Performing Risk Assessments for Sustainable Futures

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Steps in Risk Assessment

- Toxicity
  - Identify potential adverse effects and levels at which effects may occur
- Exposure
  - To how much of the chemical will the environment or people be exposed?
- Risk characterization
  - Compare toxicity to exposure

Risk Assessment

- Three types of risk assessments performed under the Sustainable Futures program
  - Aquatic
  - Non-Cancer Human Health
  - Cancer Human Health
- Each type of risk assessment uses different methods

When to Perform a Risk Assessment

- Industrial Chemicals
  - Risk assessment usually performed for chemicals with moderate or high toxicity concern levels for Sustainable Futures
    - See presentation slides on aquatic toxicity assessment for details on assigning concern levels
- High Exposure Potential
  - High Production Volume and resulting high exposure potential may trigger risk assessment for low toxicity compounds, per Exposure-Based Policy

    http://www.epa.gov/opptintr/newchems/pubs/expbased.htm

Steps in Assessing Aquatic Risk Under Sustainable Futures

✓ = Discussed in previous presentation
X = Not yet discussed

Step 1. ✓ Develop a standard aquatic toxicity profile

Step 2. X Determine concentration of concern

Step 3. ✓ Calculate potential exposures

✓ Concentration and duration

Step 4. X Risk Characterization

X Compare potential environmental concentrations to effect levels

Step 1. Develop a Standard Aquatic Toxicity Profile

- Standard profile includes 6 endpoints

ACUTE	CHRONIC
Fish 96-hr LC50	Fish ChV
Daphnid 48-hr LC50	Daphnid ChV
Green algae 96-hr EC50	Green algae ChV

- If ECOSAR does not predict an endpoint, acute-to-chronic ratios can be used fill data gaps
  - Appropriate acute-to-chronic ratios must be determined

Step 1. Develop Standard Aquatic Toxicity Profile: Isodecyl Acrylate Example

Endpoint	Predicted Value (mg/L)
96-hr Fish LC50	0.900*
48-hr Daphnid LC50	0.550*
96-hr Green Algae EC50	0.070
Fish ChV	0.005
Daphnid ChV	0.060†
Green Algae ChV	0.020†

*** The log Kow was slightly above the cutoff for fish and daphnid acute toxicity; therefore, the value is reported, but no effect at saturation may occur**

† These values were calculated using an ACR ratio of 10 for daphnids and a ratio of 4 for green algae

Step 2. Determine the Concentration of Concern

- Concentration of concern (COC)
  - Sometimes called the concern concentration (CC)
  - Harm to the aquatic environment is more likely to occur if the COC is exceeded
- Calculating the COC
  - COC is calculated for acute and chronic effects

Calculating an Acute COC

- Two ways to calculate an acute COC
  - Using Measured Data
    - Acute COC = Lowest valid acute No Observable Effect Concentration (NOEC) in a species
  - Using Predicted Data (ECOSAR)
    - Acute COC = Fish LC50/5

      = Daphnid LC50/5

      = Algal ChV (if predicted) or EC50/4

Calculating an Acute COC Isodecyl Acrylate Example

Endpoint	Predicted Value (ECOSAR)	Acute COC
96-hr Fish LC_{50}	900 ppb*	200 ppb
48-hr Daphnid LC_{50}	550 ppb*	100 ppb
96-hr Green Algae EC_{50}	70 ppb	20 ppb
* Log Kow was slightly above the cutoff for this effect; however, because the log Kow was very close to the cutoff, assume that effects may occur in the absence of supporting analog data		

Calculating a Chronic COC

- Chronic COC = Lowest ChV/10, rounded up to 1 significant digit (e.g., a COC of 18 is rounded up to 20)
  - ChV = Geometric mean of the NOEC and LOEC, is predicted by ECOSAR or calculated using an acute-to-chronic ratio

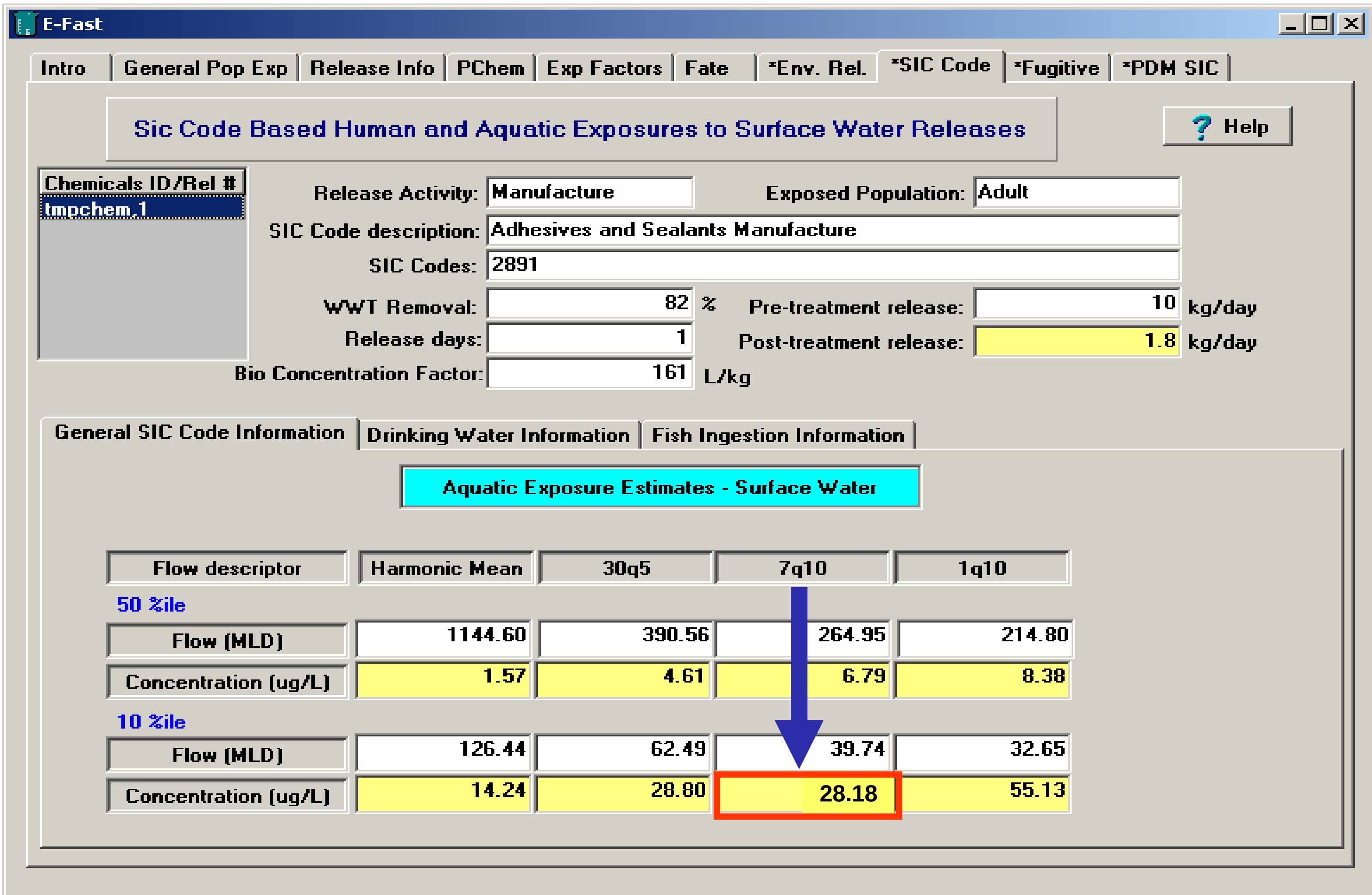
Calculating a Chronic COC Isodecyl Acrylate Example

- COC = Lowest ChV/10
  - 32-Day fish ChV = 0.005 mg/L (5 ppb)
  - Chronic COC = 5 ppb/10 = 0.5 ppb
  - Because the COC < 1 ppb and supporting analog data were not identified, the chronic COC = 1 ppb

Step 3. Determine Potential Exposure Concentrations

- Key exposure value calculated by E-FAST is Predicted Environmental Concentration (PEC)
  - Also called surface water concentration (SWC)
  - The PEC is the concentration of the chemical calculated to be in receiving waters
    - Simple stream flow dilution model
    - 7Q10 for 10^{th} percentile facility

Step 3. Determine Potential Exposure Concentrations: Results for Isodecyl Acrylate



E-FAST calculated a PEC of 28.18 ppb (µg/L)

Step 4. Risk Characterization

- Compare the PEC to the chronic and acute COC
- Chronic Risk
  - Potential for risk exists if PEC > COC for at least 20 days per year
  - Low potential for risk if PEC < COC or if the PEC > COC for less than 20 days per year
- Acute Risk
  - Potential for risk exists if PEC > acute COC

Step 4. Risk Characterization: Isodecyl Acrylate Example (cont.)

Chronic Risk to the Aquatic Environment

- COC = 1 ppb based on lowest ChV (predicted 32-day fish ChV from ECOSAR)
- PEC = 28 ppb (E-FAST)
- PEC (28 ppb) > COC (1 ppb); however, the COC is exceeded for only 1 day per year

Conclusion = Low potential for chronic risk to the aquatic environment

Step 4. Acute Risk Characterization: Isodecyl Acrylate Example

Acute Risk to Fish

- **Predicted LC_{50} value = 900 ppb**
- **Acute COC = 900/5 =** 200 ppb
- **PEC =** 28 ppb
- **Therefore, COC (200 ppb) < PEC (28 ppb)**

Conclusion: Low potential for acute risk exists for fish because the PEC < the acute COC

Step 4. Acute Risk Characterization: Isodecyl Acrylate Example

Acute Risk to Daphnids

- Predicted LC_{50} = 550 ppb
- Acute COC = 550/5 = 100 ppb
- PEC = 28 ppb
- Therefore, COC (100 ppb) < PEC (28 ppb)

Conclusion: Low potential for acute risk exists for daphnids because the PEC < the acute COC

Step 4. Acute Risk Characterization: Isodecyl Acrylate Example

Risk to Algae

- **Algal EC_{50} = 70 ppb**
- **Acute COC = 70/4 = 20 ppb**
- **PEC = 28 ppb**
- **PEC > Acute COC so there is a potential for short-term risk**
  - **PEC is between the algae ChV and EC_{50} so expect algal inhibition to be less than 50%; and**
  - **Water release will occur only one time per year, so risk may not be unreasonable because algae expected to recover**

Conclusion: Some risk may occur; however, due to the magnitude and duration of the potential effects, the risk may not be unreasonable

Steps in Assessing Human Health Risk

- Step 1. Identify potential hazards
- Step 2. Determine if the identified hazard(s) pose risk to exposed individuals
  - A. Identify dose levels associated with each hazard
  - B. Determine how much of the chemical humans are expected to be exposed to in the workplace, during use of consumer products, or through releases to the environment
  - C. Compare the doses shown to cause adverse effects to the expected doses in humans
    - Calculate a Margin of Exposure (MOE) for all effects

Step 1. Identifying Potential Hazards

- **All potential hazards need to be assessed**
  - **Quantitative risk assessment only performed for reproductive, developmental, systemic, neurotoxic, and immunotoxic effects**
- **Sensitization, mutagenicity, and irritation studies do not allow for NOAEL/LOAEL determinations**

Step 1. Identifying Potential Hazards (cont.)

- Data on chemical preferred over analog data
- Hazard may be identified using category data; however, toxicity studies are needed to perform risk assessment
  - Quantitative risk assessment can only be performed if NOAEL or LOAEL values are identified on the chemical or an analog

Step 1. Identifying Potential Hazards: Isodecyl Acrylate Example

- Hazard concerns identified for isodecyl acrylate
  - Developmental toxicity by analogy to isooctyl acrylate
  - Skin sensitization by analogy to isooctyl acrylate, octyl acrylate, and hexyl acrylate
    - See non-cancer hazard assessment presentation slides for more detail

Step 2. Risk Characterization

- **Goal of risk characterization**
  - **Compare levels of a chemical that may cause toxic effects with levels that people may be exposed**
- **Quantitative analysis based on Margin of Exposure (MOE)**
  - **MOE = Toxicity Value/Exposure Value**

Step 2. Risk Characterization (Margin of Exposure Analysis)

- Steps in Calculating a MOE
  - A: Determine levels (doses or concentrations) associated with adverse effects
    - Convert to mg/kg-day
  - B: Determine levels people may be exposed (general population and workers)
    - Exposure values may include acute or chronic values
    - Adjust exposure values to account for different routes of exposure (if possible and necessary)
  - C: Perform the calculation
    - MOE = Toxicity value / Adjusted Exposure Value
    - Interpretation of the MOE depends on the types of values used to calculate the MOE

Step 2a. Determine Doses Associated with Adverse Effects

- Goal: Identify dose levels that have been associated with hazard endpoints
  - Use the process described for toxicity assessments
- Key values needed from toxicity studies
  - No Observed Adverse Effect Level (NOAEL) (preferred)
  - Lowest Observed Adverse Effect Level (LOAEL)
- Convert all concentrations to mg/kg-day
  - Guidance at the following URLs:
    - http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=15263
    - http://www.who.int/ipcs/en/

Step 2b. Exposure Assessment

- Goal: Determine how much of the chemical people are expected to be exposed
  - Environmental exposures to general population (E-FAST)
  - Worker Exposure (CHEMSTEER)

Step 2b. Exposure Assessment (cont.)

Key exposure values used in risk assessment

- Potential lifetime average daily dose
  - Abbreviated LADD (CHEMSTEER) or LADDpot (E-FAST)
  - Represents chronic exposures over a lifetime; generally used for cancer risk calculations
- Potential average daily dose
  - Abbreviated ADD (CHEMSTEER) or ADDpot (E-FAST)
  - Represents chronic exposure to contaminated drinking water over the duration of exposure; generally used for non-cancer calculations
- Acute dose rate
  - Abbreviated APDR (CHEMSTEER) or ADRpot (E-FAST)
  - Used in acute toxicity and developmental toxicity risk assessments

Step 2b. Exposure Assessment (cont.)

- **Environmental exposures to general population (E-FAST)**
  - **Multiple exposure scenarios**
  - **Drinking water ingestion**
  - **Fish ingestion**
  - **Fugitive emissions**
- **Consider all exposure scenarios for the risk assessment**

Step 2b. Exposure Assessment (cont.)

- Occupational exposures (CHEMSTEER)
  - Multiple exposure scenarios are calculated
  - All possible exposure scenarios are considered in the risk assessment
  - Exposure values given in mg/kg-day

Step 2b. Exposure Assessment (cont.)

- Toxicity data often available for only one exposure route (e.g., oral or inhalation)
- 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 value if potential risk exists without the adjustment

Step 2b. Exposure Assessment (cont.)

- **Exposure route adjustment is based on absorption differences across exposure routes**
  - **Not appropriate for portal of entry effects**
  - **Adjustment may vary by exposure route**
- **Absorption differences can be estimated using measured data (chemical or analog) or by chemical and physical properties**
  - **Molecular weight, Kow, water solubility, physical state**

Step 2b. Adjusting Exposure Values Dermal Exposure

- **Only adjust exposure value if potential risk exists without the adjustment**
- **Initial adjustment for dermal exposure from oral toxicity data:**
  - **Assume 10% dermal absorption (multiply exposure value by 0.1) for chemicals with MW > 500 AND log Kow <-1 or >4**
  - **Assume 100% dermal absorption for all other chemicals**
- **Further refine absorption assumption using analog data if potential risk still exists**

Step 2c. Calculate a Margin of Exposure (MOE)

MOE = NOAEL (or LOAEL)/appropriate exposure value

- **Guidance for selecting exposure value:**
  - **Use acute dose rate for developmental and acute toxicity**
  - **Use Average Daily Dose (ADD) for systemic non-cancer effects**
  - **Cannot determine MOE for some endpoints (e.g., genotoxicity, sensitization)**
- **MOE > 100 implies low risk if NOAEL is used for toxicity value**
- **MOE > 1000 implies low risk if LOAEL is used for toxicity value**

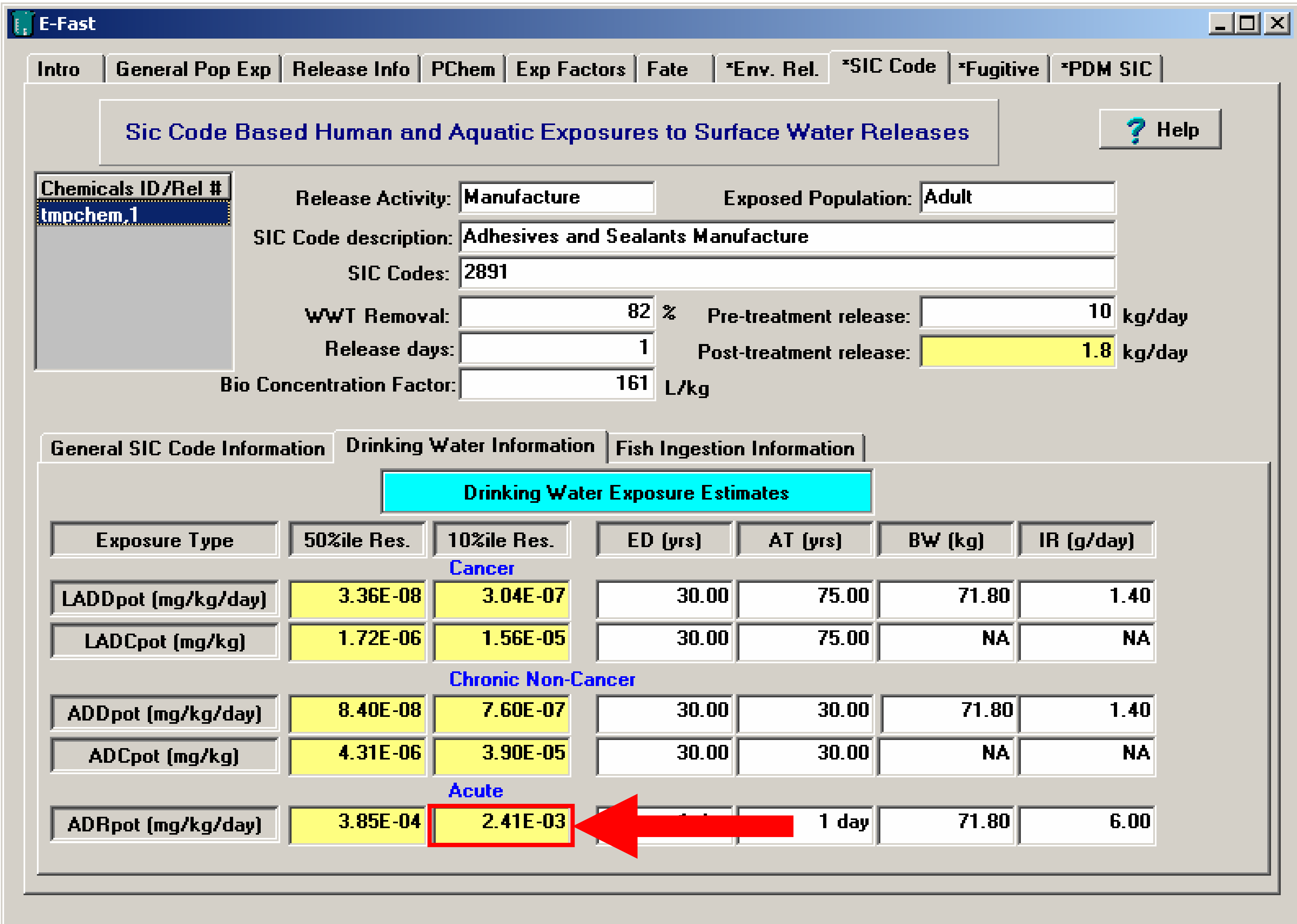
Risk Characterization
Isodecyl Acrylate Example

- **Step 2a. Hazard Concerns**
  - **<u>Developmental toxicity</u>: LOAEL = 1000 mg/kg-day in rats dosed via oral gavage**
    - **A NOAEL was not identified**
      - **1000 mg/kg-day was the only dose tested**
  - **<u>Skin sensitization</u>: NOAEL/LOAEL for skin sensitization is not applicable**

Risk Characterization Isodecyl Acrylate Example

- Step 2b. Exposure assessment, general population
  - E-Fast determined that the highest environmental exposures are expected to occur via drinking water ingestion
    - Average daily dose (ADD) = 4.7 x 10^{-7} mg/kg-day (drinking water)
    - Acute dose rate (ADR) = 1.5 x 10^{-3} mg/kg-day
      - Acute dose rate used because concern is developmental toxicity (see interpretive guidance document)

Exposure Assessment (General Pop.): Isodecyl Acrylate Example



Risk Characterization
Isodecyl Acrylate Example

- **Risk characterization (environmental exposure, general population)**
  - **MOE = LOAEL/ADR**
    - **LOAEL = 1000 mg/kg-day; ADR = 1.5 x 10^{-3}**
  - **MOE = 1000 mg/kg-day/1.5 x 10^{-3} mg/kg-day**
  - **MOE = 6.7 x 10^{5}**
- **Because the MOE >> 1000, low risk is implied**

Exposure Assessment (Occupational Exposure): Isodecyl Acrylate Example

- Occupational inhalation exposure (CHEMSTEER)
  - Exposure to vapors
  - Acute Potential Dose Rate (APDR) = 4.3×10^{-2} mg/kg-day
    - Assumptions: 60 kg person (female)
    - APDR may be adjusted if inhalation toxicity data are not available

APDR = 4.3×10^{-2} mg/kg-day

Step 2c. Risk characterization Isodecyl Acrylate Example

- **Risk characterization (occupational exposure)**
  - **Vapor exposure MOE**
    - **MOE = LOAEL/APDR**
    - **MOE = 1000 mg/kg-day/4.3 x 10^{-2} mg/kg-day**
    - **MOE = 2.3 x 10^{4}**
- **Because the MOE > 1000, low risk is implied**

Exposure Assessment (Occupational Exposure): Isodecyl Acrylate Example

Occupational dermal exposure (CHEMSTEER)

- **Highest exposure occurs via dermal route**
  - **Acute Potential Dose Rate (APDR) = 7.4 mg/kg-day**
  - **Assumptions: 60 kg person (female) because the effect is developmental toxicity; usually assume a 70 kg person (male) for other effects**
  - **APDR may be adjusted if dermal toxicity data are not available**

APDR = 7.4 mg/kg-day

Step 2c. Risk characterization Isodecyl Acrylate Example

- Risk characterization (occupational exposure)
  - Dermal exposure MOE
    - MOE = LOAEL/APDR
    - MOE = 1000 mg/kg-day / 7.4 mg/kg-day
    - MOE = 135
- **Because the MOE < 1000, some potential for risk is implied**

Step 2c. Risk characterization Isodecyl Acrylate (cont.)

- **Because the dermal exposure MOE implied potential risk, adjust dermal absorption values if possible**
  - **Analog data indicate that dermal absorption is ≈25% of oral absorption**
    - **Multiply dermal exposure value by 0.25**
    - **MOE = 1000 mg/kg-day/(7.4 mg/kg-day x 0.25)**
    - **MOE = 540**
- **Because the MOE < 1000, some potential for risk is implied**

Step 2c. Risk characterization Isodecyl Acrylate (cont.)

- Repeat process for <u>all hazards</u> that allow for MOE calculations identified in the toxicity assessment
  - The effect observed at the lowest dose does not always result in the greatest risk because:
    - May assess different hazards using different toxicity values (NOAEL vs. LOAEL)
    - May assess different hazards using different exposure values (ADR vs. ADD)

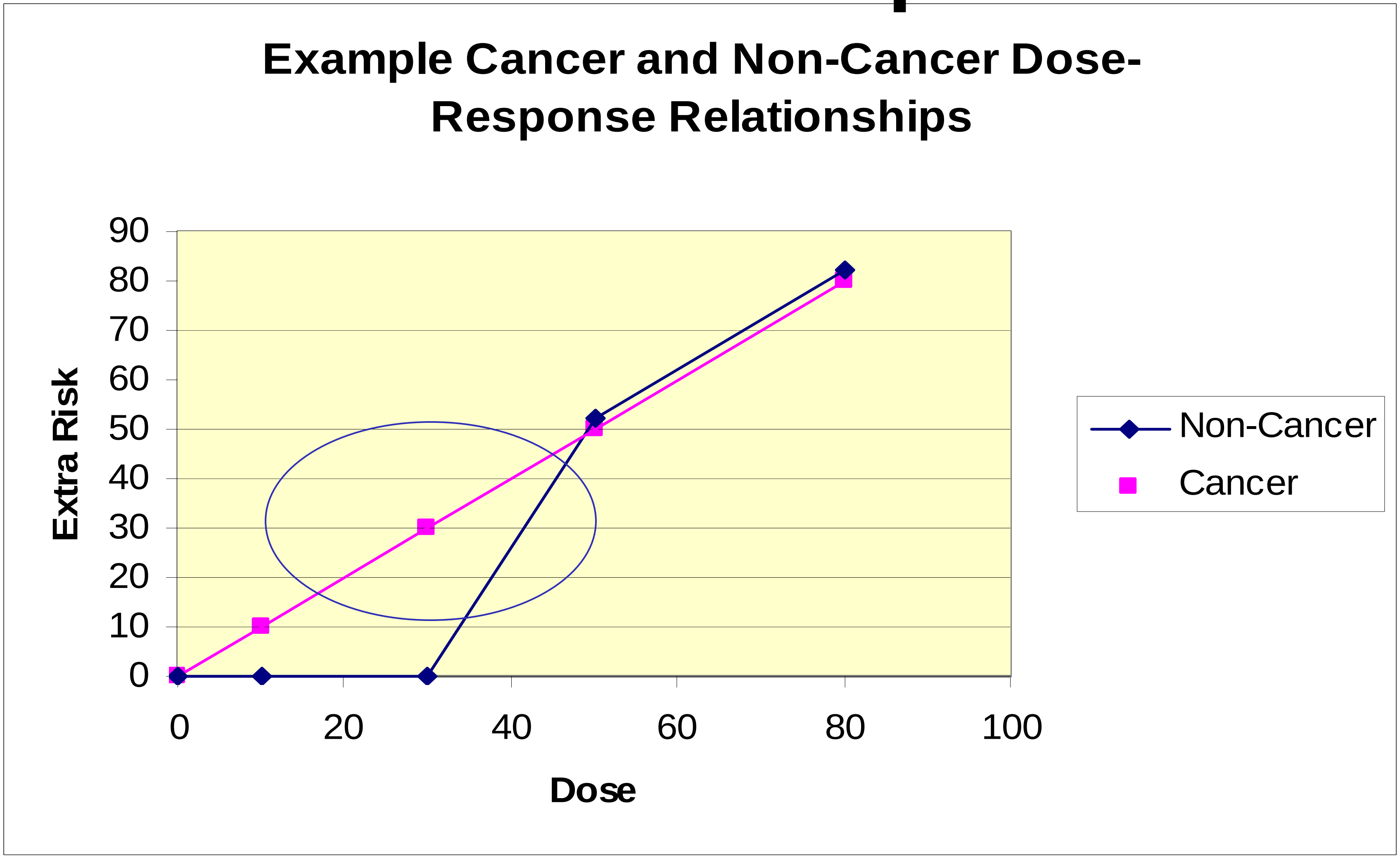
Non-Cancer Risk Assessment Summary for Isodecyl Acrylate

Hazard Concern	**Developmental Toxicity**
Lowest MOE, Environmental Exposure *	**6.7×10^5**
Lowest MOE, Occupational Exposure ^	**540**
Conclusion ***Based on drinking water exposure** **^ Based on dermal exposure**	**<u>Environmental exposure:</u> the MOE is >1000; therefore, low risk is implied** **<u>Occupational exposure:</u> The MOE is <1000; therefore some potential risk is implied for occupational exposure via the dermal route**

Why is the Cancer Risk Screen Different than the Non-Cancer Risk Screen?

- Most non-cancer effects
  - Assume that safe exposure level exists
- Most carcinogens
  - No “safe” exposure level
  - Any exposure to carcinogen results in increased probability of getting cancer

Comparison of Example Cancer and Non-Cancer Dose-Response Relationships



Performing a Cancer Risk Assessment for Sustainable Futures

Same four steps as performed for non-cancer assessment

- 1. Hazard identification
- 2. Dose-response assessment
  - Requires statistical software package
    - GLOBAL 86, Benchmark Dose Software (BMDS)
- 3. Exposure assessment
  - Similar to non-cancer risk assessment
- 4. Risk characterization
  - Calculate probability of cancer occurring as a result of exposure

Hazard Assessment

- **Hazard assessment conducted using predicted data (OncoLogic) or measured data on the chemical or analog.**
- **Measured data on the chemical or an analog needs to be identified to perform *risk* assessment**
  - **Bioassay in laboratory animals**
  - **Epidemiology study**

Dose-Response Analysis

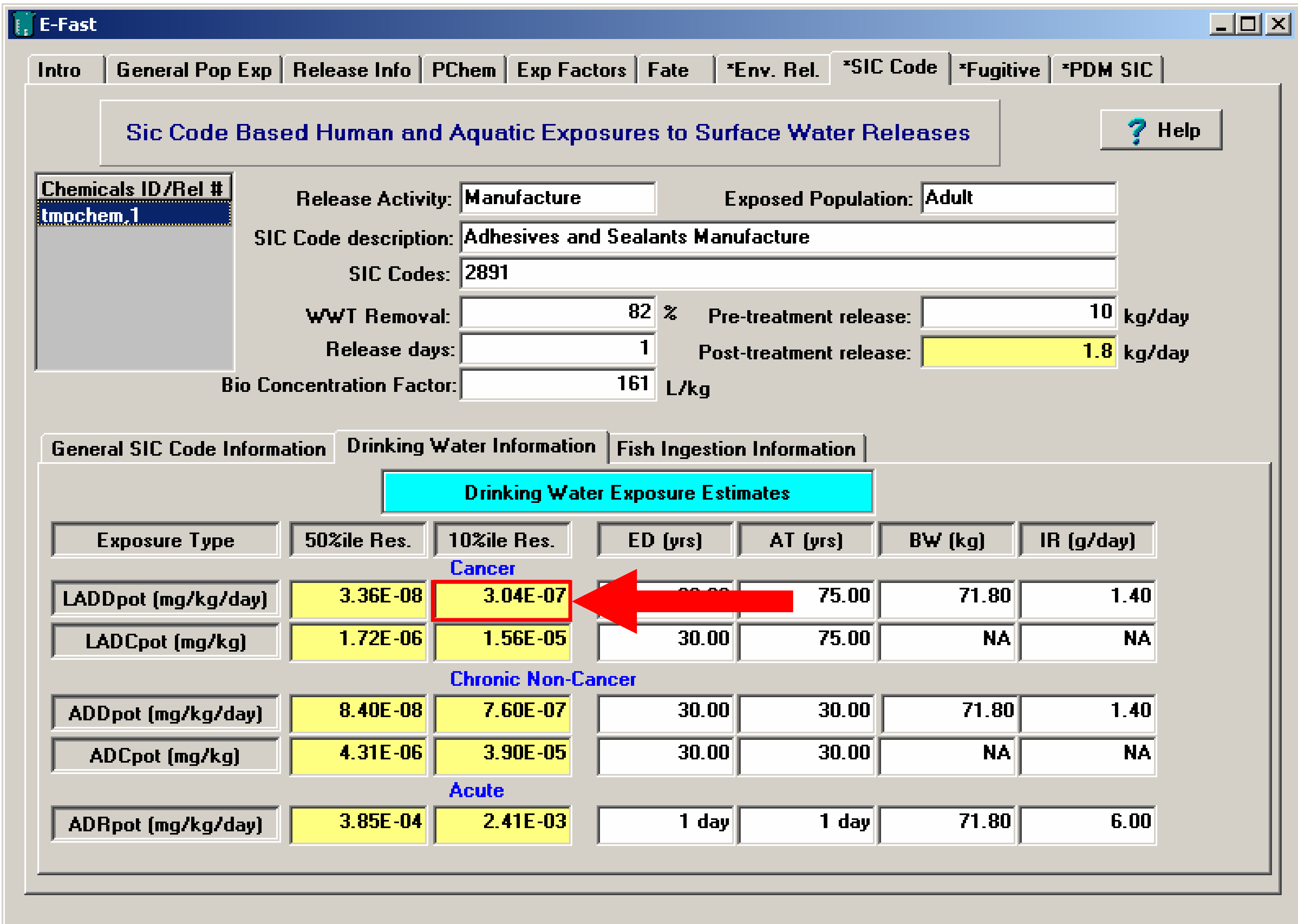
Calculate a slope factor

- Increased risk per mg/kg-day of exposure
- Used to calculate risk at low doses
- Calculated using Benchmark Dose Software
  - Free download at http://cfpub.epa.gov/ncea/

Exposure Assessment

- Identical to the assessment performed for the non-cancer risk assessment
- Exposure values, however, are averaged over a longer duration to reflect a lifetime of exposure
  - Lifetime average daily dose (LADD)
- Default Exposure Factors:
  - Lifetime = 70 yrs; Human Body Weight = 70 kg (adult)

Step 3. Exposure Assessment: Isodecyl Acrylate Example



Risk Characterization

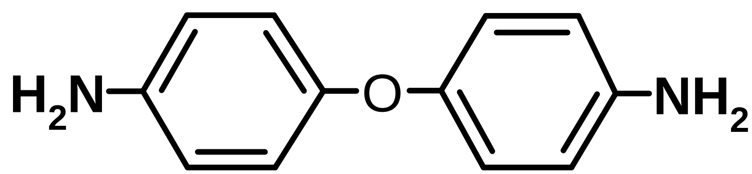
- Excess cancer risk =
  exposure (mg/kg-day) $\times$ slope factor (mg/kg-day)$^{-1}$
  - LADD $\times$ slope factor

- Under the New Chemicals Program, we generally have concern for exposures that give a risk > 1×10^{-6} (1 in 1,000,000) for exposure to the general population and >1×10^{-5} for worker exposure

Cancer Risk Assessment Example

- Isodecyl acrylate has low cancer concern; therefore, risk assessment is not needed

- Example chemical: Oxydianiline



Cancer Risk Assessment Example

Chemical	=	**Oxydianiline**
Slope Factor	=	**0.099 (mg/kg-day)$^{-1}$**
LADD	=	**0.0029 (mg/kg-day)**
Excess Cancer Risk	=	**3 x 10^{-4}**
		(0.099 x 0.0029)

Under the New Chemicals Program, we generally have concern for exposures that give a risk of 1x10^{-6} or greater (1 in 1,000,000). Therefore, we would want to see a reduction in the potential exposure.

Default Exposure Factors:

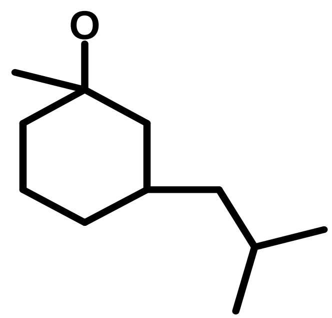
Lifetime = 70 yrs

Human Body Weight = 70 kg (adult)

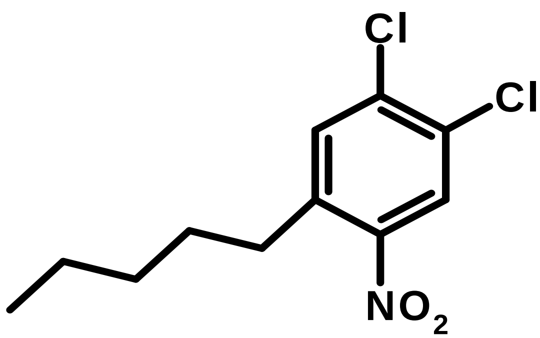
Risk Assessment on Example Chemicals (Handout)

Hands on Training Session:

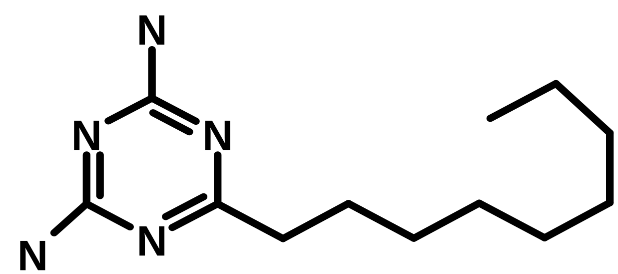
Risk Assessment



Example 2



Example 1



Example 3