3 Getting Started by Identifying Existing Data

The data search process described here simply is:

First: Does this chemical belong to a class of chemicals that is known to present concerns?
Second: Can I find publicly available measure data?

Remember that experimental / measured data from a well conducted laboratory study should *always* be used in preference to model estimations. Screening models, like those in Sustainable Futures / P2 Framework, are constructed with conservative defaults and give conservative estimates. Screening models can be used when data are unavailable or to supplement available data.

3.1 Initial Data Search

3.1.1 EPA New Chemical Categories Report

As detailed at http://www.epa.gov/opptintr/newchems/pubs/chemcat.htm, in the late 1980s many submitted PMNs went through a highly resource-intensive detailed review (a "standard review") by EPA. EPA has been able to streamline the process after accumulating extensive experience with chemical and toxicological properties of numerous chemical groups. Chemicals with shared properties are grouped into categories, enabling both PMN submitters and EPA reviewers to benefit from the accumulated data and knowledge of previous decisions. Currently, there are 56 categories. Establishing Chemical Categories has streamlined the new chemical review process. Based on current information, the Agency takes action to control potential risks to health or the environment on approximately 10 percent of the PMNs submitted. Only 2-3 percent of the total number of PMNs submitted (20-30 percent of the above 10 percent) now undergo a standard review, while the remaining 7-8 percent are identified as members of the New Chemicals Program chemical categories.

Chemical substances described in the categories are not necessarily those of greatest concern to the Agency, but are the chemicals for which sufficient history has been accumulated so that hazard concerns and testing recommendations are well known and vary little from chemical to chemical within the category. Of course, the categories are not intended to be a comprehensive list of all substances that may be subject to further action in the New Chemicals Program.

EPA will periodically update the Chemical Categories Report. The following is a list of chemical categories included in the most recent version dated August 2010.

- Acid Chlorides
- Acid Dyes and Amphoteric Dyes
- Acrylamides
- Acrylates/Methacrylates
- Aldehydes
- Aliphatic Amines
- Alkoxysilanes
- Aluminum Compounds
- Aminobenzothiazole Azo Dyes
- Anhydrides, Carboxylic Acid
- Anilines, Dianilines
- Anionic Surfactants
- Azides
- Benzotriazoles
- Benzotriazole-hindered phenols
- Boron Compounds

- Cationic Dyes
- Cationic (quaternary ammonium) surfactants
- Cobalt
- Diazoniums
- Dichlorobenzidine-based Pigments
- Dithiocarbamates
- Epoxides
- Esters
- Ethylene Glycol Ethers
- Hydrazines and Related Compounds
- Hindered Amines
- Imides
- Diisocyanates
- ß-Naphthylamines, Sulfonated
- Lanthanides or Rare Earth Metals
- Neutral Organics
- Nickel Compounds
- Nonionic Surfactants
- Organotins
- Peroxides
- Persistent, Bioaccumulative, and Toxic (PBT) Chemicals
- Phenolphthaleins
- Phenols
- Phosphates, Inorganic
- Phosphinate Esters
- Polyanionic Polymers (& Monomers)
- Polycationic Polymers
- Polynitroaromatics Respirable, Poorly Soluble Particulates
- Rosin
- Stilbene, derivatives of 4,4-bis(triazin-2-ylamino)-
- Thiols
- Substituted Triazines
- Triarylmethane Pigments/Dyes with Non-solubilizing Groups
- Vinyl Esters
- Vinyl Sulfones
- Zinc, Soluble Complexes
- Zirconium Compounds

Each Categorical Description includes the following information, summarized from the Acid Chlorides Chemical Category Description.

Category: <u>Acid Chlorides</u> Environmental Toxicity

Definition. This category includes carbonyl chlorides (R-C[=O]Cl) and sulfochlorides (R-S[=O]Cl) where R may be either aliphatic or aromatic. Toxicity is limited by the fact that this class of compounds hydrolyzes and also, probably, if the octanol/water partition coefficient (Kow) is above a log Kow value of 8. It has been assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will probably be excluded in the future once this assumption is confirmed with toxicity information. However, toxicity information is needed to confirm this assumption.

Hazard Concerns. Acute toxicity for three members of this category are available and all have been shown to be moderately toxic to aquatic organisms (i.e., acute toxicity values between 1 and 100 mg/L): benzoyl chloride, fish 96-h LC50 = 35.0 mg/L, an aromatic dicarboxyl dichloride, fish 96-h LC50 = 6.2 mg/L, and benzene sulfochloride, fish 48-h LC50 = 3.0 mg/L. All of these tests have been done with the static method using nominal concentrations. It is unclear just how acid chlorides are toxic to aquatic organisms. It is known that acid chlorides hydrolyze to the carboxylic/sulfonic acid and HCl. It is not known if the toxic effect is the result of (1) absorption of the acid chloride and hydrolysis within the membrane, or (2) the HCl produced from the hydrolysis. It is known that the carboxylic/sulfonic-acid hydrolysis products are of low toxicity.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on Kow and MW when enough information is obtained. In general, when the log Kow value is < 8, the environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log Kow is > 8, testing will be requested until enough information is obtained to determine whether these compounds will have no toxic effects at saturation. Generally, members of this category will have MWs of less than 1000 but testing of members with a MW > 1000 may be requested to confirm whether acid chlorides have to be absorbed to be toxic.

General Testing Strategy. The testing strategy for acid chlorides will consist of two steps. (1) Hydrolysis as a function of pH at 25 °C (40 CFR 796.3500) will be recommended. Depending on the outcome of this

environmental fate testing and reassessment, (2) the aquatic base set of environmental toxicity tests will be recommended for aquatic exposures with the fish acute toxicity test done once or twice.

Chronic toxicity testing for aquatic organisms include: the fish early life state toxicity test, the daphnid partial life cycle toxicity test and the algal toxicity test.

The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm acute toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.
October, 1990

3.1.2 Chemicals Known to Cause Local and Systemic Effects

These lists were compiled by EPA scientists and are provided here are for illustrative purposes – these lists are not intended to be comprehensive.

CHEMICALS CAUSING LOCAL EFFECTS

Eye Effects

- Chemical properties/considerations relevant to eye effects include:
- Acidity
- Basicity/alkalinity
- Chemical burns (isocyanates, mustards)
- Interaction with proteins (metal salt deposition, quinones, etc.)
- Mechanical abrasions
- Solvent effects
- Surfactancy

Toxicity, Irritation, Corrosion to the Skin Consider:

- Acidity
- Basicity/alkalinity
- Chemical burns
- Lipophilicity
- Mechanical abrasions
- Solvent effects
- Surfactancy

Dermal/Contact Sensitization Consider:

- Electrophilic or nucleophilic groups that could haptenize protein through covalent modification, for example: Aldehydes, ketone, codicils, quinones, other conjugated, unsaturated functional groups, epoxy groups.
- Structural similarities to classes of contact allergens (parent chemical) or impurities belonging to known classes of contact allergens, for example: Antibiotics, Chlorinated antiseptics, Dyes (azo, amine), Formaldehyde releasers, Mercurials, Metals (nickel, chromium, cobalt), Natural products (plant rosins, balsams), and Preservatives.

Photo-toxicity and Photosensitization Consider:

- Chemical structures that are UV absorbing (such as highly conjugated aromatics), for example: Furocoumarins, Polycyclic aromatics, and Porphyrins.
- Structural similarity to systemic agents that cause photoreactions, for example: Non-steroidal anti-inflammatory agents, Sulfonamides, and Tetracyclines.

Local Toxicity to the Gastrointestinal Mucosa Consider:

- Local effects in the G.I. tract will be mediated by solubility, irritation, corrosivity, and local metabolism.
- For irritant and corrosive effects, consider the factors elaborated above for eye and skin.
- For metabolic activation, consider the factors elaborated upon below.

Toxicity to the Respiratory System Consider:

- Irritants that may cause asthma, a disease characterized by (1) airway obstruction that is reversible, (2) airway inflammation, and (3) airway hyperresponsiveness. Classes of compounds that can cause asthma include: Aldehydes, Anhydrides, Isocyanates, and Metals.
- Irritant materials may cause upper airway reactivity (e.g., bronchitis)
- Water soluble, reactive materials (e.g., formaldehyde) may cause nasal or upper airway toxicity an/or irritation
- Particulates and fibers of a particle size that results in deep lung deposition may potentially cause chronic lung injury. Such injury is mediated by inflammatory responses, lung overload, and sustained cell turnover. Examples include: Fibers with a certain length to width ratio (e.g., asbestos), and Particulate dusts (silica, clays, talcs).
- Other classes of respiratory toxicants include: Ammonia and volatile, basic amines, Isocyanates, Metal carbides, Metal oxides, Metal dusts and fumes, Nitrogen oxides, Surfactants, and Transition metals, arsenic, beryllium.

Systemic Toxicity Mediated by Intrinsic Chemical Reactivity or Biotransformation to Reactive Toxicants

Systemic organ toxicity is frequently mediated by the presence of reactive functional groups (whether present in the parent compound or introduced via biotransformation). Reactive compounds or metabolites may exert toxic effects by modification of cellular macromolecules (structural and functional cellular proteins, DNA). This can result in destruction or dysfunction of the target molecules. In addition, covalent modification of target molecules which are covalently modified may render them "foreign" or antigenic (capable of eliciting an immune response). DNA-reactive chemicals have genotoxic potential.

Toxicity Caused by Electrophiles Structural "Red flags" for chemicals containing electrophilic centers include:

- Acyl halides
- Aryl halides
- Azides, – and S-mustards
- Epoxides, strained rings (e.g., sultones)
- Nitroso groups
- Polarized, conjugated double bonds (e.g., quinones, a, ß unsaturated ketones, esters, nitriles)

Functional groups which undergo metabolism to electrophilic centers include:

- Alkyl esters of sulfonic or phosphonic acids
- Aromatic compounds with functional groups that can yield benzylic, aryl carbonium or Nitronium ions
- Aromatic nitro, azo or amine groups
- Conjugated aromatics that undergo epoxidation

Toxicity Caused by Free Radical Formation Compounds which can accept or lose electrons can mediate free radical formation through redox cycling. Structural "Red flags" include:

- Aminophenols

- Catechols, quinines, hydroquinones
- Metal complexes (iron and chromium)
- Peroxides
- Phenothiazines
- Polycyclic aromatics

Systemic Toxicity Associated with Receptor-Mediated Mechanisms Some compounds exert toxicity through substitution for known or unknown tissue receptor ligands. Classes of compounds that could exert toxicity though such mechanisms include:

- Environmental estrogens (putative hormone receptor ligands)
- Fibrates, phthalates (peroxisome proliferator receptor agonists)
- Polychlorinated aromatics (Ah receptor ligands)
- Retinoids (retinoic acid receptor ligands)

Target Organ and Functional Toxicity

Toxicity to the Liver As the primary organ of biotransformation, the liver is susceptible to toxicity mediated by chemical reactivity, as described above. Other agents with toxicity to the liver include:

- Chlorinated hydrocarbons
- Metals, etc.

Toxicity to the Kidney Classes of compounds that are potential nephrotoxins include:

- Amines
- Certain classes of systemic drugs
- Halogenated aliphatic hydrocarbons
- Heavy metals
- Herbicides
- Insoluble salts that precipitate in the kidney (e.g., calcium complexes)
- Mycotoxins
- Organic solvents

Toxicity to the Respiratory System Effects of inhaled respiratory toxicants were addressed above.

Neurotoxicity Chemicals/Classes of compounds which may manifest neurotoxicity include:

- Acids and thioacids
- Arylamide and related substances
- Acrylamides
- Alcohols
- Aliphatic halogenated hydrocarbons
- Alkanes
- Aromatic hydrocarbons
- Carbon disulfide and organic sulfur -containing compounds
- Carbon monoxide
- Catecholamines
- Certain classes of systemic drugs
- Chlorinated solvents
- Cyanide
- Cyclic halogenated hydrocarbons
- Environmental estrogens
- Ethylene oxide
- Gamma-diketones
- Inorganic nitrogenous compounds
- Isocyanates
- Ketones

- Lead
- Mercury compounds
- Metals and metalloids other than mercury and lead
- Nitriles
- Organic nitrogens
- Organophosphates
- Organophosphorus compounds
- Organotins
- Certain Pesticides
- Phenols and related substances
- Phosphorus
- Protein cross-linking agents
- Psychoactive drugs
- Pyridines (e.g., MPTP)

CHEMICALS CAUSING SYSTEMIC EFFECTS

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

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

Genetic Toxicity Classes of compounds that manifest genetic toxicity are often electrophilic agents capable of modifying DNA. Such agents may act as gene mutagens, clastogens or aneugens. Compounds that can intercalate into DNA, free radical generators or chemicals that induce oxidative damage may also act as gene mutagens, clastogens or aneugens.
Mutagenic structural alerts include:

- Acrylates and methacrylates
- Aliphatic or aromatic nitro groups
- Aliphatic or aromatic epoxides
- Alkyl hydrazines
- Alkyl esters of phosphonic or sulfonic acids
- Alkyl aldehydes
- Aromatic ring N-oxides
- Aromatic azo groups
- Aromatic and aliphatic aziridynyl derivatives
- Aromatic alkyl amino or dialkyl amino groups
- Aromatic and aliphatic substituted alkyl halides
- Aromatic amines and N-hydroesters of aromatic amines
- Carbamates
- Chloramines
- Halomethanes
- Monohaloalkanes
- Multiple-ring systems
- N-methylol derivatives
- Nitrogen and sulfur mustards
- Nitroso compounds
- Propiolactones and propiosultones
- Vinyls and vinyl sulfones

Reproductive Toxicity Classes of compounds which may manifest reproductive toxicity include:

- Alcohols

- Alkylating agents
- Chlorinated hydrocarbons
- Certain Fungicides
- Certain Herbicides
- Hydrazines
- Certain Insecticides
- Metals and trace elements
- Nonylphenols
- Plastic monomers
- Solvents (e.g., glycol ethers, benzene, xylenes)
- Steroids or steroid receptor ligands

Developmental Toxicity Classes of compounds which may manifest developmental toxicity include:

- Acrylates
- Androgenic chemicals
- Anilines
- Boron containing compounds
- Chelators
- Chlorobiphenyls
- Compounds which have potential for mutagenicity and oncogenicity
- Epoxides
- Lead
- Lithium
- Mercury
- Nitrogen Heterocyclic compounds
- Phthalates
- Retinoids
- Salicylates
- Short-chain branched carboxylic acid (e.g., valproic acid)
- Small benzenes
- Synthetic steroids (e.g., diethylstibesterol)
- Triazines
- Vinyl groups

Blood Toxicity Classes of compounds which may manifest developmental toxicity include:
Simple aromatic amines and azo dyes that undergo azo reduction to release aromatic amines

3.1.3 Search for Publicly Available Measured Data

Remember that before using any screening level model, a thorough search for measured data should be conducted. Measured data should be used if available instead of estimated (predicted) data because estimation methods, such as these screening models, contain inherent uncertainties. Appendix C of this document lists publicly-available sources for these types of data:

- Physical / Chemical Property and Environmental Fate
- Human Health Hazard
- Environmental Hazard
- Environmental Release
- Exposure Parameter and Population

The data sources included in this document are not intended to represent the only or best sources of data available. Readers are strongly encouraged to conduct their own searches for data.

The URLs of certain Internet sites are listed in this document to provide information to readers. Readers are cautioned that due to the dynamic nature of the Internet, these URLs may have been changed from the time of the writing of this document. In case a URL is no longer correct, the user is advised to use any of the publicly available Internet search engines to locate the correct URL.

3.2 Estimated Data are Not Subject to TSCA Sec. 8(e) Reporting

Anyone using the Sustainable Futures methods should be aware that estimations of a chemical's properties or toxicity made using screening level models and methods *are NOT subject* to TSCA §8(e) reporting. The June 3, 2003 TSCA 8(e) Guidance (68FR33129) states that knowledge of a "substantial risk of injury to health or the environment" should be reported to the Agency. However, modeling information *alone* is not reportable under TSCA §8(e) or under voluntary "For Your Information" (FYI) submissions. For example, if an EPISuite™ model run indicates a chemical is likely to migrate into and contaminate ground water, or if an OncoLogic™ evaluation indicates a chemical may cause cancer, these results alone are not reportable under TSCA §8(e). For more information on TSCA §8(e) reporting requirements see http://www.epa.gov/oppt/tsca8e/.

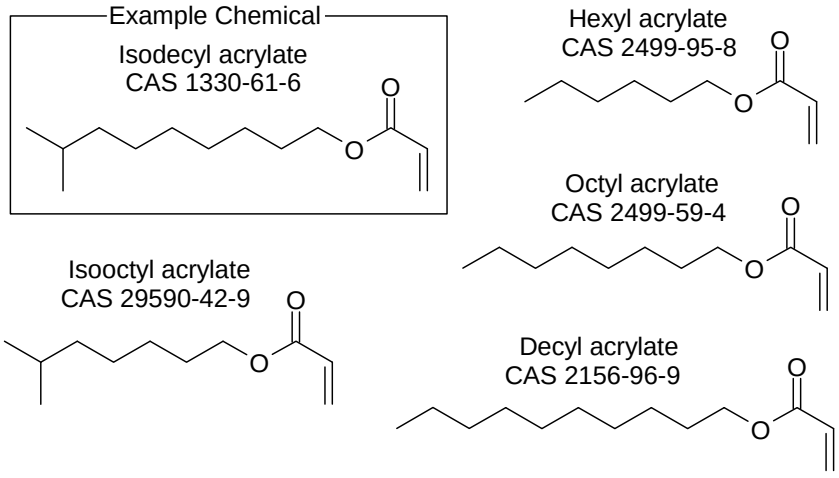
3.3 Analog Searching Techniques

It's an obvious statement to say that, even if it has data, an analog is useless if it is not a close chemical analog, however finding a "good" analog can sometimes be a challenge.

3.3.1 What Makes a Good Analog?

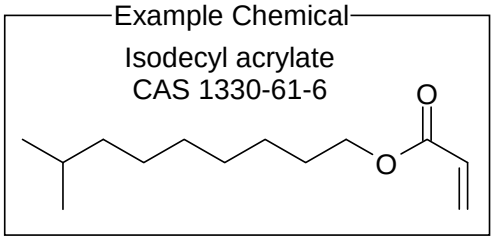
If data are not available on the chemical of interest, the next step is searching for close analogs that have data. The first question is "what makes a good analog"? Good analogs are similar both in size and in type / number of functional groups (substructures) present.

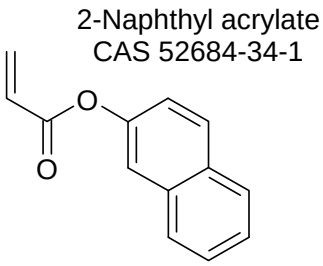
Characteristics of an Appropriate Analog
Both the molecular size and functional groups present are representative of the chemical of interest. Analog does not contain biologically active groups that are NOT represented on chemical of interest. Shown below are good analogs for Isodecyl acrylate. The mechanisms of action for these good analogs will be similar to that of Isodecyl acrylate.

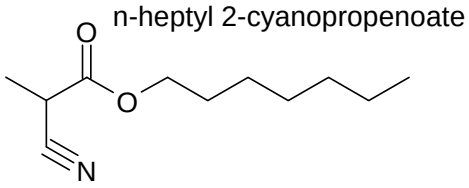


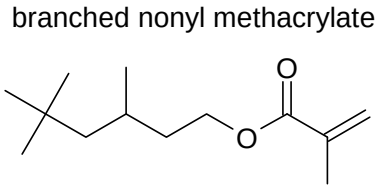
Characteristics of a Poor Analog

The molecular size and functional groups present in the analogs shown below are NOT representative of the chemical of interest. The analogs contain functional groups that are NOT representative of the chemical of interest, but not expected to be representative of toxicity (e.g., steric hindrance)









3.3.2 Publicly Available Databases that Allow Substructure Searching

Some of the publicly available databases that allow substructure searching include:

- CHEMIDplus http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp
- CHEMFINDER - Searching ChemBioFinder.Com is FREE, however users must login or register. http://www.cambridgesoft.com/databases/login/?serviceid=128
- TSCATS http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384
- Analog Identification Method (AIM) http://aim.epa.gov. See Chapter 9 of this document for more information on using AIM.

3.4 Searching for Measured Data on the Sample Chemical, Isodecyl Acrylate

IMPORTANT NOTE: When the Sustainable Futures Summary Assessment for the sample chemical Isodecyl acrylate (CAS RN 1330-61-6) was first developed for training, many of the currently available on-line data sources mentioned below were not available. The major data sources located then were found in TSCATS and obtained from the EPA TSCA Public Docket. It was decided that the current SF assessment on Isodecyl acrylate could still be a useful teaching tool without being updated to incorporate the newly located data.

Measured data for Isodecyl acrylate, CAS RN 1330-61-6 or for close analogs were located in the following sources:

ISODECYL ACRYLATE DATA

TOXNET http://toxnet.nlm.nih.gov/index.html located data in the following:

- TOXLINE Toxicology Literature Online 2 References on air sampling
- Hazardous Substances Data Bank HSDB http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
  http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@na+ISODECYL ACRYLATE
- ChemIDplus Chemical Identification/Dictionary:

File Locator

DSL	Domestic Sub. List of Canada
EINECS	EU Inv of Exist. Comm. Chem Sub
HSDB	Hazardous Substances Data Bank
Haz-Map	Occ. Exposure to Haz. Agents
PubChem	PubChem
PubMed	Biomedical Citations From PubMed
RTECS	Reg. of Toxic Eff. of Chem. Sub.
TOXLINE	NLM TOXLINE on TOXNET
TSCAINV	EPA Chem. Sub. Inventory

Internet Locator

CAMEO	NOAA CAMEO Chemicals
EPA Envirofacts	EPA Master Chemical Integrator
EPA HPVIS	EPA High Prod Vol Info System
EPA SRS	EPA Substance Registry System
SRC DATALOG	Syracuse Res. Corp. DATALOG

Superlist Locator

HPV	EPA High Production Vol. Chem.
MPOL	Marine Pollutants List

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

ACToR http://actor.epa.gov/actor/GenericChemical?casrn=1330-61-6

EPA's Substance Registry Services (SRS)
http://ofmpub.epa.gov/sor_internet/registry/substreg/searchandretrieve/advancedsearch/externalSearch.do?p_type=SRSITN&p_value=85035

ANALOG DATA
TSCATS http://java.epa.gov/oppt_chemical_search/ found seven records for analog isooctyl acrylate, CAS 29590-42-9

IUCLID Data Set for an analog isooctyl acrylate