dermally exposed; Mutagenicity: Negative in Ames test and mouse lymphoma test;**
  - **Cancer: Negative in limited dermal bioassay in mice**
- **Data Sources**
  - **TSCATS: 8e-1524**
  - **Toxline: Gordon et al., 1991, Gordon et al., 1998**
  - **CCRIS: Gordon et al., 1991**

Step 4. Locate Measured Toxicity Data (Analog 2)

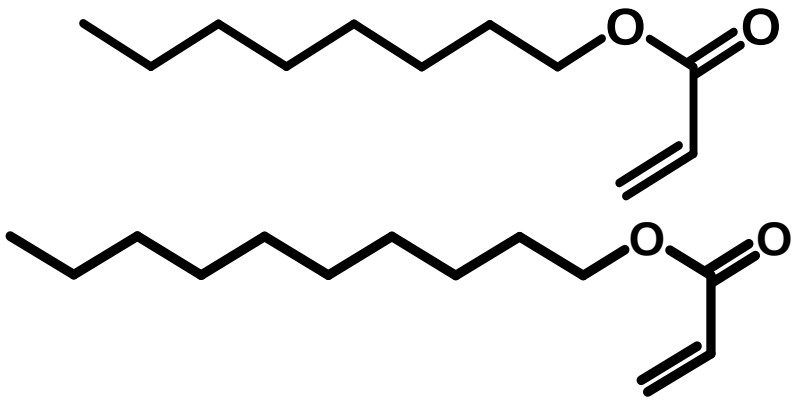
- Analog:



- Toxicity Data
  - Positive:
    - Induced dermal sensitization in Guinea pigs
  - Negative: No data located
- Data Sources
  - TSCATS: 8e-14572

Step 4. Locate Measured Toxicity Data (Analog 3)

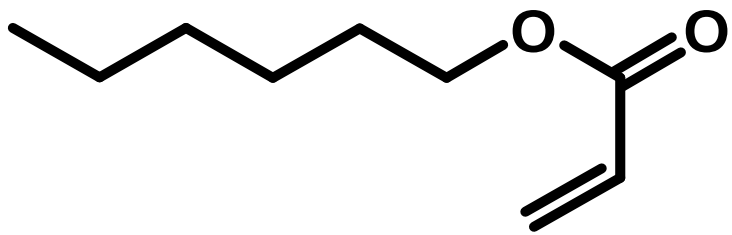
- Analog (mixture):



- Toxicity Data
  - Positive:
    - Skin Sensitization
  - Negative:
    - No data located
- Data Sources
  - TSCATS: 8e-11424

Step 4. Locate Measured Toxicity Data (Analog 4)

- Analog:



- Toxicity Data
  - Positive:
    - Induced sensitization in human volunteers
  - Negative:
    - Mutagenicity (Ames test)
- Data Sources
  - TSCATS: 8(e)-3774
  - CCRIS (Waegemaekers et al., 1984)

Step 5. Guidance in Assigning EPA Concern Levels

Concern Level	Criteria	Exposure and Risk Assessment Needed?
HIGH	Evidence of adverse effects in human populations Conclusive evidence of severe effects in animal studies	Yes
MODERATE	Suggestive animal studies in analog data Class known to produce toxicity	Yes
LOW	No concern identified	No

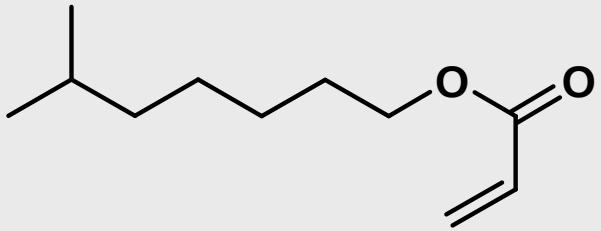
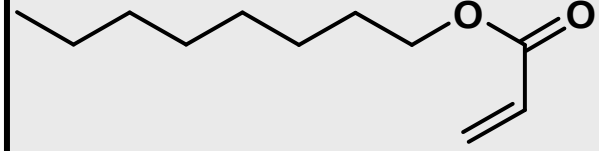
Interpreting Hazard Concern Levels

- Risk assessment is performed only if high or moderate hazard concern is identified
- Distinction between moderate and high concern is not critical to Sustainable Futures Assessment

Step 5. Guidance in Assigning EPA Concern Levels (cont.)

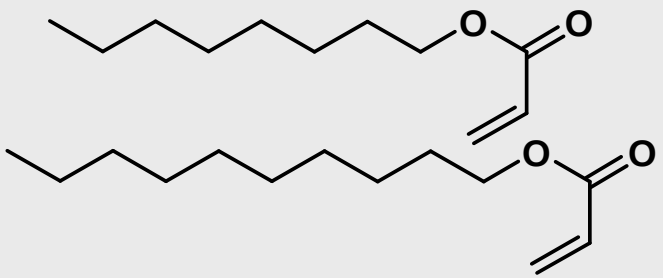
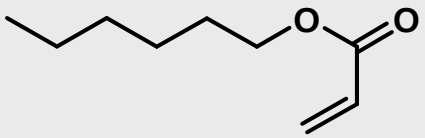
- **Hazard endpoints used in assigning concern levels**
  - **Systemic Toxicity**
    - **Includes reproductive, developmental, neurotoxicity, target organ toxicity, etc.**
    - **Environmental vs. occupational exposures**
  - **Endpoints not generally used as sole basis for assigning concern levels for PBT scores**
    - **Skin sensitization and irritation**
    - **Mutagenicity**

Step 5. Assign EPA Concern Level to Isodecyl Acrylate

Analog	Hazard Concern	Basis for Concern	Concern Level
	Developmental Toxicity	Induced skeletal variations at the only dose tested (1000 mg/kg, oral gavage)	Moderate
	Dermal Irritation	Induced marked irritation in rats	Moderate*
	Dermal Sensitization	Induced sensitization in Guinea pigs	Moderate*

*** Although there is moderate concern for dermal sensitization, this endpoint may not contribute to the overall hazard concern for isodecyl acrylate for purpose of PBT score regulation. Warnings should be included in MSDS.**

Step 5. Assign EPA Concern Level to Isodecyl Acrylate

Analog	Hazard Concern	Basis for Concern	Concern Level
	Dermal Sensitization	Induced sensitization in mice	Moderate*
	Dermal Sensitization	Induced sensitization in humans	High*

*** Although there is moderate to high concern for dermal sensitization, this endpoint may not contribute to the overall hazard concern for isodecyl acrylate for purpose of PBT score regulation. Warnings should be included in MSDS.**

Step 5. Guidance in Assigning EPA Concern Levels

Concern Level	Criteria	Exposure and Risk Assessment Needed?
HIGH	Evidence of adverse effects in human populations Conclusive evidence of severe effects in animal studies	Yes
MODERATE	✓ Suggestive animal toxicity studies for chemical or analog(s) Class known to produce toxicity	Yes
LOW	No concern identified	No

Hands on Training Session: Non-Cancer Toxicity Assessment

Example 1	Example 2	Example 3