8 Non-Cancer Human Health Hazard Screening Protocol

Assessing Non-Cancer Effects

Currently OPPT does not have computerized methods or models for estimating non-cancer human health effects. There are other models that are commercially available, however OPPT does not use them to evaluate and regulate chemicals under TSCA. OPPT scientists base their evaluations on experimental data for the compound of interest. If data are not available on the chemical of interest then data on closely related analogs are evaluated to predict hazards. Various types of toxicity studies are considered including acute, subchronic, and chronic toxicity experimental studies. This chapter discusses the step-wise process followed by OPPT scientists when evaluating potential non-cancer human health hazards of new chemical submissions under TSCA.

Factors to Consider in Health Hazard Assessment

The major factors that must be considered when conducting a health hazard assessment are:

- Chemical toxicity data,
- Analogue toxicity data,
- Chemical Class toxicity data,
- Mechanistic considerations, and
- Professional judgment.

8.1 Non-Cancer Health Hazard Endpoints

8.1.1 Endpoints Generally Used to Assign Hazard Concern

OPPT assigns a human health hazard score, and supports the Toxicity call in the PBT score, by evaluating endpoints that are typically associated with numeric no adverse effect levels (NOAEL) or lowest adverse effect levels (LOAEL). These endpoints include:

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)

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

8.1.2 Other Important "Non-quantitative" Endpoints

There are other significant endpoints not associated with NOAELs or LOAELS and not used to support the Toxicity call in the PBT score. These endpoints provide non-quantitative data (positive, negative, severe, etc) and cannot be used to support a quantitative risk assessment like the endpoints listed above. These "non-quantitative" endpoints include:

- Mutagenicity,
- Skin Sensitization, and
- Irritation (eye, skin, respiratory).

Concerns for these endpoints should always be identified in material safety data sheet (MSDS) or other safety documents. These endpoints should always be considered when evaluating potential exposure pathways and possible personal protective equipment (PPE) for workers.

8.2 Five Steps in Conducting a Non-Cancer Hazard Screen

The five steps in conducting a non-cancer hazard assessment that are discussed below include:

Step 1: Locate relevant toxicity data on the substance itself and report the information in the Sustainable Futures Summary Assessment Worksheet.

Step 2: Determine if the chemical is a member of a category known to be associated with hazards.

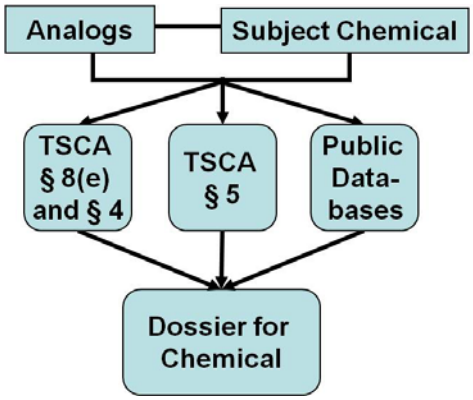
Step 3: Determine if the chemical belongs to a class often associated with local or systemic effects.

Step 4: Identify appropriate analog(s) with data if data on PMN chemical is not sufficient to allow for toxicity characterization. Analog data should never be used in place of measured data from properly conducted laboratory studies on the chemical itself.

Step 5: Assign a HAZARD concern level (Low, Moderate, or High).

8.2.1 Step 1: Search for Toxicity Data on the Chemical of Interest

The general search strategy used by OPPT is shown at the right. All relevant data are collected from TSCA submissions under Section 8(e) (Substance May Present Risk), Section 4 (Chemical Testing), and Section 5 (New Chemicals). These Sections of TSCA are summarized at http://www.epa.gov/lawsregs/laws/tsca.html.



Publicly available data sources are listed in Appendix C of this manual. Some of the major sources include:

- ChemIDplus and ChemIDplus Lite http://chem.sis.nlm.nih.gov/chemidplus/
- CompTox (Computational Toxicology Research) http://www.epa.gov/comptox/#
- DSSTox (Distributed Structure-Searchable Toxicity) Database Network http://www.epa.gov/ncct/dsstox/
- eChemPortal OECD Global Portal to Information on Chemical Substances http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en
- ECOTOX (ECOTOXicology) Database provides single chemical toxicity information for aquatic and terrestrial organisms EPA ORD http://cfpub.epa.gov/ecotox/
- HPVIS (High Production Volume Information System) http://www.epa.gov/hpvis/
- Integrated Risk Information System (IRIS) http://www.epa.gov/iris/
- International Agency for Research on Cancer (IARC) http://www.iarc.fr/
- International Uniform Chemical Information Database (IUCLID) http://iuclid.eu/
- Merck Index http://themerckindex.chemfinder.com/TheMerckIndex/Forms/Home/ContentArea/Home.aspx
- National Toxicology Program (NTP) http://ntp.niehs.nih.gov/
- ToxFAQs™ http://www.atsdr.cdc.gov/toxfaqs/index.asp
- TOXNET http://toxnet.nlm.nih.gov/
- TSCATS (Toxic Substance Control Act Test Submission Database) http://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm

Important Study Details to Record

When toxicity studies are located on the chemical of interest it is important to record the critical details from the studies. These specific details include:

- Hazard concern that is identified
- Type of study (e.g., 2-generation reproductive toxicity study, 28-day repeated-dose study)
- Study duration
- Animal species
- 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
- References (include who conducted the study, study date, study code number, etc.)

Important Factors to Consider when Evaluating Available Data

It is important to remember that finding NO data is NOT equivalent to finding negative (indicative of low toxicity) data. Hazard concerns are always based on scientific judgment and if conflicting data exist, a weight-of-evidence approach should be used to support conclusions.

Chemical Absorption

Absorption is necessary for some chemicals to exert toxic effects. Absorption may vary by exposure route. For example the same chemical may be poorly absorbed through the skin but well absorbed through the lung and GI tract. Absorption can be estimated using measured data (chemical or analog) or based on physical / chemical properties such as molecular weight, Kow, water solubility, and physical state (solid, liquid, gas).

It may be necessary to extrapolate across exposure routes. An example is when the exposures of concern occur by dermal contact and the only toxicity data available are oral studies. In cases like this the assessor can compare the relative absorption rates for each route and adjusting the effects level (NOAEL or LOAEL) as necessary. For example, if the oral systemic toxicity NOAEL is 100 mg/kg/bw, workers are exposure by dermal contact, absorption rates are via GI 100% and via skin 50% you adjust the NOAEL by multiplying by ratio of 100/50 x NOAEL. Essentially the dose through the skin would have to be twice that of the dose through the GI to reach the same level seen in the oral NOAEL. This method does have inherent uncertainties and the assumptions should be clearly explained in the assessment.

Extrapolation across exposure routes is NOT appropriate or relevant if portal of entry effects are seen such as when the chemical causes irritation.

Dermal Absorption

Generally the following types of chemicals absorb well through the skin:

- Liquid chemicals with log P values from 2 to 4,
- Liquid chemicals with MW <500,
- Formulated products with surfactants and detergents, and
- Small molecular weight amines and carboxylic acids.

The following types of chemicals generally absorb poorly through the skin:

- Solids (have increased absorption if the melting point is at approximately skin temperature),
- Chemicals with MW >500, and
- Charged chemicals and salts.

Other Important Properties to Consider

When evaluating toxicity studies it is important to consider other chemical-specific properties contributing to toxicity of the chemical of interest including:

- Biological activity – chemical is known to be active in living organisms often in a dose-dependent manner;
- Metabolism – does the chemical metabolize into other potentially toxic or reactive metabolites;
- Bioactivation – even if the chemical is relatively inactive when absorbed does it become reactive through metabolic process;
- Pharmacokinetics – how does the organism react to the chemical including absorption, metabolism, distribution, and biotransformation; and
- Distribution – could the chemical move from site of absorption to become localized in certain tissues?

Toxicity studies on appropriate analogs could mitigate the need to consider these factors separately.

NOTE: The search for toxicity data on isodecyl acrylate is discussed at the end of this chapter.

8.2.2 Step 2: Determining if a Chemical Belongs to a Category of Concern

U.S. EPA New Chemical Category Report

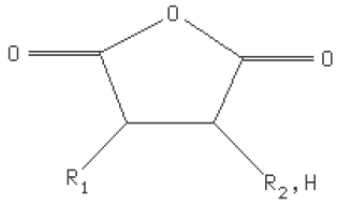
After more than twenty-five years of experience in the review of PMNs OPPT has developed enough experience with certain groups of chemicals which have similar chemical and toxicological properties to be able to group them into categories. Each category statement describes the molecular features a new chemical must have to be included in the category, the boundary conditions (molecular weight, equivalent weight, the log of the octanol/water partition coefficient (log P), or water solubility) that would determine inclusion in (or exclusion from) the category, and standard hazard and fate tests to address concerns for the category. Compiling these category descriptions has allowed OPPT and PMN submitters to benefit from the accumulated data and past decisions made on each category.

The Chemical Categories Report currently includes more than 50 categories. It is important to note that the categories included are not necessarily those with highest hazard concerns but those for which sufficient history has been accumulated so that hazard concerns and testing recommendations can be described with little variation from chemical to chemical.

Here is an example of a Category Statement for Anhydrides, Carboxylic Acid

Category: Anhydrides, Carboxylic Acid Human Health

Definition. Any molecular structure containing one or more carboxylic acid anhydride groups is considered to be a member of the category for new chemical purposes . . . .



Hazard Concerns. Carboxylic acid anhydrides are of concern for potential pulmonary sensitization based on data for phthalic, trimellitic, isopropylidene bis(phthalic), and sulfonyl bis(phthalic) anhydrides . . . .

Boundaries. Structures with a carboxylic acid anhydride equivalent weight of >5,000 are presumed not to pose a hazard under any conditions . . . .

General Testing Strategy
The following tests are usually prescribed for carboxylic acid anhydrides found to pose a potentially unreasonable risk . . . .

8.2.3 Step 3: Determine if the Chemical Belongs to a Class Known to Cause Local or Systemic Effects

Appendix D of this document describes "Chemicals Causing Local Effects or Chemicals Causing Systemic Effects". This list is not intended to be exhaustive, but is provided for informational purposes to assist in screening level evaluation of chemicals. Here is an example of class information included in Appendix D:

Immunotoxicity (Immunosuppression / Autoimmunity) Classes of compounds which may manifest immunotoxicity include:

- Heavy metals
- Organic solvents
- Certain Pesticides
- Polyhalogenated aromatic hydrocarbons

8.2.4 Step 4: Identify Appropriate Analog(s) with Measured Data

If measured data are not available on the chemical of interest, the next step is search for close chemical analogs that have measured data so that you can predict toxicity of the untested chemical based on its structural similarity to tested chemicals. Substructure or similarity searches can be conducted in the publicly available databases that allow substructure searches such as these two sources below listed in Appendix C of this document:

ACToR (Aggregated Computational Toxicology Resource) available on the EPA ORD's CompTox (Computational Toxicology Research) web site allows structure searching. http://actor.epa.gov/actor/faces/SearchByStructure.jsp

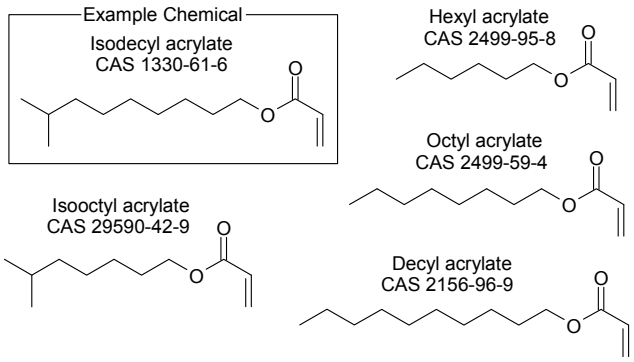
ChemIDplus and **ChemIDplus Lite** contain numerous chemical synonyms, structures, regulatory list information, links to other databases containing chemical information, and allows substructure searching. NIH http://chem.sis.nlm.nih.gov/chemidplus/

DSSTox (Distributed Structure-Searchable Toxicity) Database Network provides a public forum for publishing downloadable, structure-searchable, standardized chemical structure files associated with chemical inventories or toxicity data sets of environmental relevance. http://www.epa.gov/ncct/dsstox/

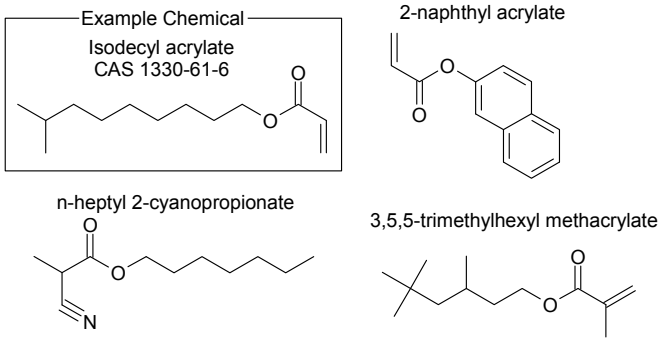
Characteristics of an Appropriate Analog

Examples of appropriate analogs for isodecyl acrylate are shown at right. The size of the analog and the functional groups present in the analog are representative of the chemical of interest, and there are no biologically active groups found in the analog that are NOT found within the chemical of interest.

EXAMPLES OF GOOD ANALOGS



EXAMPLES OF POOR ANALOGS



Different mechanistic pathways are expected for these chemicals.

Characteristics of a Poor Analog

Examples of poor analogs for isodecyl acrylate are shown to the left. The size of the analog and the functional groups present in the analog are NOT representative of chemical of interest, and there are biologically active groups present in the analog that are NOT found within the chemical of interest. These chemicals are expected to have mechanistic pathways that differ from those of isodecyl acrylate.

8.2.5 Step 5: Assign a Hazard Concern Level

Hazard Concern	Definition Based on Experimental Data
Low	No basis for concern identified or systemic toxicity with NOAEL > 1000 mg/kg/day; only minor clinical signs of toxicity; liver and/or kidney weight increase or clinical chemistry changes with LOAEL ≥ 500 mg/kg/day
Moderate	Suggestive animal studies for chemical or analog(s) or chemical class known to produce toxicity or organ pathology (gross and/or microscopic) with LOAEL < 500 mg/kg/day; clinical chemistry changes and organ weight changes at < 500 mg/kg/day; NOAEL < 1000 mg/kg/day
High	Evidence of adverse effects in humans or conclusive evidence of severe effects in animal studies. Death, organ pathology (microscopic) at LOAEL ≤ 100 mg/kg/day; multiple organ toxicity; NOAEL ≤ 10 mg/kg/day.

A complete risk assessment is necessary if the hazard concern is identified as high or moderate. Low hazard chemicals are dropped from further review because by their nature they will not result in risk (remember risk = hazard X exposure).

One exception to the rule of “no risk assessment needed if hazard concern is low” is PMNs that meet the Exposure-Based criteria. TSCA section 5(e) gives EPA the authority to regulate PMNs with production volumes (PVs) ≥ 100,000 kg/year based on either the potential risk presented by the substance ("risk-based") or the potential for substantial production volume and substantial or significant human exposure or substantial environmental release ("exposure-based"). Action under section 5(e) for a new chemical substance is taken based on either or both of these authorities. The guidelines to assist in identifying new chemical substances received as PMNs which would meet the "exposure-based" finding are explained on the New Chemicals Exposure-Based Policy web page. The web page also has a link to Exposure-based testing, which is usually required via a negotiated section 5(e) consent order.

8.3 Search for Toxicity Data on Isodecyl Acrylate

A search online for toxicity data on isodecyl acrylate (CAS RN 1330-61-6) yielded the following results for the non-cancer health effects endpoints contained in the Sustainable Futures Summary Assessment Worksheet section on **NON-CANCER HEALTH EFFECTS** (shown below). Here are links to the references located:

IUCLID Data Set for an analog isooctyl acrylate

HPVIS http://www.epa.gov/chemrtk/hpvis/index.html has data on isodecyl acrylate and HPV Hazard Characterizations on the HPV web site has HPV Final Test Status and Data Review for 1330-61-6 *NOTE: This data source was not available when the Sustainable Futures Summary Assessment Worksheet for the example chemical isodecyl acrylate was first developed. These data are not included in the SF Assessment in this document. It was decided that the assessment would not lose any value as an example if the data were not included.*

The following TSCA sec. 8(e) data sources were obtained by visiting the OPPT Nonconfidential Information Center (NCIC) (also referred to as the public docket) which is the official repository and administrative record for submitted TSCA Sections 4 and 8 studies as well as documents related to EPA's testing action development and risk assessment and risk management activities. The NCIC is open from 8:30 am to 4:30 pm Monday through Friday EST, excluding legal holidays, and is located in Room B102, EPA West, 1301 Constitution Avenue NW, Washington, DC 20004. Internet address: oppt.ncic@epa.gov

8(e)-1524 TSCATS Database. TERATOLOGY SCREEN IN RATS (C190, C-181, C-183, C-236, C-253, C-254, C-255, C-256, C-257, C-258, C-259) (FINAL REPORT) WITH ATTACHMENTS AND COVER LETTER. U.S.EPA/OPTS Public Files: Fiche#: OTS0534620, Doc#: 88-920000170

8(e)-11424 TSCATS Database. INITIAL SUBMISSION: MOUSE EAR SWELLING TEST WITH OCTYL DECYL ACRYLATE WITH COVER LETTER DATED 10/27/92; U.S.EPA/OPTS Public Files: Fiche#: OTS0571362, Doc#: 88-920009705.

8(e)-14572 TSCATS Database. INITIAL SUBMISSION: ACRYLATE DE N-OCTYLE, SKIN SENSITIZATION TEST IN GUINEA-PIGS (MAXIMIZATION METHOD OF MAGNUSSON, B. AND KLIGMAN, A.M.), with cover letter dated 10/15/99; U.S.EPA/OPTS Public files: Fiche#: OTS0559819, Doc#: 88-000000012.

8(e)-3774 TSCATS Database. INITIAL SUBMISSION: LETTER CONCERNING INFORMATION ON THE CHEMICAL SUBSTANCE HEXYL ACRYLATE WITH ATTACHMENTS (SANITZED); U.S.EPA/OPTS Public Files: Fiche#: OTS0536468, Doc#: 88-000024168.

Chemical Carcinogenesis Research Information System (CCRIS) has data reports on the analogs hexyl acrylate (2499-95-8) and isooctyl acrylate (29590-42-9)

8.4 Entering Data in the Sustainable Futures Worksheet

The data identified are entered in the Sustainable Futures Summary Assessment Worksheet, Non-Cancer Health Effects section, shown below.

NON-CANCER HEALTH EFFECTS:	
Acute Toxicity	Low by analogy to isooctyl acrylate, based on acute LD50 >5000 mg/kg for rats by oral gavage (IUCLID 29590-42-9)
Irritation	Positive by analogy to isooctyl acrylate (Gordon et al. 1991)
Skin Sensitizer	Positive based on dermal sensitization of analogs in lab animals and humans (8e-11424, 8e-14572, 8e-3774)
Reproductive Effects	No relevant data identified
Developmental Effects	Moderate by analogy to isooctyl acrylate, which produced skeletal variations in the offspring of rats treated orally during pregnancy; LOAEL = 1,000 mg/kg-day (8e-1524)
Immune System Effects	No relevant data identified
Neurotoxicity	No relevant data identified
Genotoxicity	Negative by analogy to isooctyl acrylate and hexyl acrylate (CCRIS)
Mutagenicity	No relevant data identified
Systemic Effects	No relevant data identified
Overall Hazard Concern for Non-Cancer Health Effects	Moderate

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