Interpretive Assistance Document

for

Assessment of Discrete Organic Chemicals

Sustainable Futures Summary Assessment

Updated June 2013

This document was developed to help compile estimation results from U.S. EPA OPPT's P2 Framework Models (http://www.epa.gov/oppt/sf/tools/methods.htm) and is used by OPPT during Sustainable Futures (SF) training described at http://www.epa.gov/oppt/sf/meetings/train.htm. Participants in the voluntary SF Pilot Project are asked to submit the information as described in this training document along with their SF PMNs in their choice of format.

NOTE: Due to the dynamic nature of the Internet, the URLs listed in this document may have changed. A search using any of the publicly available search engines should locate the new URL.

Interpretive Assistance Document for Sustainable Futures Summary Assessments

This document was developed to help interpret estimations from the Sustainable Futures / P2 Framework models. Information is also included here which helps assign concern levels to estimations based on criteria from U.S. EPA's New Chemicals Program http://www.epa.gov/oppt/newchems/index.htm. The information set out in this document are not final Agency actions, but are intended solely to provide assistance with review. They are not intended, nor can they be relied upon, to create any rights enforceable by any party in litigation with the United States. EPA officials may decide to follow the guidance provided in this document, or to act at variance with the guidance, based on an analysis of specific circumstances. **PLEASE NOTE:** It is strongly suggested that any Sustainable Futures Summary Assessment provide an interpretation of model estimations relative to potential risk for the chemical being evaluated.

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Availability of Sustainable Futures / P2 Framework Models

EPISuite: http://www.epa.gov/opptintr/exposure/pubs/episuite.htm
ECOSAR: http://www.epa.gov/opptintr/newchems/tools/21ecosar.htm
Analog Identification Methodology (AIM): http://www.epa.gov/oppt/sf/tools/aim.htm
OncoLogic: http://www.epa.gov/oppt/newchems/tools/oncologic.htm
E-FAST: http://www.epa.gov/opptintr/exposure/pubs/efast.htm
ChemSTEER: http://www.epa.gov/opptintr/exposure/pubs/chemsteerdl.htm

NOTE: Due to the dynamic nature of the Internet, the URLs listed in this document may have changed. A search using any publicly available search engine with "EPA" and the model name in the search field will likely link you to the most recent model webpages.

PHYSICAL/CHEMICAL PROPERTIES AND ENVIRONMENTAL FATE ESTIMATIONS

EPISuite™ - Running the Models

The modules in EPISuite can be used by either running the EPI platform which automatically initiates a run of all models, or by running each individual module as a stand alone program. Please note, when running the programs individually as stand alone models, the user has the ability to change many default parameters that would otherwise be unavailable through the larger EPI platform.

EPISuite™ - Entering Data

The chemical structure can be entered using SMILES notation - or - if the chemical has a CAS Registry Number, the CAS numbers may be entered and the structure will be retrieved from the EPISuite™ built-in database if available. EPISuite™ also has a name look-up function and drawing template. If any experimental data are available for the chemical, then all data should be entered into the input screen for EPISuite™. Experimental data can be retrieved from the built-in PHYSPROP database in EPISuite™ by entering the chemical identifier, and choosing the PhysProp button in the upper left corner. For chemicals that are known liquids with no experimental MP data, enter 20 deg C as an experimental MP into the input screen for all EPISuite™ predictions.

EPISuite™ - Output Screen

The program can be run in two modes, and the option window to select a mode is located in the bottom right portion of the data entry screen. When the program is run in **"summary" mode**, the user will only be provided the quantitative /qualitative results for each endpoint with no supplemental information on how the endpoint was predicted. However, in **"full" mode**, the user will be given additional information regarding derivation of the prediction such as the fragments identified which are relevant to the endpoint, coefficient values, corrections factors, etc. For further explanation on the underlying methods used in EPISuite please refer to the EPISuite webpage at: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Interpreting EPISuite Results or Using Available Measured Data to Characterize Chemicals

Melting Point and Boiling Point - Estimated by MPBPWIN

MP < 25 deg C	Chemical is assessed as a liquid
MP > 25 deg C	Chemical is assessed as a solid
BP < 25 deg C	Chemical is assessed as a gas

Vapor Pressure - Estimated by MPBPWIN

$\geq 10^{-4}$	Chemical mostly in the vapor (gas) phase
10^{-5} - 10^{-7}	Chemical in the vapor and particulate phase
$\leq 10^{-8}$	Chemical mostly in the solid phase

For chemicals with a VP < 10^{-6}, there is low concern for inhalation exposure.

Water Solubility (mg/L) - Estimated by WSKOWWIN

> 10,000	Very soluble
> 1,000 - 10,000	Soluble
> 100 - 1,000	Moderate solubility
> 0.1 - 100	Slightly soluble
< 0.1	negligible solubility

Log K_{ow} (Log P) - Estimated by KOWWIN

< 1	Highly soluble in water (hydrophilic)
> 4	Not very soluble in water (hydrophobic)
> 8	Not readily bioavailable
> 10	Not bioavailable - difficult to measure experimentally

Henry's Law Constant (atm-m^3/mole) - Estimated by HENRYWIN

$\geq 10^{-1}$	Very volatile from water
10^{-1} - 10^{-3}	Volatile from water
10^{-3} - 10^{-5}	Moderately volatile from water
10^{-5} - 10^{-7}	Slightly volatile from water
$< 10^{-7}$	Nonvolatile

If experimental vapor pressure ***and*** water solubility data are available and entered as input data into EPISuite™, then the VP/Wsol estimate (instead of the bond or group estimation method) should be used.

Atmospheric Oxidation Half-life - Estimated by AOPWIN

≤ 2 hours	Rapid
2 hrs - ≤ 1 day	Moderate
> 1 day - ≤ 10 days	Slow
>10 days	Negligible
>2 days	Has potential for long range transport in air

Hydrolysis Rates - Estimated by HYDROWIN

- Only Esters, Carbamates, Epoxides, Halomethanes, and certain Alkyl Halides are estimated in HYDROWIN.

Biodegradation - Estimated by BIOWIN: 7 Models available in EPISuite™

1. Probability of Rapid Biodegradation: BIOWIN Linear and Nonlinear

> 0.50 Likely to biodegrade fast
< 0.50 *Not* likely to biodegrade fast

2. Expert Survey Biodegradation: Primary and Ultimate Degradation

Predicted Rating	**Time Required for Biodegradation**	**Predicted Rating**	**Time Required for Biodegradation**
5.0	Hours	3.0	Weeks
4.5	Hours - days	2.5	Weeks - months
4.0	Days	2.0	Months
3.5	Days - weeks	1.0	Longer

3. Biodegradability in the MITI-1 (OECD 301C) test: MITI Linear and MITI Nonlinear

> 0.50 Ready Biodegradable
< 0.50 Not Ready Biodegradable

4. Ready Biodegradability Prediction based on a Bayesian battery approach:

Yes = Ready biodegradable
No = Not ready biodegradable

Soil Adsorption Coefficient (Log K_{oc}) - Estimated by PCKOCWIN

≥ 4.5	Very strong sorption to soil and sediment, *negligible migration potential to groundwater*
3.5 - 4.4	Strong sorption to soil and sediment, *negligible to slow migration potential to groundwater*
2.5 - 3.4	Moderate sorption to soil and sediment, *slow migration potential to groundwater*
1.5 - 2.4	Low sorption to soil and sediment, *moderate migration potential to groundwater*
< 1.5	Negligible sorption to soil and sediment, *rapid migration potential to groundwater*

Bioconcentration Factors - Estimated by BCFWIN

> 5000	High bioconcentration potential
1000 - 5000	Moderate bioconcentration potential
< 1000	Low bioconcentration potential

STPWIN - Percent Removal in Sewage Treatment Plants

Gives an indication of the percent removed from biodegradation (Bio P), sludge adsorption (Bio S), and aeration (Bio A) in a POTW or Sewage Treatment Plant.

Default Method: Assumes negligible biodegradation, (half-life = 10,000 hours) is the default value for the primary clarifier (P), aeration vessel (A), and final settling tank (S) unless otherwise specified in the input screen for EPISuite™.

Draft Method: Biodegradation accounted for (based on results from BIOWIN 1-6) in calculation of STP removal, in addition to P, A, and S tanks as noted above.

**Unless experimental data indicate otherwise, the EPA will not use a value greater than 90% when determining rate of removal from STP.*

LEV3EPI - Fugacity Model

Provides overall persistence derived from a level III multimedia model. Gives an indication of which environmental compartment the chemical is expected to partition to and calculates an approximate overall environmental persistence time. The level III model considers degradation (unlike level I and II models) and can be run for a variety of release scenarios.

WVOL - Volatilization from Water

Uses molecular weight, Henry's Law Constant, and water solubility to estimate an ***upper*** limit for volatilization from a body of water. The model ***does not*** take into account potential adsorption to sediment and suspended organic matter when the K_{oc} is high, which can increase the volatilization half-life significantly. Therefore, if the K_{oc} for a given chemical is high, the volatilization half-lives for a model river and model lake are expected to be significantly lower than predicted in WVOL.

PBT POTENTIAL ESTIMATIONS

PBT Profiler - U.S. EPA describes Persistence, Bioaccumulative, and Toxicity (PBT) criteria in the PBT category for Premanufacture Notices in the Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances at http://www.epa.gov/opptintr/newchems/pubs/pbtpolcy.htm and in the final rule for TRI reporting of PBT Chemicals http://www.epa.gov/triinter/lawsandregs/pbt/pbtrule.htm#rule. These criteria are used by the PBT Profiler to estimate PBT potential of chemicals.

These PBT criteria are:

PERSISTENCE	Not Persistent	Persistent	
Water, Soil, Sediment*	< 60 d	≥ 60 d	≥ 180 d
Air**	< 2 d	> 2 d	
BIOACCUMULATION	Not Bioaccumulative	Bioaccumulative	
Fish BCF*	< 1000	≥ 1000	≥ 5000
TOXICITY	Not Toxic	Toxic	
Fish ChV*	> 10 mg/L *or* No Effects at Saturation	0.1-10 mg/L	< 0.1 mg/L

NOTES: The PBT Profiler is not appropriate for certain types of chemicals, such as metals. Before using the PBT Profiler determine if the chemical being evaluated is appropriate for running in the PBT Profiler. Extensive information is provided within the on-line model at www.pbtprofiler.net
* New Chemical Program Criteria
** TRI Reporting Criteria

The EPA DOES NOT use the PBT Profiler to regulate chemicals. The toxicity assessment performed by the PBT Profiler only considers potential hazards due to chronic exposure to the aquatic environment and does not perform a quantitative human health hazard assessment. When the Agency reviews a chemical for its PBT characteristics, they also consider potential human health effects due to environmental exposure in addition to aquatic toxicity. ***In the U.S. EPA New Chemicals Program, EPA maintains a "no release to the environment" policy for all chemicals identified as PBTs.***

AQUATIC TOXICITY HAZARD

Developing a Full Standard Aquatic Toxicity Profile

The standard EPA New Chemicals Program aquatic toxicity profile consists of 3 acute values (fish LC_{50}, daphnid LC_{50}, and algae EC_{50}) and 3 chronic values (fish ChV, daphnid ChV, and algae ChV); the algae EC_{50} value and algae ChV value are generally derived from a single 72 to 96-hour algae toxicity study that assess multiple algae life cycles. EPA/OPPT generally focuses on aquatic toxicity to fresh water organisms because most releases of industrial chemicals go to fresh water bodies. Terrestrial and marine species are evaluated on a case by case basis depending on the releases of the chemicals.

Toxicity profiles may be created from actual toxicity data, predicted values (ECOSAR), analog data and/or chemical category information. Acute to chronic ratios may be used when extrapolating from acute to chronic toxicity and vice-versa. In some instances, the parent compound may hydrolyze to more toxic moieties and these should be considered when preparing a complete aquatic toxicity profile.

Toxicity values (endpoint/duration) generally used to fulfill the standard aquatic toxicity profile are:

Organism	Acute Toxicity Values	Chronic Toxicity Values
Fish (Freshwater)	96-hour LC_{50}	ChV
Daphnid (Aquatic Invertebrate)	48-hour LC_{50}	ChV
Algae (Aquatic Plant)	72- or 96-hour EC_{50}	ChV

The ChV, or Chronic Value, is defined as the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC). One way to represent the ChV value mathematically is:

ChV = 10^([log (LOEC x NOEC)]/2)

ECOSAR ™ - Model Outputs

The ECOSAR model will output LC_{50}, EC_{50}, and ChV values and in most cases will provide predictions for all the endpoints listed above. The equations used to derive the predictions, as well as resulting estimates are not species specific. When collecting studies for inclusion in the training sets, standard test species were preferred as identified in OCSPP guidelines for aquatic toxicity testing. Therefore, the equations are not intended to assess toxicity to only a single species, but rather to the general freshwater trophic levels they represent (fish, aquatic invertebrates, and aquatic plants).

Application of Acute-to-Chronic Ratios

In the absence of measured or estimated data for an endpoint, an acute-to-chronic ratio may be applied to help fulfill a standard profile. The acute-to-chronic ratio (ACR) is an empirically derived ratio of acute values to chronic values (acute value/chronic value), that in some cases are class-specific. ACRs reported in the literature vary broadly. In most cases it is difficult to calculate class specific ACRs because only a small number of comparable tests are available or the validity of literature data could not be checked. To date, valid experimental data for developing a universally accepted class-specific ACR model is limited because rarely are such data available (Ahlers et al. 2006, Raimondo et al. 2007). In general, accepted acute-to-chronic ratios for fish and daphnid are set at 10 within the EPA/OPPT New Chemicals Program. Information obtained from analyzed databases indicate that for algae and other aquatic plants the acute to chronic ratios are lower than for fish and invertebrates. Algae/plant EC_{50}s are not actually based on lethality but rather on growth rate or biomass production. For the case of unicellular algae, which usually constitute the most common information, the tests from which EC_{50}s (acute) and

ChVs (chronic) are derived from shorter duration studies typically lasting 3-4 days, but cover several generations and in most cases acute and chronic values are actually obtained from the same study. The ACR for algae that is currently used in the EPA/OPPT New Chemicals Program is 4. The derivation of this value is based on direct comparison of the ECOSAR 1999 neutral organics green algae 96 hr EC_{50} equation to that of the 1999 neutral organics green algae ChV equation.

For some classes, ECOSAR will use acute-to-chronic ratios (with corrections for Kow) to estimate an endpoint. When this occurs, the ECOSAR output flags the estimate indicating it is derived from an ACR and therefore (based on discussion above) has some inherent uncertainty.

Summary Table of Acute-To-Chronic Ratios for Chemical Classes by Trophic Level

Acute-To-Chronic Ratio			
Class	Fish	Daphnid	Green Algae
Neutral Organics	10	10	4
Classes with Excess Toxicity	10	10	4
Polycationic Polymers	18	14	4
Nonionic Surfactants	5	5	4
Anionic Surfactants	6.5	6.5	4

Evaluating Chronic Toxicity

In the absence of experimental chronic toxicity studies, the following alternative approaches may be used to characterize the chronic toxicity endpoints:

Use of ECOSAR Predictions

EPA's ECOSAR program uses a collection of data for analogous substances as defined in the ECOSAR Class Definition sheets and the chemical's characteristics to predict a chronic effect level which is called a (ChV). In general, when data are available to support ECOSAR predictions of chronic effects, these predictions should be representative of chronic population-level effects since the prediction is derived from chronic studies of analogous substances that took into consideration such non-lethal effects as reproductive impairment, neurotoxicity, and growth impairment. **Where predictive methods are available for estimating a ChV value from a chronic data set, these values may be preferred over application of acute-to-chronic ratios (to an empirical acute data set on the chemical) because they may better reflect potential non-lethal observations from chronic exposures for the chemical class.**

Use of an Analogous Substance

If an ECOSAR class has insufficient data to support a chronic hazard call, an alternative approach to characterizing chronic hazard would be to identify an analog with chronic data. The Analog Identification Methodology (AIM) tool or other similar tools can aid reviewers in identifying analogous chemicals with data, although users are responsible for determining the appropriateness of the analog. Full study reports should be provided in the initial PMN for identified analogous substances.

Using Measured Data to Fulfill Acute and Chronic Endpoints

The hazard classification scheme presented below for determining a low, moderate, or high aquatic toxicity concern was established based on standard endpoints and durations shown in the table above. When identifying studies to fulfill these standard endpoints, priority is given to experimental studies over estimated values, if the studies are judged to be scientifically sound and appropriate for the endpoint. However, laboratory studies may report results for different endpoints (EC_{10}) or durations (24 hr) other

than those typically used in the standard profile. These data points may still be used to support a hazard classification, but in some cases may need to be adjusted or extrapolated for comparison purposes within a hazard classification scheme or for comparison with other model data. For example, typical laboratory studies will report the NOEC and LOEC from a chronic test, and not a ChV. Furthermore, experimental data for one taxa is not sufficient to support the hazard characterization of other taxa. For example, daphnid studies cannot be used to characterize hazard for fish or algae. Some additional key considerations when determining scientific soundness of studies are listed below. In general, OPPT uses OCSPP guidelines as a foundation when considering study quality.

1) Control Response - If controls are not responding adequately (as indicated in OCSPP guidelines), there is no basis from which to compare treatment groups and, thus, the study may be considered invalid. Keep in mind that certain group sizes allowed in OCSPP guidelines will result in study invalidation due to an insufficient control response if just one control death occurs.

2) Stability of test substance in solution should be demonstrated. The preferred method for this is analytical determination of test concentrations. If instability is suspected, the test system should be selected for fish and daphnid to address the issue (e.g., static-renewal or flow-through test systems). Time-weighted mean measured concentrations should be considered for algae testing as well.

3) Use of filtration of test solutions should be accompanied by an acceptable method for analytically determining test concentrations and study results should be based on mean measured concentrations. Keep in mind the difficulty this may pose if the test substance is a complex mixture; there are alternatives to filtration identified in OCSPP guidelines.

4) When testing complex mixtures with varying low solubility components, test solutions should be generated for each test concentration; serial dilution of a single stock solution will likely not be accepted.

5) High water hardness levels (>180 mg CaCO3/L) or high total organic carbon levels (>2 mg/L) may invalidate a study, especially if the tested substance is of a class of compounds thought to be neutralized by these high levels. In general, physiochemical parameters of the test system (e.g., pH, DO) should remain within OCSPP guideline recommendations.

6) If the chemical identity and composition/purity are not sufficient to associate the study with the PMN substance, the study may not be considered appropriate. Also, if a purity of <90% is reported and the remaining impurities are not reported, the study may not be considered valid.

7) If insufficient study details are provided and EPA cannot determine study adequacy or fully interpret the results, the study may be considered unacceptable.

EPA's New Chemical Category Document

In the late 80's after several years of experience in the review of PMNs, EPA had enough accumulated experience to group PMN chemicals with shared chemical and toxicological properties into categories which enabled EPA reviewers to benefit from the accumulated data and past decisional precedents on similar chemicals, allowing reviews to be greatly facilitated. Currently, there are a total of 56 categories and approximately 70 percent of these categories have information related to aquatic hazard or risk determination which may be used to help define a chemicals hazard profile. The EPA New Chemicals Category document can be found at: http://www.epa.gov/oppt/newchems/pubs/cat02.htm.

It is important to note that substances which fall into the categories are not necessarily the chemical substances of greatest concern to the Agency. That is, the categories may not be made up of the most hazardous chemicals, but rather they include chemicals for which sufficient history has been accumulated so that hazard concerns and testing recommendations vary little from chemical to chemical within the category.

Chemical Hydrolysis

Data or information on a chemical's hydrolysis rate (hydrolysis half-life) can determine if other chemical degradates should be considered during the course of the ecotoxicity assessment. If the hydrolysis half-life is *less than one hour*, then the degradation products will be what enter the actual aquatic environment and should be assessed for concerns. If the half-life is *greater than one hour, but less than 14 days*, then both the intact parent chemical and its products should be reviewed. If the half-life is *greater than 14 days*, then only the parent chemical is generally assessed. This window of 14 days is based on the average residence time through a waste water treatment facility before a chemical is released to the aquatic environment where is my pose toxicity to the aquatic life.

Assigning Aquatic Toxicity Hazard Concern Levels

Once a standard aquatic toxicity hazard profile has been constructed, the classification paradigm below may be used to determine if the chemical has a low, moderate, or high concern for toxicity.

SF Concern Level	ECOSAR Results
Low	All 3 acute values are >100 mg/L, AND all three chronic values are >10.0 mg/L, or there are "No Effects at Saturation" (or NES). NES occurs when a chemical is not soluble enough to reach the effect concentration, i.e., the water solubility is lower than an effect concentration, or, for liquids, when K_{ow} criteria are exceeded for an endpoint. For solids, NES is expected if K_{ow} exceeds the specific SAR K_{ow} cutoffs, or the effect concentration is more than one order of magnitude ($\geq$10 X) less than water solubility.
Moderate	Any of the 3 acute values are between 1.0 mg/L and 100 mg/L, OR any of the chronic values are between 0.1 mg/L and 10.0 mg/L
High	Any of the 3 acute values are <1.0 mg/L, OR any of the chronic values are <0.1 mg/L

NOTES: K_{ow} cutoffs are specific to each chemical class used in ECOSAR. The criteria can be found on the bottom of the results screen for ECOSAR or in the ECOSAR Help Menu under the SAR classes list.

For further explanation on the underlying methods used in ECOSAR please refer to the ECOSAR webpage at: http://www.epa.gov/oppt/newchems/tools/21ecosar.htm

Deriving a Chronic Concentration of Concern (Chronic COC) for Moderate to High Concern Chemicals

For chemicals classified as having a moderate to high toxicity hazard based on the paradigm above, a chronic concentration of concern (COC) for the most sensitive species needs to be determined. This value is necessary as input to the E-FAST model for calculating downstream aquatic exposure exceedance durations which will be needed for all moderate to high hazard concern chemicals during the subsequent exposure and risk assessment. For chemicals with a low hazard concern, typically an exposure assessment will not be done (assume low potential for risk) EXCEPT for chemicals that meet the EPA New Chemical Production Volume or Exposure based triggers which are outlined on the EPA website at: http://www.epa.gov/opptintr/newchems/pubs/expbased.htm

Chronic COC for the most sensitive species = Lowest ChV / (10)

Example calculation:
Daphnid ChV = 0.02 mg/L
Calculated daphnid chronic COC = (0.02 mg/L) /10 = 0.002 mg/L (ppm)

If ONLY an NOEC value (and not a ChV) is available from what appears to be the most sensitive species, that value can be used to derive a chronic COC by applying the same assessment factor of 10. Even though using an NOEC value from a study represents setting a more conservative toxicity value, there is

still uncertainty associated with extrapolation from lab to field studies that needs to be accounted for. Therefore a factor of 10 is still applied, with an understanding that the approach yields setting a more conservative chronic COC or threshold level. If only an LOEC is available from a chronic test, it is a likely indication that you have a poorly designed test, and study validity should be questioned.

The only time an assessment factor is not used (or more correctly an AF of 1) is for an actual field study or when an extensive species sensitivity distribution is available.

PLEASE NOTE: COCs are rounded up to 1 significant digit (e.g., a COC of 1.75 ppb is rounded up to 2 ppb) because the assessment factor applied to calculate COCs are 1 significant digit. EPA does not typically report COCs less than 1 ppb due to costs/limitations in reliable analytical methods to test below 1 ppb. Therefore, no values less than 1 ppb (traditional lower detection limit) should be reported; unless SAR, analogs, or experimental data analysis directly support a COC < 1 ppb.

The derivation and further use of acute and chronic COCs for risk determination are explained in more detail on page 9 under the Risk Assessment section.

HUMAN HEALTH HAZARD

Human Health Hazard - Non-Cancer

Currently there are no computerized models for the evaluation of non-cancer health effects. Analysis is based on identification of experimental data for either the chemical of interest or an appropriate analog(s). The endpoints covered under non-cancer effects cover a broad range of acute, subchronic, and chronic endpoints. Typically the endpoints used to assign a hazard concern 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
- ✓ Mutagenicity
- ✓ Skin Sensitization
- ✓ Irritation (eye, skin, respiratory)

The types of information that should be collected when reviewing experimental studies include the hazard concern identified, the type of study and duration (e.g., 2-generation reproductive toxicity study, 28-day repeated-dose study), the animal species used, the exposure route (oral gavage, diet, dermal, inhalation), the effect levels (lethal dose 50% mortality [LD50], no adverse effect levels [NOAEL], and/or lowest adverse effect levels [LOAEL]), and the reference. Additional guidance for evaluating studies can be found at http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm. Also note that finding no data in the public domain for a particular endpoint is NOT equivalent to negative data for that endpoint. No data simply means you have a data gap. There may also be occasions when conflicting data exist and a weight of evidence approach is recommended to support conclusions.

EPA's New Chemical Category Document

In the late 80's after several years of experience in the review of PMNs, EPA's had enough accumulated experience to group PMN chemicals with shared chemical and toxicological properties into categories which enabled EPA reviewers to benefit from the accumulated data and past decisional precedents on analogous compounds. Currently, there are a total of 55 categories and approximately half of these categories have information related to human health hazard or risk determination which may be used to help define a chemicals hazard profile. The EPA New Chemicals Category document can be found at: http://www.epa.gov/oppt/newchems/pubs/chemcat.htm.

It is important to note that substances which fall into the categories are not necessarily the chemical substances of greatest concern to the Agency. That is, the categories may not be made up of the most hazardous chemicals, but rather they include chemicals for which sufficient history has been accumulated so that hazard concerns and testing recommendations vary little from chemical to chemical within the category.

Criteria for Assigning Non-Cancer Hazard Concern Levels:

SF Concern Level	Definition - 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.

For chemicals identified as having a moderate or high hazard concern level, those compounds will continue through the risk assessment paradigm and receive an exposure assessment and subsequent screening level risk characterization. Therefore, distinction between moderate and high concern is not critical because in both cases, the chemicals will continue on the same path.

<u>Assessment of Carcinogenicity Potential</u>

The assessment methods are different for carcinogenicity versus other non-cancer endpoints. This is because unlike non-cancer effects, the default assumption is that there is no acceptable threshold for carcinogens that act by genotoxic mechanisms. Therefore, the question becomes do we have any reason to believe that the chemical could cause toxicity (cancer) at any perceivable exposure level? EPA/OPPT currently uses two methods to address this question. The first method is through experimental data on the chemical of interest or an appropriate analog using laboratory or epidemiology studies.

The types of information that should be collected when reviewing experimental studies include number of animals dosed with test substance and with what vehicle (e.g., water or corn oil) for majority of life, what tissues were examined for tumors at the end of the exposure period (or in animals that die prior to scheduled sacrifice), the number of animals in treatment groups with tumors as compared to the number of animals in control group(s) with tumors in same tissue, is there a statistically significant increase in number of animals with cancer at one or more dose(s), is there a statistically significant trend in number of animals with tumors, were there rare tumor(s) identified, were animals given appropriate doses (ideal?

MTD? Overly toxic?), etc. Additional guidance for evaluating study adequacy can be found at http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm.

Interpretation of Experimental Cancer Data:

SF Concern Level	Definition - Experimental Data
Low	Negative experimental data
Moderate	Positive cancer bioassay in experimental animals ***or*** chemical class known to produce carcinogenic effects
High	Positive experimental data in humans (e.g. epidemiology study)

The second method for assessing carcinogenicity potential is a computer-based expert system called OncoLogic®. OncoLogic® mimics the thinking and reasoning of human experts using knowledge based rules for chemical classes to predict cancer concern. The model assigns a baseline concern level ranging from low to high using expert rules for known chemical classes and then evaluates how substituent on the chemical may affect carcinogenicity potential. Some of the major components the models considers are electronic and steric factors, metabolic factors, differences in mechanisms of action, and variations on the basic physicochemical properties of molecules.

Interpretation of OncoLogic® Results:

SF Concern Level	OncoLogic Results	Definition - OncoLogic® Result
Low	Low	Unlikely to be a carcinogen
Further Research Needed	Marginal	Likely to have equivocal carcinogenic activity
Moderate	Low-Moderate	Likely to be weakly carcinogenic
	Moderate	Likely to be moderately active carcinogen
High	Moderate-High	Highly likely to be a moderately active carcinogen
	High	Highly likely to be a potent carcinogen

NOTE: Measured data from a properly conducted study on the SF chemical or a relevant analog should be used before, or in conjunction with predicted data.

AT COMPLETION OF THE HAZARD CHARACTERIZATIONS FOR EACH AREA:
Continue with exposure characterizations if a moderate or high hazard concern has been identified for *any* area/endpoint.

EXPOSURE ESTIMATIONS

Estimating Worker [Industrial] Exposures:

LADD, ADD, and APDR values will be estimated by **ChemSTEER**

Lifetime Average Daily Dose (LADD): The predicted lifetime exposure used to determine cancer risk usually based on an average lifetime about 75 years. LADD = (Exp x ED x EY)/(BW x AT x 365 days/yr) , where the averaging time (AT) is 75 years.

Potential Average Daily Dose (ADD): The predicted dose that represents potential chronic exposure is based on repeated exposures approximating an average of 40 years representing an individual's potential working lifetime. ADD = (Exp x ED x EY)/(BW x AT x 365 days/yr) , where averaging time (AT) is 40 years

Potential Acute Dose Rate (APDR): The predicted acute dose rate that represents acute exposure is usually on one 8-hour working day exposure duration.

Estimating General Population Human Exposure Doses:

LADDpot, ADDpot, and ADRpot values will be estimated by **E-FAST.** The **10% percentile values (mg/kg/day)** are used for an SF Assessment.

Lifetime Average Daily Dose (LADDpot): The predicted lifetime exposure used to determine cancer risk usually based on an average lifetime about 75 years. LADD = (Exp x ED x EY)/(BW x AT x 365 days/yr) , where the averaging time (AT) is 75 years.

Potential Average Daily Dose (ADDpot): The predicted dose that represents potential chronic exposure is based on repeated exposures approximating an average of 40 years representing an individuals potential working lifetime. ADD = (Exp x ED x EY)/(BW x AT x 365 days/yr) , where averaging time (AT) is 40 years

Potential Acute Dose Rate (APDRpot): The predicted acute dose rate that represents acute exposure is usually on one 8-hour working day exposure duration.

*****Because E-FAST does not currently estimate an ADDpot directly but is often needed for the risk assessment, please note an ADDpot can be calculated from the LADDpot by simply multiplying by 75/40 to adjust for averaging times as noted in the equations above.***

NOTE: For the purposes of an SF Summary Assessment, the defaults for average lifetime, body weight, exposure duration, and ingestion rate are pre-set in both ChemSTEER and E-FAST and should not be changed unless accurate data for these inputs are available. For information on standard values used by EPA, please see the EPA Human Exposure Factors Handbook website: http://cfpub.epa.gov/si/si_public_record_Report.cfm?dirEntryId=12464&CFID=4796643&CFTOKEN=22142442&jsessionid=4a30480e15cd540720536c431957516d474b

Estimating Aquatic Exposure Concentrations:

To run E-FAST and evaluate aquatic exposures, you will need to input the lowest chronic **Concentration of Concern (COC)** based on the toxicity values derived in the Aquatic Toxicity section. After running E-FAST, two specific values will need to be recorded from the model to complete the aquatic exposure/risk evaluation:

1) Predicted Environmental Concentration (PEC):
Amount expected to be found in surface water after release from industrial processes; also called surface water concentration (SWC). Estimated values can be determined using E-FAST and found under the "General SIC Code Information" tab in the results screen. The **10% percentile, 7Q10 stream concentrations (μg/L)** are used for an SF Assessment.

2) # of Days Exceeded (days / %year):
E-FAST will predict how many days per year the PEC exceeds the user entered chronic COC. The number of days the chronic COC is exceeded can be found at the bottom of the "**PDM SIC or PDM SITE**" tab in the output screen of E-FAST.

The potential for chronic risk to aquatic organisms may exist ONLY if the PEC exceeds the chronic COC for 20 days or more per year. If exposure occurs for 20 days or more per year the concentration of the chemical in surface water may reach levels associated with chronic effects (Lynch et al., 1994). The 20-day criterion is derived from partial life-cycle tests (Daphnid chronic and fish early life-stage tests) that typically range from 21 to 28 days in duration. Low concern for chronic risk exists if the COC is exceeded on fewer than 20 days per year.

RISK ESTIMATIONS

Reminder: RISK = HAZARD x EXPOSURE

For chemicals with a moderate or high hazard concern for either aquatic toxicity or human health, the potential aquatic and human exposure concentrations must be estimated to characterize potential risk. If a low concern for either hazard area is identified (hazard approx. = 0) or very low exposure is identified (exposure approx. = 0), then it is assumed there is a low concern for risk because of the relationship between hazard and exposure (Hazard x Exposure = Risk). The sections below will demonstrate how to complete a screening level risk characterization for both the aquatic environment and the human population.

Estimating Aquatic Risk

Determine an Acute and Chronic Concentration of Concern (COC):

Option 1: For chemicals identified under the hazard section as presenting moderate to high toxicity (page 7) ***AND*** E-FAST determined the PEC ***DID EXCEEDED*** the chronic COC for 20 days or more per year, then an acute and chronic COC should be determined for each endpoint in the standard profile as shown below. It is suggested that the units be converted to ppb (ug/L) for the purposes of comparison with exposure values from E-FAST which are in ppb (ug/L).

Acute COC for fish = LC_{50} / (5)
Acute COC for daphnia = LC_{50} / (5)
Acute COC for algae = ChV value (preferred) or EC_{50} / (4)

Chronic COC for fish = ChV / (10)
Chronic COC for daphnia = ChV / (10)
Chronic COC for algae = ChV / (10)

Option 2: For those chemicals which E-FAST determined the PEC ***DID NOT EXCEED*** the chronic COC for 20 days or more per year, then only a set of acute COCs, as shown below, need to be determined as the chemical is not expected to reside in the water column at high enough concentrations, for a long enough duration, to produce chronic effects (> 20 days).

Acute COC for fish = LC_{50} / (5)
Acute COC for daphnia = LC_{50} / (5)
Acute COC for algae = ChV value (preferred) or EC_{50} / (4)

Example calculations for Acute and Chronic COC are provided below:

Fish LC_{50} = 0.10 mg/L: calc. Acute COC = (0.10 mg/L) /5 = **0.02 mg/L (ppm) = 20 (ug/L) ppb**
Daphnid ChV = 0.02 mg/L: calc. Chronic COC = (0.02 mg/L) /10 = **0.002 mg/L (ppm) = 2 (ug/L) ppb**

Remember, COCs are rounded up to 1 significant digit. Also, most COC values less than 1 ppb are rounded up to 1 ppb for the assessment due to limitations in reliable analytical methods to test below 1 ppb, should verification be needed. No values less than 1 ppb (traditional lower detection limit) should be reported; unless SAR, analogs, or experimental data analysis directly support a COC < 1 ppb.

To Determine Acute Aquatic Risk

The potential for acute risk to aquatic organisms exists if the predicted environmental concentration (PEC) is greater than the acute concentration of concern (COC).

If Acute COC > PEC Low concern for risk
If Acute COC < PEC Potential for risk

To Determine Chronic Aquatic Risk

The potential for chronic risk to aquatic organisms exists if the PEC exceeds the chronic COC (for the most sensitive species) for 20 days or more per year. If this occurs, it is suggested that a comparison be completed for each species to determine if the risk is only to the most sensitive species, or all species and what the quantitative exceedance is. This information may help in the risk management steps or in designing a testing strategy to confirm the hazard/risk. Therefore it is recommended that all 3 chronic COCs be compared to the predicted environmental concentration (PEC) as done above for the acute COCs:

If Chronic COC > PEC Low concern for risk
If Chronic COC < PEC Potential for risk

EXAMPLE Worksheet for Identification of Acute and Chronic Risk to Aquatic Organisms:

Acute Endpoint	Value	Factor	Acute COC	PEC	Risk?
Fish LC50	79 ppb	5	20 ppb	55 ppb	**Yes**
Daphnid LC50	110 ppb	5	20 ppb	55 ppb	**Yes**
Algae EC50	83 ppb	4	21 ppb	55 ppb	**Yes**

COCs are typically rounded to 1 significant digit because the factors used to derive COCs are only 1 significant digit. Example E-FAST run indicates that the PEC exceeds the chronic COC for the most sensitive species (fish) for 25 days per year, so there is potential for risk to at least one species. Create a profile to determine if there is a chronic risk to the other two species as well:

Chronic Endpoint	Value	Factor	Chronic COC	PEC	Risk?
Fish ChV	18 ppb	10	2 ppb	55 ppb	**Yes**
Daphnid ChV	27 ppb	10	3 ppb	55 ppb	**Yes**
Algae ChV	67 ppb	10	7 ppb	55 ppb	**Yes**

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Example Summary of Aquatic Risk : There is potential for acute risk to all organisms because the acute COCs for those organisms exceed the PEC. There is a concern for chronic risk as the chronic COCs for all organisms exceed the PEC and the exceedance is expected to occur for more than 20 days per year. Overall there is a concern for both acute and chronic risk to the aquatic environment.

Estimating Human Health Non-Cancer Risk

For the determination of risk to the human population from non-cancer human health effects, a quantitative value called the Margin of Exposure (MOE) is calculated. This "margin" is essentially the established "safety buffer" between the hazardous effects level (dose) and the predicted exposure dose. If hazard data for ANY of the non-cancer health effect endpoints indicate a moderate or high hazard concern, then an MOE should be determined for each of those endpoints.

MOE = toxicity effect level / exposure dose

The EPA/OPPT utilizes margins of exposure that they believe are sufficiently protective of human health. When referring to non-cancer effects, these acceptable margins of exposure or "safety buffers" range between 100X or 1000X protective of human health depending on the type of non-cancer data identified. The lower the MOE (margin between the toxicity effect level and the exposure dose), the more likely a chemical is to pose an unreasonable risk. For example, if the margin indicates that a particular toxicity effect level is 10,000X higher than the expected exposure doses to the human population, there is little concern for that effect as it is unlikely the concentrations will ever reach levels where toxicity is a concern. But, if the toxicity level is only 1X higher than the exposure dose and if one considers potential uncertainty in experimental measurement, there is a significant chance the exposure dose may reach the toxicity effect level. In this case there is a concern for potential non-cancer risk. The subsequent pages give more in-depth guidance on the determination of MOE for acute and chronic risk from occupational and general population exposures.

Quantitative risk assessments are typically only performed for reproductive, developmental, systemic, neurotoxic, and immunotoxic effects when moderate or high concerns have been identified for the endpoints. Sensitization, mutagenicity, and irritation studies do not provide NOAEL/LOAEL determinations, so quantitative assessment of risk is not as straightforward. However, if there are concerns for sensitization, irritation, or mutagencitiy - these effects need to be documented and concerns conveyed on all safety documents. Also, if a concern for endpoints like sensitization and/or irritation exists, an exposure assessment should still be conducted to determine what pathways of exposure may be of concern or to determine appropriate personal protective gear to mitigate risks.

The following table shows the human health non-cancer endpoints and the acute/chronic exposure value used to calculate the MOE for each endpoint.

Endpoint	Exposure dose used for MOE calc.
Single Dose Studies	
Acute Toxicity	ADRpot (acute) *Acute risk is ONLY assessed for chemicals with an LD_{50} value < 50 mg/kg.
Repeated Dose Studies	
Irritation	Can not be used to determine MOE
Skin Sensitizer	Can not be used to determine MOE
Reproductive Effects	ADDpot (chronic)
Immune System Effect	ADDpot (chronic)
Developmental Toxicity	ADRpot (acute)
Genotoxicity	Can not be used to determine MOE
Mutagenicity	Can not be used to determine MOE
Neurotoxicity	ADDpot (chronic)
Systemic Effects	ADDpot (chronic)

Acute Risk to Workers and the General Population using a MOE_{acute}:

NOTE: When the acute toxicity studies indicate LD_{50} values > 50 mg/kg for a chemical, there is no need to calculate a Margin of Exposure (MOE) for acute risk and a low concern for acute risk is assumed.

However, if an LD_{50} < 50 mg/kg has been identified for the chemical of interest or an analog, a MOE_{acute} should be calculated and the potential for acute risk to the human population needs to be evaluated.

Margin of Exposure (MOE) based on Acute Exposure:
And MOE_{acute} is the ratio of the identified acute effect level (typically LD_{50} value determined in health hazard section) to the estimated acute dose rate (predicted from ChemSTEER and E-FAST).

$MOE_{acute,}$ Occupational = LD_{50} (mg/kg) / ADR (from ChemSTEER)
$MOE_{acute,}$ General Population = LD_{50} (mg/kg) / ADRpot (from E-FAST)

MOE < 1000 indicates potential for risk
MOE ≥ 1000 indicates low concern for risk

Chronic Risk to Workers and the General Population using a $MOE_{chronic}$:

NOTE: Regulatory decisions are most often based on the following human health effects: reproductive; immune; developmental; neurotoxicity; and systemic.

Margin of Exposure (MOE) based on Chronic Exposure: A $MOE_{chronic}$ is the ratio of the No-Observed Adverse-Effect-Level (NOAEL) or the Lowest-Observed Adverse-Effect-Level (LOAEL) for the effect (determined in health hazard section) to the estimated exposure value (predicted from exposure models). If both a NOAEL and LOAEL are available, then the NOAEL value is used for calculation of the MOE.

$MOE_{chronic}$, Occupational = NOAEL or LOAEL (Non-Cancer) / APDR or ADD (from ChemSTEER)
$MOE_{chronic}$, General Population = NOAEL or LOAEL (Non-Cancer) /ADRpot or ADDpot (from E-FAST)

For Calculation based on NOAEL:
MOE < 100 indicates potential for risk
MOE ≥ 100 indicates low concern for risk

For Calculation based on LOAEL:
MOE < 1000 indicates potential for risk
MOE ≥ 1000 indicates low concern for risk

For MOE values based on ***developmental toxicity data*** a body weight of 60 kg can be used as input in the exposure models (override defaults of approximately 70 kgs representing the male population) because this particular endpoint is only assessed in females. Also, developmental toxicity can occur from a single exposure at "just the right time during gestation" so developmental toxicity is based on the acute exposure dose rate (APDR or ADRpot) instead of a chronic dose – as shown above in the table.

Example Worksheet for Identification of the Potential for Acute and Chronic Risk to Human Health based on a Non-Cancer MOE:

Population	Effect	NOAEL	LOAEL	Exposure	MOE
Occupational	Systemic	40 mg/kg-d	200 mg/kg-d	1.8×10^{-2} mg/kg-d ChemSTEER ADD	2222
	Neurotox	40 mg/kg-d	200 mg/kg-d	1.8×10^{-2} mg/kg-d ChemSTEER ADD	2222
General Population	Systemic	40 mg/kg-d	200 mg/kg-d	2.1×10^{-6} mg/kg-d E-FAST ADDpot	1.9×10^{7}
	Neurotox	40 mg/kg-d	200 mg/kg-d	2.1×10^{-6} mg/kg-d E-FAST ADDpot	1.9×10^{7}

The MOE used to evaluate Risk from Occupational Exposure = 2222 for both systemic and neurotox
The MOE used to evaluate Risk from General Population Exposure = 1.9×10^{7} for both systemic and neurotox

Therefore, there is low concern for risk from occupational exposure or exposure to the general population because each MOE is greater than 100 (based on studies with a NOAEL).

Absorption Adjustments

Toxicity data are often available for only one exposure route (e.g., oral or inhalation), but the exposure scenarios may include several exposure routes. Exposure concentrations predicted by E-FAST and CHEMSTEER may need to be adjusted to extrapolate across exposure routes (e.g., oral to dermal). Only adjust exposure values if potential risk exists without the adjustment. Exposure route adjustment is based on absorption differences across exposure routes and is therefore NOT appropriate for portal of entry effects. Absorption differences can be estimated using measured data (chemical or analog) or by evaluating differences in physical-chemical properties between analogs. Molecular weight, Kow, water solubility, physical state will often play a predominant role in determine absorption differences.
For example, a rule of thumb on dermal absorption used in the EPA/OPPT New Chemical Program assumes 10% dermal absorption (multiply exposure value by 0.1) for chemicals with MW > 500 AND log Kow <-1 or >4 and assume 100% dermal absorption for all other chemicals.

It is recommended that adjustments only be investigated and considered if potential risk exists without the adjustment. Otherwise an assessor might complete a lot of extra work on a chemical that even under worst case assumptions (assume 100% absorption) still posed a low concern for risk.

Estimating Human Health Cancer Risk

Evaluation procedures typically not covered in an SF Training Workshop. Additional information and link to Cancer Risk Assessment Models can be found under the "Additional Information" section of the workshop binders.

General Overview for a Cancer Risk Assessment:

NOTE: For the purposes of a Sustainable Futures P2 Assessment, a human health cancer risk assessment will not be required, but a cancer health hazard assessment should be completed for the chemical.

For Occupational Exposure Doses: LADD will be calculated by **ChemSTEER**

For General Population Exposure Doses: LADDpot will be calculated by **E-FAST**.

Slope Factor (q1*)(mg/kg-day)$^{-1}$ (Calculated) = A measure of individual's extra risk (increased likelihood) of developing cancer for each incremental increase in exposure to a chemical. It approximates the upper bound of the slope of the dose-response curve using the linearized multistage procedure at low doses. The calculation of a slope factor requires tools that are not provided in the P2 Framework but can downloaded from the web for free. The software package is called "The Benchmark Dose Software (BMDS)", and can be found at http://cfpub.epa.gov/ncea/

Cancer Risk = LADD or LADDpot (mg/kg-day) x Slope Factor (q1*) (mg/kg-day)$^{-1}$

Generally, a cancer risk of > $1x10^{-6}$ (1 in 1,000,000) for the general population and > $1x10^{-5}$ (1 in 100,000) for worker exposure indicates the potential for risk.

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