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DRAFT Chemical X Case Study – Application of Uncertainty Framework

Background

The Transatlantic Risk Assessment dialogue began in 2008 as a forum for discussion of issues related to risk assessment among Canada, the European Union (EU), and the United States (US). Some of the key goals of the dialogue were developing common risk assessment frameworks, sharing best practices, and fostering collaboration on emerging issues.

One area of risk assessment frameworks that the Transatlantic Risk Assessment workgroup determined was important for developing consensus was uncertainty. This topic has been identified across regulatory bodies but has not been addressed formally by current frameworks. Addressing uncertainty in risk assessment is important to regulatory bodies for three main reasons: to increase transparency, increase consensus for risk assessment, and enable more informed decisions by risk managers.

Over the course of 2010, the workgroup has been developing a draft framework to address uncertainty in risk assessment. The workgroup then decided to perform an initial test of the draft framework by conducting several case studies of existing risk assessments.

For the purpose of this case study, uncertainty must be defined. Uncertainty is the lack of complete information for a given point of interest. Uncertainty should not be confused with variability: the range of possible values or outcomes for a given endpoint.

Purpose

The purpose of this case study is to identify uncertainty in the risk assessment of chemical X, a chemical analyzed in risk assessment submitted to a governmental body. The identity of the chemical is not revealed so as to focus the discussion on the utility of the method proposed for characterizing and communicating uncertainty rather than on the specific effects of chemical X.

Methods

This case study involved a retrospective analysis of the sources and magnitude of uncertainty in an assessment of Chemical X. Both the human health and ecological risk assessments for Chemical X were reviewed to characterize the uncertainty in the assessments. Relying on only a retrospective analysis without benefit of discussion with the risk assessors who actually prepared the assessment of Chemical X presented some challenges for the application of the uncertainty framework. Applying the uncertainty framework to an ongoing risk assessment is expected to resolve some of problems encountered during this case study.

In this section, the methods used to identify and characterize uncertainty will be discussed. The primary resource used for the case study of Chemical X was the Draft Framework for Evaluating Uncertainty. It must be noted that this framework is a working draft and will continue to be revised. For this case study, version 8 of the draft framework was consistently used to avoid encountering any potential problems by using different versions of the draft framework. This draft framework was developed using existing frameworks addressing uncertainty from the

European Food and Safety Authority (EFSA) and the Intergovernmental Panel on Climate Change (IPCC).

In order to identify sources of uncertainty the risk assessment must be read thoroughly. When this draft framework is used retroactively, identification of sources of uncertainty can be difficult if a risk assessment does not explicitly state when uncertainty exists. Ideally, in the future when a framework for identifying uncertainty exists, risk assessors will use the framework as part of the risk assessment process. As uncertainties are identified, one must organize them in a logical and transparent method. For this case study, tables were generated to record pertinent information while also being concise.

The next step in the process involves characterizing the uncertainties that have been identified. For each aspect of the risk assessment where uncertainty was identified, a table was constructed that identified a potentially uncertain aspect of the risk assessment, enumerating the elements contributing to the overall uncertainty. Each uncertainty should be characterized as qualitative and/or quantitative. Those that are qualitative should be explained thoroughly so that they may be used to inform the risk assessor's decisions. Quantitative uncertainties should be represented numerically in terms of magnitude and direction to determine if and how they would affect the final numerical value for a given endpoint.

It should be noted that even if an uncertainty is identified, making a judgment about the magnitude and direction of that uncertainty will not always be possible. However, it is still important to identify all sources of uncertainty for transparency.

Uncertainty in the Human Health Assessment

This case study focused on two chapters of the risk assessment of Chemical X: human health hazard assessment and human exposure assessment. After implementing the use of the draft framework for evaluating uncertainty, uncertainty tables were constructed to organize and communicate the uncertainties that existed as well as other relevant information. Uncertainty tables for the Human Health Assessment of Chemical X are found in Appendix A. For the sake of simplicity, the numerical scale in the draft framework, which ranges from 0.01x to 100x, was used to characterize the refined value for a given endpoint identified as containing uncertainty. The scale used for each respective risk assessment should be adjusted to the magnitude of the largest quantitative uncertainties.

Three tables were generated to characterize uncertainty for the Chemical X Human Health Assessment (Tables are in Appendix A). Table 1 contains the uncertainties identified in the human health hazard assessment chapter. This table is organized similar to a typical progression of a hazard section of a risk assessment. For example, five broad categories were used to organize the data chronologically: critical effect, dose response, interspecies extrapolation, intraspecies extrapolation, and route-to-route extrapolation. While eight sources of uncertainty were identified, only one of these uncertainties could be quantified. This was largely due to a lack of information in the risk assessment related to each source of uncertainty. Due to this lack of information, it was difficult to draw any general conclusions regarding hazard uncertainty.

The exposure assessment chapter was organized into Table 2 and Table 3 for worker exposure and consumer exposure scenarios, respectively. This was mainly due to the differences in primary exposure routes; workers' main exposure pathway was inhalation while consumers' main exposure pathway was oral. Also, by separating the exposure scenarios, there is less confusion in the presentation of the sources of uncertainty. A primary source of uncertainty for occupational exposure arose from lack of any sampling data. All exposure values were based on using the Estimation and Assessment of Substance Exposure (EASE) model. The risk assessment assumed the midpoint of the model's exposure value as a "typical" exposure and the upper bound as a "relative worst case" endpoint. The risk assessment states that the occupational exposure values are an overestimation in order to be precautionary.

For the consumer exposure scenario, the primary sources of Chemical X are food and water. In general, the risk assessment underestimated the consumer exposure. This was primarily due to three sources of Chemical X: mineral supplements, municipal drinking water, and mineral water. Mineral supplements were excluded from exposure calculations. The risk assessment also made the assumption that Chemical X levels in mineral and drinking water would be under 1mg/m3 due to the EU drinking water directive despite sampling data that was above this level. It is also important to note that for drinking water, regional differences in Chemical X concentrations exist due to natural sources from soils rich in a constituent form of Chemical X.

Suggestions for Improvement of Framework

After using Chemical X as a case study for applying the draft framework for evaluating uncertainty, suggestions for improving the framework were identified. The main recommendation for improving the framework is that it should be used during the risk assessment process. In other words, applying the framework after a risk assessment is complete is not ideal. Identifying sources of uncertainty is more difficult if a risk assessor does not have the raw data in hand. Generally, a summary of data is presented in a risk assessment rather than raw data so if uncertainty is not identified and/or communicated in a risk assessment, applying this framework is difficult.

A high degree of transparency facilitates identification of uncertainty. Detailed explanations of decisions, calculations, studies, etc. allow one to determine if uncertainty exists. This draft framework is most useful for risk assessments that are transparent in their decisions and rational.

Another suggestion for future application of the draft framework is to first generate a conceptual model for a given scenario. For example, creating a visual representation of exposure routes of a given chemical may identify a source of uncertainty not addressed in the risk assessment.

Deciding what action to take once an uncertainty has been identified is challenging. This is especially true for qualitative uncertainties. Again, this is another reason why identifying and addressing uncertainties as part of the risk assessment process is ideal.

Uncertainty in the Ecological Risk Assessment

This case study only examined risk to pelagic freshwater organisms from use of chemical X by one industry sector - producers of chemical X. Uncertainties associated with the derivation of the freshwater organism hazard value (Table 1) and the exposure estimates (Table 2) for the water column and in the output stream of a sewage treatment plant (STP) are presented in a set of uncertainty tables similar to those created for the Human Health Risk Assessment above. Risk to freshwater organisms was estimated by comparing the ratio of the exposure estimates or Predicted Exposure Concentration (PEC) divided by the hazard value or Predicted No Effect Concentration (PNEC) to one (Table 3). Ratios that exceeded one denoted risk while ratios less than one did not. The risk to freshwater organisms and the overall uncertainty associated with the risk value is presented at the conclusion of the uncertainty tables (Appendix B).

Manager's Summary

The primary goal of identifying uncertainty in risk assessments is to enable risk managers to make more informed decisions. A manager's summary was created to communicate the results of the uncertainty analysis in a format easily accessible by risk managers (Append C)

APPENDIX A. UNCERTAINTY TABLES FOR CHEMICAL X - HUMAN HEALTH RISK ASSESSMENT

Table 1. Human Health Hazard Assessment

Risk Assessment Element	Route	Input	Uncertainty	Parameter	Value / Range	Factor	Comments about uncertainty associated with the risk assessment element	Uncertainty Magnitude and Direction
Critical Effect	Primarily Oral	primarily animal studies	No	Qualitative			relatively complete database with cancer, developmental, and reproductive studies	
Dose Response	Oral	sub-chronic and chronic animal studies	No	Quantitative			target organ: testes (p76); effects on male and female fertility over 3 generation rat study were observed (p86, 102)	
	Oral	Worker-DNEL chronic oral	Yes	Qualitative / Quantitative	fertility factor: 2	?	additional factor of 2 used in Worker-DNEL calculation to address uncertainty in effects of female fertility, unclear how factor was derived (p103)	?
	Dermal	repeated dose toxicity	Yes	Quantitative		?	several human poisoning cases exist but exact doses are difficult to derive (p82); oral study used to establish DNEL (p104)	?
	Inhalation	Worker-DNEL acute inhalation	Yes	Quantitative	correction factor: 2		correction factor of 2 was applied to calculation because primary human study underestimated exposure levels; no intraspecies factor used because key study conducted with humans at workplace (p100); nasal and throat irritation, cough,	

Risk Assessment Element	Route	Input	Uncertainty	Parameter	Value / Range	Factor	Comments about uncertainty associated with the risk assessment element	Uncertainty Magnitude and Direction
							and nasal discharge observed (p 67, 71)	
	Inhalation	repeated dose toxicity	Yes	Quantitative		?	No studies available human or animal (p81); oral study used to establish DNEL	?
Route-to-Route Extrapolation	Dermal	absorption rate	No	Quantitative	0.50%		human voluntary study, worst case scenario (p57)	
	Inhalation	absorption rate	Yes	Quantitative	assumed 100% as worst case scenario (p59)	?	unclear amount of absorbed inhaled Chemical X, blood X levels should be used instead of intake levels (p56)	-
Interspecies Extrapolation	Inhalation	Worker-DNEL chronic inhalation	Yes	Quantitative	toxicodynamic factor: 2.5	?	route-to-route extrapolation: oral NOAEL used to extrapolate inhalation NOAEC; RA does not use route-to-route factor because covered by 2.5x factor for toxicodynamic differences (p103, 104)	+
	Dermal / Oral	Worker-DNEL chronic oral	No	Qualitative / Quantitative	interspecies factor: 7.5		interspecies factor reduced from 10 to 7.5 based on renal clearance of Chemical X in rats being 3x faster than humans instead of standard 4x (p103)	

Risk Assessment Element	Route	Input	Uncertainty	Parameter	Value / Range	Factor	Comments about uncertainty associated with the risk assessment element	Uncertainty Magnitude and Direction
Intraspecies Extrapolation	Oral	General Pop. DNEL chronic oral	No	Quantitative	intraspecies factor: 10		standard intraspecies factor applied for variation in sensitivity among general population (p103)	
	Dermal / Inhalation	Worker-DNEL chronic dermal	Yes	Quantitative	intraspecies factor: 5	?	route-to-route extrapolation: oral NOAEL used to extrapolate dermal NOAEL; RA does not use route-to-route factor, uses intraspecies factor of 5 because key study conducted with workers at workplace (p104)	+

Table 2. Worker Exposure Assessment

Route	Input	Uncertainty	Parameter	Value / Range	Factor	Comments	Magnitude and Direction
Routes Considered	inhalation and dermal	No	Qualitative			no incidental oral exposure (p233)	
Inhalation / Dermal	conversion factors used for equivalent X dose	No	Quantitative			(p235)	
Inhalation / Dermal	no sampling data for inhalation or dermal exposure, used EASE model	Yes	Quantitative	unique range for each exposure scenario	Inhalation: 0.18-1x Dermal: 0.18-1x	explanation of model (p232, 233); model exposure values: midpoint is "typical" exposure, upper bound is "Relative Worst Case" (RWC) (p236); RA admits over-estimation of exposure values therefore precautionary in absence of sampling data (p 237, 246)	Inhalation: - -Dermal: - -
Inhalation	main route of exposure	No	Qualitative			p233	
Inhalation	TWA used for duration calculation	No	Quantitative			typical OSHA TWA calculation (p253)	
Inhalation	packaging liquid products	Yes (negligible)	Qualitative	potential but low exposure	?	assumes no aerosol generated therefore no inhalation exposure (p247)	•
Inhalation	Occupational Exposure Limit (OEL); (equivalent to PEL)	Yes	Quantitative	Chemical X mg/m3; Chemical X form 1 10mg/m3	1-10x	OEL's based on TWA, different standards for different EU member states (p234)	+ +
Dermal	dermal exposure is cumulative	No	Qualitative			p252	

Route	Input	Uncertainty	Parameter	Value / Range	Factor	Comments	Magnitude and Direction
Dermal	Personal Protective Equipment (PPE)	Yes	Quantitative	960cm2, surface area of hands, face, forearms	?	RA assumes no PPE; however 100% protection from clothing (p232, 233)	+
Dermal	Personal Protective Equipment (PPE)	Yes	Quantitative	960cm2, surface area of hands, face, forearms	?	RA assumes no PPE worn by workers (p232, 233) but surveyed workers reported using PPE (p239, 247)	-
Dermal	modifying factors used for duration calculation instead of TWA	Yes	Quantitative	example: Table 9.39: from RA: typical = 0.50, RWC = 1.03mg/cm2/day; if OSHA 8hr TWA method is used: typical = 0.24, RWC = 0.53mg/cm2/day	0.48-0.51x	instead of using TWA, each task is modified in various mixed exposure scenarios; only four ranges for modifying factors, see table 9.38 (p253); RA admits dermal exposure calculation is overestimation (p252)	-

Table 3. Consumer Exposure Assessment

Route	Input	Uncertainty	Parameter	Value / Range	Factor	Comments	Magnitude and Direction
Routes Considered	measured routes: inhalation, dermal, and oral	Yes	Qualitative			study design, i.e. maximum use of given product may vary widely	+
Inhalation / Oral	indirect environmental exposure: air and soil	Yes (negligible)	Qualitative	relative exposure in µg X/day, negligible		(p269, 270)	•
Oral	main route of exposure	No	Qualitative			p273	
Oral	other dietary source: mineral supplements	Yes	Quantitative	1-10mg X/person/day	1-10x	although this source is identified, it is not included in exposure calculations (p269, 273)	+ +
Oral	drinking water	Yes	Quantitative	mean: <0.6mg X/LEU, Greece/Italy/Cyprus >5mg X/L, from measurement data	1-5x	EU Drinking Water Directive: Xcontent limited to 1mg X/L however some regions will exceed this level due to naturally high Xcontent in drinking water (p270-271)	+ + (specific regions)
Oral	mineral water	Yes	Quantitative	0.0005 - 4.35mg X/L; highly variable, mean: 0.55mg X/L	1.375-4.35x	typical=0.4mg X/L, RWC=1mg X/L; RA assumes EU Drinking Water Directive will limit X content in mineral water to 1mg X/L(p271)	+ +
Dermal	Xcontent in products	No	Quantitative	max allowed: cosmetics 5%, bath 18%, hair 8%, etc.		covered by Cosmetics Directive, not considered in RA (p264)	

Route	Input	Uncertainty	Parameter	Value / Range	Factor	Comments	Magnitude and Direction
Dermal	detergents and fertilizers	Yes (negligible)	Quantitative	relative exposure in µg X/day, negligible		p266, 267	•

APPENDIX B. UNCERTAINTY TABLES FOR CHEMICAL X - ECOLOGICAL RISK ASSESSMENT

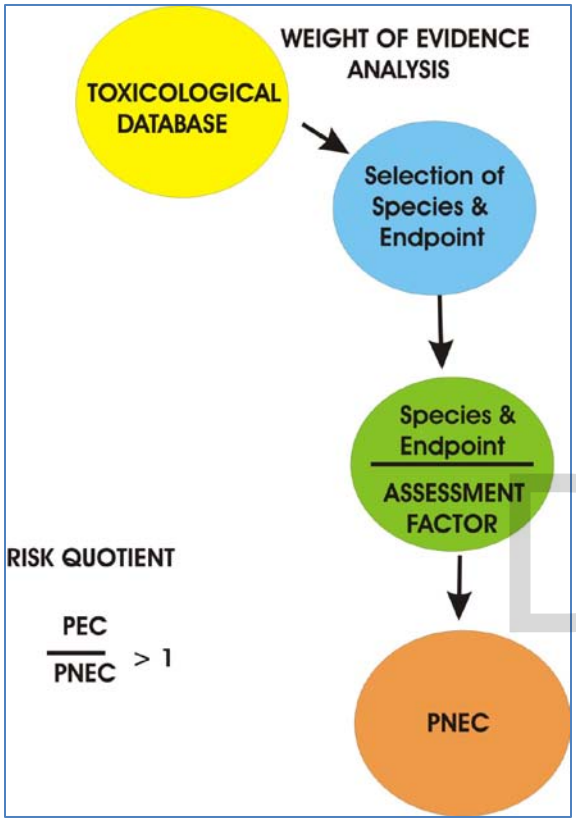

Figure 1. Conceptual Model - Freshwater Hazard (PNEC) derivation

Table 1. Hazard Assessment – Freshwater Organisms

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Toxicity test database	NA	Perhaps value could be an order of magnitude lower if insects had been included in the database	The lowest value for toxicity is used to derive the PNEC for all aquatic species. The more robust the database, the better chance that a set of class-specific values could be selected; no reptiles or fungi represented in database; the lowest value from a list of all tested species may not reflect the relevant environmental concentration of X that could affect the functioning of the ecosystem or important interspecific relationships (food web issues, competition, nutrient cycling, etc.)	All relevant aquatic species not represented (FW insects should be included)	-	True toxicity value lower than predicted	+	True risk higher than predicted
				Splitting the invertebrates from the vertebrates demonstrates due to different effects (endpoints)	-	True toxicity value lower than predicted	+	True risk higher than predicted
				Environmental form of X does not match form of X in toxicological test	-/+	True value could be lower or higher	-/+	True risk could be lower or higher
Duration of effect in risk assessment - acute v chronic	NA	Order of magnitude around PNEC value	Acute risk not considered. If exposure is to discrete pulses of X separated in time, the acute exposure may be more relevant. If so the chronic exposure likely overestimates risk given the same endpoint. A different endpoint might be selected if acute rather than chronic exposure of interest	Exposure period too long (chronic rather than acute)	+	True value may be higher	-	True risk may be lower

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Method to derive PNEC (assessment factor method used instead of statistical extrapolation method.)	NA	Assessment factor method more transparent than SSD method - no appreciable uncertainty added due to choice of this method	Unclear whether acute or chronic exposure is of interest, although I assume only chronic is of concern; assessment factor method selects lowest value from among database of available toxicity tests. Lowest value reported is for growth in a fish - slightly reduced growth may not be biologically significant and not represent appreciable "risk"	Lowest toxicity value for growth in fish may overestimate true biologically relevant value	+	True value may be higher (biologically and ecologically relevant value may be higher)	-	True risk may be lower
			Data on aquatic insects missing; this introduces too much uncertainty to calculate the SSD. Uncertainty introduced into risk assessment due to lack of analysis of key functional groups in FW. Unclear whether a key group will be affected and generate food web or ecosystem function issues	Lack of data on insects introduces too much uncertainty to calculate SSD	-/+	No value calculated true parameter value higher or lower	-/+	True risk could be lower or higher

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Lowest value for toxicity test - 34 d Brachydanio spp	1.8 mg X/L	Less than an order of magnitude - at most + or - 10%	This value is from a chronic test using X where the endpont is the NOEC for growth - measured in dry weight. The study reported different values for growth in the summary v. the results section and it is unclear which is correct - RA authors assume lower value is correct; It is unclear how dry weight was estimated in the study and there was no discussion of measurement difficulties (perhaps a source of uncertainty with the study?)	Dry weight may under or over estimate wet weight	-/+	True value could be lower or higher	-/+	True risk could be lower or higher
Assessment factor derivation	10	Could be as much as an order of magnitude in the PNEC	Value from REACH manual - used when 3 long-term chronic tests from three different trophic levels are available (but only one test is used?) It is difficult to tell what this 10X factor is designed to account for - presumably some type of UC. Whether a factor of 3, 10 or 100 is used has an effect on the demoninator in the risk quotient. The outcome of the risk assessment is sensitive to the choice of this parameter, but there is no discussion of this in the RA other than REACH citation	No experiments available for insects, the target group for X insecticides. REACH methodology requires three long-term chronic tests over three trophic levels but does not require use of insects in a trophic level test when assessing risk from insecticide	+	True value lower than predicted and assessment factor should be higher than estimated	+	True risk higher than predicted

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Derivation of the FW PNEC from assessment factor and species selected	0.18 mg X/L	Order of magnitude around PNEC value	Uncertainty as to whether selecting the lowest toxicty value from a set of at least three long-term toxicity tests across three trophic levels results in a value that is higher than necessary or lower than necessary - uncertainty from selection of right species and endpoint and assessment factor	Overall UC for PNEC combining above four factors	-/+	True PNEC could be lower or higher	-/+	True risk could be lower or higher
Toxicity test database for STP organisms	NA	Few tests on functional response of STP	Few functional effects tested; single species tests not as useful.	Effects on the functioning of microbial community more relevant than single species tox tests without relationship to ecosystem function	-/+	True value could be lower or higher	-/+	True risk could be lower or higher
Mortality NOEC for toxicity test - 28 d Chironomid spp	17.5 mg X/L	Used to estimate denominator in risk quotient	NOEC rather than EC50 used; foundational study was guideline study (OECD 209) designed to provide a rapid screening method (estimation of EC50) and not to estimate a EC10. The NOEC used in lieu of EC10 and then divided by 10 to get the PNEC	Mortality endpoint and not functioning of microbial community	-/+	True value could be lower or higher	-/+	True risk could be lower or higher

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Assessment factor derivation	10	Used to estimate denominator in risk quotient	No discussion of rationale behind selecting an assessment factor of 10; Selection of this value could affect the risk assessment outcome	Rationale for selecting assessment factor of 10 unclear	-/+	True value could be lower or higher	-/+	True risk could be lower or higher
Derivation of the PNEC from assessment factor	1.75 mg X/L	Denominator in risk quotient	This value may be overprotective if STP species can acclimate to higher X concentration in intake as suggested in a pilot study, however the X content of the intake to industrial STPs may be higher than the pilot plant and it may be species will not be able to acclimate to high concentrations from industrial plants		-/+	True value could be lower or higher	-/+	True risk could be lower or higher

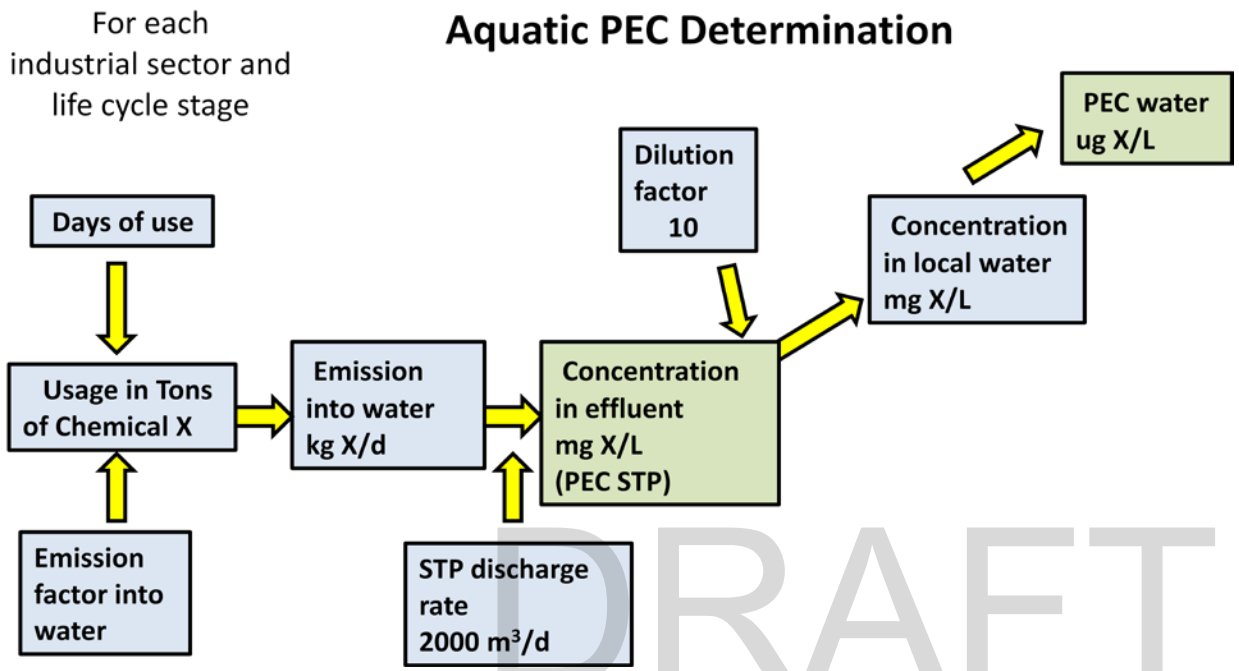

Figure 2. Conceptual Model for Deriving the PEC

Table 2. Exposure Assessment – Freshwater Organisms

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Generic scenario								
Assumed no emission reduction measures applied	0	If emission reduction measures had been used, the exposure in the generic scenario could likely be lower than the current estimate	Default assumption of no reduction may be too high		-	True value lower than predicted	-	True risk value may be lower than predicted
Days of use	300	Used to calculate emission into water and eventually the PEC	Default days of use - may be too low	Uncertain as to whether use includes every day of the year as the default indicates	+	True value higher than predicted	+	True risk value may be higher than predicted
Tons of B2O3 used	14363 Tons	Used to calculate emission into water and eventually the PEC	Default value may be too low or too high	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Emission factor into water	0.003	Used to calculate emission into water and eventually the PEC	Default emission factor for water - Actual value may be higher or lower	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Emission into water	44.6 kg B/d	Used to calculate the PEC	Default value may be too low or too high	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
STP discharge rate	2000 m3/d	Used to calculate the PEC	Default value may be too low or too high	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Dilution factor	10	Used to calculate the PEC	Default dilution rate - actual value may be higher or lower	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Concentration in local water	2231 ug/L	Used to calculate the PEC			-/+	True value may be higher or lower	-/+	True risk may be higher or lower
PEC generic scenario	2341 ug X/L	Numerator in risk quotient	Default values used to calculate generic RQ	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
PEC Specific scenario								

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Assumed no emission reduction measures applied	0	Used to calculate the PEC	Emission rate will be lower if any emission reduction measures are used	Uncertainty as to whether emission reduction measures are used	-	True value for emission rate will be lower	-	True risk value will be lower
Days of use	365	Used to calculate the PEC	The more days producers emit to the water, the higher the concentration in water	Uncertainty as to whether production plants operate every day of the year	-	True value may be lower if plants don't operate all year	-	True risk value will be lower
Tons of B2O3 used (average)	14403	Used to calculate the PEC	Value is average value in survey of producers	Uncerainty as to whether average is representative	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Emission factor into water	0.03	Used to calculate the emission rate into water	Default emission rate - acatual value may be higher or lower	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Emission into water (kg/d)	36.8 kg B/d							
STP discharge rate	2000 m3/d	Used to calculate the PEC	Default value may be too low or too high	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Dilution factor	10	Used to calculate the PEC	Default dilution rate - actual value may be higher or lower	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Concentration in local water	1838 ug/L	Used to calculate the PEC			-/+	True value may be higher or lower	-/+	True risk may be higher or lower
PEC (average)	1948 ug/L	Numerator in risk quotient	Average survey results used to calculate RQ	Uncertain as to representativeness of the average values	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Tons of B2O3 used (maximum)	24339	Used to calculate the PEC	Value is maximum from survey of producers	Uncerainty as to whether average is representative	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Emission factor into water	0.03	Used to calculate the emission rate into water	Default emission rate - acatual value may be higher or lower	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Emission into water	62.1 kg B/d	Used to calculate the concentration in effluent	Actual rate may be higher or lower		-/+	True value may be higher or lower	-/+	True risk may be higher or lower
STP discharge rate	2000 m3/d	Used to calculate the PEC	Default value may be too low or too high	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Dilution factor	10	Used to calculate the PEC	Default dilution rate - actual value may be higher or lower	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
Concentration in local water	3107 ug/L	Used to calculate the PEC		Uncertain as to representativeness of the values flowing from other variables	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
PEC (Maximum)	3217 ug/L	Numerator in risk quotient	Maximum survey results used to calculate RQ	Uncertain as to representativeness of maximum values	-	True value may be lower	-	True risk may be lower
PEC STP release (total) mg X/kg dw sediment	180 ug X/L	Numerator in risk quotient	Assume no removal of Xin the STP	Uncertain as to representativeness survey values and lack of X removal in STP	-	True value may be lower	-	True risk may be lower

Component	Value	Uncertainty transferred to the dependent entity	Comments	Description of Uncertainty	Uncertainty Magnitude direction PARAMETER VALUE	Relationship of estimated value to "true" parameter value	Uncertainty Magnitude direction for RISK ESTIMATE	Relationship of estimated value to "true" risk Impact of this parameter on risk estimate
Generic scenario								
PEC Surface freshwaters	2341 ug X/L	Numerator in risk quotient	Default values used to calculate generic RQ	Uncertain as to representativeness of the default value	-/+	True value may be higher or lower	-/+	True risk may be higher or lower
PNEC FW organisms (pelagic)	0.18 mg X/L	Order of magnitude around PNEC value	Uncertainty as to whether selecting the lowest toxicty value from a set of at least three long-term toxicity tests across three trophic levels results in a value that is higher than necessary or lower than necessary - uncertainty from selection of right species and endpoint and assessment factor	Overall UC for PNEC combining above four factors	-/+	True PNEC could be lower or higher	-/+	True risk could be lower or higher
RQ FW organims in surface FW	13.006						-/+	True risk may be higher or lower
Specific scenario (average)								
PEC Surface freshwaters	1948 ug/L	Numerator in risk quotient	Average survey results used to calculate RQ	Uncertain as to representativeness of the average	-/+	True value may be higher or	-/+	True risk may be higher or

				values		lower		lower
PNEC FW organisms (pelagic)	0.18 mg X/L	Order of magnitude around PNEC value	Uncertainty as to whether selecting the lowest toxicty value from a set of at least three long-term toxicity tests across three trophic levels results in a value that is higher than necessary or lower than necessary - uncertainty from selection of right species and endpoint and assessment factor	Overall UC for PNEC combining above four factors	-/+	True PNEC could be lower or higher	-/+	True risk could be lower or higher
RQ FW organisms in surface FW	10.822						-/+	True risk may be higher or lower
Specific Scenario (Maximum)								
PEC Surface freshwaters	3217 ug/L	Numerator in risk quotient	Maximum survey results used to calculate RQ	Uncertain as to representativeness of maximum values	-	True value may be lower	-	True risk may be lower
PNEC FW organisms (pelagic)	0.18 mg X/L	Order of magnitude around PNEC value	Uncertainty as to whether selecting the lowest toxicty value from a set of at least three long-term toxicity tests across three trophic levels results in a value that is higher than necessary or lower than necessary - uncertainty	Overall UC for PNEC combining above four factors	-/+	True PNEC could be lower or higher	-/+	True risk could be lower or higher

			from selection of right species and endpoint and assessment factor					
RQ FW organims in surface FW	17.872						-/+	True risk may be higher or lower

APPENDIX C. Chemical X Uncertainty Summary for Managers

Overall assessment of human health uncertainty (hazard and exposure):

Occupational exposures: while hazards may be slightly underestimated, exposure scenarios may lead to slight overestimates. Our overall judgment, based on uncertainties, is that it is likely (66-90% probability) that the risk estimates are accurate (close to the true value).

Consumer exposures: hazards may be slightly underestimated and exposures may also be underestimated (1-10x). The uncertainties associated with exposure provide the largest source of uncertainty and are underestimated. Our overall judgment is that it is unlikely (10-33% probability) that the risk estimates are accurate; our judgment is that they underestimate risk. Additional data on oral exposures would help to improve confidence in the assessment.

In both exposure scenarios, it is important to note that uncertainties, which cannot be quantified, exist.

Information below is provided regarding key parameters and their associated uncertainty. This information can be used to plan long term research to address data gaps.

Human Health Risk Evaluation Key parameters:

Hazard (safe level determination)

Dose response	overall uncertainty not quantifiable
Route to route extrap.	Worst case scenario used, slight overestimation (1-3x overestimate)
Interspecies extrap.	May lead to a slight underestimate (1-3x underestimate)
Intra species extrap.	May lead to a slight underestimate (1-3x underestimate)

Overall Hazard: looking at only the quantifiable uncertainties, they err on side of a slight underestimate of the hazard

Exposure Assessment

Occupational Exposure:

Inhalation	modeling may lead to an overestimate (3-10x overestimate)
Dermal	modeling may lead to an overestimate (3-10x overestimate) 100% clothing may lead to a slight underestimate (1-3x underestimate) Assumption of no PPE may lead to a slight overestimate (1-3x overestimate) Use of modifying factors may lead to a slight overestimate (1-3x overestimate)

Overall Occupational Exposure: looking at only the quantifiable uncertainties, they err on the side of a ~~slight~~ overestimate of occupational exposure

Consumer Exposure:

Oral:	some dietary sources ignored, may lead to underestimate (3-10x underestimate) Some drinking water exposures underestimated (3-10x underestimate)
Dermal	Uncertainties not quantifiable

Inhalation	Uncertainties not quantifiable

Overall Consumer Exposure: looking at only the quantifiable uncertainties, they err on the side of an underestimate of consumer exposure.

Overall assessment of Ecological uncertainty (hazard and exposure):

While hazards may be slightly overestimated they represent a worst case scenario for the most sensitive species, exposure scenario uncertainty is not quantifiable. Our overall judgment, based on uncertainties, is that it is likely (66-90% probability) that the risk estimates are accurate. It is also important to note that there were uncertainties that could not be quantified.

Additional data on exposure inputs would help to improve confidence in the assessment.

Information below is provided regarding key parameters and their associated uncertainty. This information can be used to plan long term research to address data gaps.

Ecological (Marine)Evaluation Key parameters:

Hazard (PNEC)

Dose response	used lowest value available, impact not quantifiable
Interspecies extrap.	Overestimate risk for tested species, for other species unknown Overall impact not quantifiable
Intra species extrap.	Assumed worst case

Overall Hazard: looking at only the quantifiable uncertainties, they err on the side of slight overestimate for those species evaluated, but representative of most sensitive species

Exposure Assessment (Environmental Concentration)

Exposure:

Water	Emission Factors used from true data, although data not representative
Terrestrial	Emission Factors used from true data, although data not representative

Overall Exposure: uncertainties not quantifiable

Template for managers summary:

1. Provide overarching summary of uncertainties.
2. Provide overall judgment of confidence.
3. Where uncertainties are great, identify major sources of uncertainty.
4. Clearly acknowledge the presence of any uncertainties which were unquantifiable.
5. Supporting information should break down key parameters and their input on assessment. This information should flow directly from uncertainty tables. And items 1-3 flow directly from the synthesis of this information. Where applicable, quantitative ranges to bound the uncertainty values should be presented.