Contaminants of Emerging Concern: A Prioritization Framework for Monitoring in Puget Sound

Contributing Authors:

C. Andrew James, Jill M. Brandenberger, Margaret Dutch, Joan Hardy, Deborah Lester, Dale Norton, Sandra M. O'Neill, Scott Redman, Irvin R. Schultz, Constance Sullivan, and James W. West

A Product of:

Puget Sound Ecosystem Monitoring Program

Toxics Workgroup

In Collaboration with:

Columbia River Toxics Reduction Workgroup

January 2015

PSEMP

PUGET SOUND ECOSYSTEM MONITORING PROGRAM

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The purpose of this document is to define a process to identify a priority group of Contaminants of Emerging Concern (CEC) for marine and freshwater monitoring programs in the Pacific Northwest. The prioritization approach includes three key principles: integrating CEC science and technology advancements; maintaining programmatic transparency; and engaging stake-holders and end users throughout the prioritization process.

A number of local and regional programs have evaluated the occurrence and impacts of CECs in the environment. There remains, however, much uncertainty associated with the extent and variability of occurrence, and associated impacts. Considering the remaining uncertainties, and the number of candidate compounds for monitoring, it was determined that a systematic prioritization process would be integral in the development of effective and efficient CEC monitoring programs.

The following elements were included in the process:

1. Develop clear objectives, define CECs, and identify target audience;
2. Use conceptual models to target appropriate media and determine frequency for monitoring;
3. Define the prioritization process;
    a. Identify chemical characteristics important to prioritization
    b. Determine how criteria/properties are incorporated
    c. Determine an approach for compounds with limited information
    d. Include consideration of biological end-points
    e. Develop a target CEC list
4. Incorporate transparency through stakeholder engagement

This generalized approach was adopted and refined for application in the region.

A first step was to define the CECs of interest. For the purposes of this exercise, CECs include compounds that:

- are primarily unregulated (i.e., do not have standards);
- are poorly characterized in terms of occurrence (and/or occurrence patterns); and
- have the potential, or are suspected, to cause adverse ecological impacts.

A key objective of a CEC monitoring program is the minimization of risk to human health and the environment. As such, it was determined that a risk-based approach would form the basis of the prioritization process. A risk-based approach entails prioritizing CECs by comparing a measure of occurrence with a measure of effect. Compounds that occur at levels higher than the selected risk threshold should be included for priority monitoring. Conceptual exposure scenarios may help refine sets of compounds for consideration by highlighting potential sources, pathways, and receptors.

Data availability will likely be limiting. Prioritizing a compound based on inadequate information can result in an unreliable ranking. It is recommended that a preliminary categorization be done based solely on data availability and data quality. Those compounds for which there is sufficient information can be subject to a prioritization. Those lacking can be categorized based on research needs (i.e., development of analytical methods, ecotoxicity evaluation, etc.).

Actual measured environmental concentrations (MEC) are preferred; the use of predicted environmental concentration (PEC) data should account for fate and transport processes, including losses through WWTPs. Not accounting for fate and transport will likely lead to poor estimates of environmental concentrations and unrealistic prioritization outcomes (Dong, Senn, Moran, & Shine, 2013). Environmental toxicity information may also be limited to only a few receptors or exposure scenarios. It may be possible to utilize other toxicological measures to estimate potential ecological impacts (Dong et al., 2013; Kumar & Xagoraraki, 2010).

In addition to a compound-focused approach, the prioritization process also includes consideration of biological endpoints for two key reasons:

1. There are scenarios where a biological response is observed in the environment but the causative agent has not been identified. Based on exposure-response and Adverse Outcome Pathway research, information about the presence of an effect may be useful in identifying an associated compound or class of compounds, which can then focus monitoring efforts.
2. The monitoring of biological endpoints can also be useful for evaluating the status and/or changes in environmental condition.

1 INTRODUCTION

Contaminants of Emerging Concern (CECs) present a challenge to environmental monitoring and management programs. There are thousands of individual compounds to consider and available data on their use, occurrence, fate, transport, and toxicity is limited. In addition, the rapidly developing state of the knowledge about these compounds requires an adaptive process. It is beneficial, then, to undertake a prioritization process that will identify the most important compound, or class of compounds, on which to focus limited resources. The objective of this work is to develop such a process.

This approach of developing an adaptive process instead of a stagnant compound list is consistent with recommendations found elsewhere. The International Joint Commission, for example, recommended that future CEC monitoring plans include a description of underlying principles and process by which priorities were established, and not just a specific list (International Joint Commission, 2009). Similarly, the NORMAN Association (a network of reference laboratories and related European government organizations for monitoring emerging substances) did not simply produce a list but rather designed a process that could be followed to evaluate groups of compounds (Dulio & von der Ohe, 2013). The process presented here is similarly flexible and adaptable and can be adjusted to specific program objectives and needs. While outcomes and recommendation developed in this work focus on conditions of Puget Sound, they could be adapted to other ecosystems.

Several steps were taken in process development including: developing a clear definition of CECs, interviewing representatives from regional agencies and programs involved in similar work, and performing a detailed review of the recent literature. These steps are described below.

1.1 Objective:

The objective of this effort is to develop a prioritization process to identify CECs and biological endpoints for current and future monitoring programs with a focus on marine and freshwater systems. The prioritization approach incorporates three key principles: the integration of science and technology advancements; maintaining programmatic transparency; and engaging stake-holders and end users. In addition, this approach accounts for advances in analytical chemistry, environmental toxicology, environmental occurrence, and changing use patterns.

1.2 Program Review and Scoping

To capture the experiences and lessons gained by others who have undertaken a similar task, a detailed literature review was performed. In addition, a set of interviews was conducted with program staff in Washington, Oregon, and California. The need for shared responsibility and leveraging across many programs was evaluated through a series of webinars with other programs studying CECs, including the Columbia River Toxics Reduction Working Group, Washington Department of Ecology (Ecology), Oregon Department of Environmental Quality (ODEQ), Southern California Coastal Waters Research Project (SCCWRP), and San Francisco Bay Regional Monitoring Program. Key lessons learned from each of these programs are summarized in Table 1.

The program review identified several steps that should be included in the development of a prioritization process for CEC monitoring in the region. Steps include:

1. Develop clear objectives and definitions of CECs, and identify the target audience
2. Use conceptual models to target appropriate media for monitoring each chemical and at what frequency
3. Define the prioritization process
    a. Define approach for compounds with limited information
    b. Identify chemical properties important to prioritization
    c. Define how chemical properties and criteria are incorporated into a ranking system (e.g., screening, weighting, etc.)
    d. Identify biological end-points to be used in the prioritization process
4. Include transparency through stakeholder engagement
    a. Create a formal review process
    b. Develop an advisory team

In addition to the procedural steps, the program review revealed several important factors that may impact the development and implementation of a prioritization process. These include:

- the availability and suitability of analytical methods;
- the relative loadings from municipal wastewater treatment facilities, stormwater, and commercial and industrial discharges;
- compound fate and transport;
- the appropriate environmental matrices (e.g., water, sediment, biota); and
- the incorporation of biological effects information.

These considerations were incorporated into the development of the prioritization process, as described below.

1.3 Definition of Contaminants of Emerging Concern

Thousands of different compounds that are used in pharmaceuticals, consumer products, and industrial applications have been identified as CECs. However, a commonly accepted definition for CECs has not been established, even amongst regulatory agencies. Prioritization schemes and studies define and limit CECs by chemical properties (Howard & Muir, 2010; Strempel, Scheringer, Ng, & Hungerbühler, 2012), by use categories or effects such as pharmaceuticals, endocrine disrupting compounds, etc. (Besse & Garric, 2008; Carlsson, Johansson, Alvan, Bergman, & Kuhler, 2006; Kumar & Xagoraraki, 2010; Murray, Thomas, & Bodour, 2010; Schriks, Heringa, van der Kooi, de Voogt, & van Wezel, 2010), or known environmental occurrence (Diamond et al., 2011; von der Ohe et al., 2011). Diamond et al. (2011) defined CECs as, “chemicals that are known or suspected to be released to aquatic environments but are not commonly regulated or monitored, and whose potential risk to ecological health are relatively unknown.” Similarly, Anderson et al. (2012) include those compounds which are, “largely unregulated and/or unmonitored in the aquatic environment.”

For the purposes of this effort, CECs are defined as compounds that:

1. are unregulated;
2. are poorly characterized in terms of occurrence (and/or occurrence patterns); and
3. have the potential, or are suspected, to cause adverse ecological or human health impacts.

It is acknowledged that there are many other compounds that may be included within a broader definition of CECs. This could include situations where new toxicological concerns are attributed to contaminants previously classified as a legacy persistent contaminant (for example) or perhaps as the result of a political or regulatory directive. However, this work will focus on compounds that fit the criteria listed above.

1.4 Literature Review – review of other prioritization efforts

A number of publications have described different prioritization approaches for monitoring CECs in the environment. Results vary greatly, not only according to the approach taken but also on how various chemical-specific properties were determined.

Roos et al. (2012), for example, compared results of nine previously-published prioritization schemes developed for a first tier prioritization process for pharmaceutically active compounds. The nine schemes included several risk-based approaches, which compared environmental concentrations (Predicted Environmental Concentration [PEC], Measured Environmental Concentration [MEC], modeled fish plasma steady state concentration, etc.) with effects concentrations (Predicted No Effects Concentration [PNEC], fish toxicity, etc.), and several approaches that did not consider exposure. Each scheme was applied to a suite of 582 active pharmaceutical ingredients. A comparison of the ranks indicated wide differences between prioritization methods. Less than a quarter of the pair-wise correlations between ranking schemes were greater than 0.5. A prioritization approach focusing solely on production volume was the least-well correlated to the other methods and was otherwise problematic due to lack of consideration of environmental fate and transport processes.

To get a measure of performance, seven well characterized compounds (in terms of environmental risk) were run through each prioritization scheme. Compounds included ethinylestradiol and levonorgestrel (high potential for adverse outcomes), carbamazepine, diclofenac, and fluoxetine (moderate potential for adverse outcomes), and atenolol and paracetamol (low potential for adverse outcomes). In general, approaches that determined risk based on chemical properties (e.g., log K_{ow}) successfully classified compounds into high, medium, or low risk categories, particularly compared to methods that utilized incomplete PECs, i.e., those that did not incorporate degradation or losses into calculation methods. The risk-based approach utilizing MEC was preferred, though a lack of environmental data may limit its application; only 12% of evaluated compounds had environmental concentration data. Authors concluded that exposure assessments require refinement and should include better information on degradation, removal in sewage treatment plants, and bioconcentration. Measured concentrations are preferred, though lack of data will limit the number of compounds that can be evaluated.

The following sections focus on recent publications that describe a process to prioritize CECs based on risk (i.e., consider both exposure and effects), chemical properties (i.e., PBT), or apply some other method (Appendix A).

1.4.1 Risk-Based Prioritization

Risk-based prioritization efforts compare measured or predicted environmental concentrations with a measure of toxicity, either to humans or one of many ecological receptors, to identify compounds with the highest probability of adverse impacts.

1.4.1.1 Ecological Risk

von der Ohe et al. (2011) applied the NORMAN framework for emerging substances (Dulio & von der Ohe, 2013) to prioritize a suite of 500 compounds occurring in European river basins based on both exposure and potential toxicity. The framework calls out three distinct steps: 1) categorize compounds into "action categories" based on the extent of environmental monitoring and toxicity data, 2) prioritize within each category according to a risk-based evaluation, and 3) a review process to validate results and update as new information becomes available. The rationale behind the first categorization step is that prioritization based on limited or low quality information will likely produce low-quality results. Data limitations are explicitly identified, along with specific follow-on actions for each compound (e.g., fund toxicological studies for compounds without sufficient information). The categorization is performed based on a decision tree approach (Figure 1). Once the compounds are sorted into categories they can be prioritized within each category according to a risk-based criteria.

von der Ohe et al. (2011) determined priorities based on the frequency of exceedance (number of sites where an effect level is exceeded) and the extent of exceedance (the magnitude by which the effects level is exceeded). Exposure was determined based on reported MECs at a given site, or the 95th percentile of all MEC values reported for all sites (MEC_{95}). Hazard was evaluated based on the lowest reported PNEC levels, either acute or chronic. In cases where no PNEC data existed, provisional PNECs were determined with predictive modeling. The frequency and extent of exceedance were calculated by:

$$\text{Frequency of Exceedance} = \frac{\sum n}{N}$$

where, n is the number of sites where MEC>lowest PNEC, and N is total number of sites

$$\text{Extent of Exceedance} = \frac{MEC_{95}}{PNEC_{min}}$$

Unit scores were then calculated based on the value of the extent of exceedance, and a priority ranking (PR) value was determined by the sum of the measures. Of the 500 compounds considered, 73 had sufficient occurrence and toxicity data to be included in Category 1 (potential hazard); the majority of which were pesticides. Approximately 44 compounds were determined to be of low risk.

In another approach, Dong et al. (2013) evaluated the 200 most-prescribed pharmaceuticals in the US, focusing on toxic loadings from WWTPs. Two key assumptions of the method were that the primary exposure pathway for pharmaceuticals was via WWTP effluent, and that relative mass loading was equivalent to relative exposure. Comparisons were made with toxic loadings (TL), defined as:

$$\text{TL} = \frac{\text{Mass Loading}}{\text{Toxicity Threshold}}$$

where:

$$\text{Mass Loading} = P_i \times u_i \times e_i \times d_i$$

P_i=prescribed mass, u_i=fraction utilized (=1), e_i=fraction excreted, and d_i=fraction discharged from WWTP.

Prescribed mass and excretion values were obtained from the literature. Fraction discharged from WWTPs is estimated utilizing the STPWIN program in U.S. EPA EPI Suite software (http://www.epa.gov/oppt/exposure/pubs/episuite.htm). The toxicity threshold was evaluated with 12 possible endpoints, including: algae 96-h EC_{50} (effects concentration for 50% of test population), algae chronic value, daphnid 48-h LC_{50} (lethal concentration for 50% of test population), daphnid chronic value, fish 96-h LC_{50}, fish chronic value, adult minimum initial dose, human LOAEL (Lowest Observed Adverse Effect Level), rat LD_{50} (lethal dose for 50% of test population), rat LOAEL, mouse LD_{50}, and mouse LOAEL.

Priority scores were calculated based on the difference between TL for a given compound compared to the mean TL for all other compounds by:

$$PS_{ij} = \frac{logTL_{ij} - \overline{logTL_j}}{Std\left(logTL_j\right)}$$

This method allows for the prioritization of compounds for which there is consumption or use data, but lack environmental measurements. Further, the approach allows focus on a specific receptor or group of receptors based on selected toxicological endpoints. The exposure scenarios, however, do not account for different transport pathways outside WWTP effluents.

Carlsson et al. (2006) evaluated risks associated with 27 common pharmaceuticals. The compounds were selected based on sales volume in Sweden and reports of environmental occurrence. As above, a risk quotient (RQ) was calculated by comparing a PEC with a PNEC. The PECs were determined through a consideration of consumption data, treatment through WWTP, and dilution (see Appendix A). The PNECs were determined based on lowest available acute LC_{50}-, EC_{50}-, or IC_{50}-values, or chronic NOEC-values with each being corrected by an appropriate safety factor (from 10-1000 depending on metric). An RQ > 1 indicated a potential risk. Paracetamol, ethinyloestradiol (EE2), oestradiol (βE2), and oestriol were found to potentially pose aquatic environmental risks based on this process. However, the authors identify a critical weakness as incomplete or inaccurate fate, transport, or chronic toxicity data, potentially contributing to erroneous results.

Besse and Garric (2008), identified priority pharmaceuticals based either on predicted occurrence or through evidence provided by one of several measures of toxicity. Previous work had demonstrated a

lack of PNEC values suitable for risk-based prioritization, and so other measures of toxicity could serve as proxies to identify priority compounds. PEC values were determined based on consumption and dilution in receiving waters, but assumed no losses through WWTPs. A secondary PEC was determined by adjusting for the percent of a compound excreted; again it was assumed there were no losses in WWTPs. Compounds were included as priorities if the PEC > 100 ng L^{-1}. Compounds were also considered priorities if: a) the chronic no observed effect concentration (NOEC) < 10 µg L^{-1}, b) there was a relevant mode of action (e.g., alter serotonin reuptake, estrogenic activity, antibiotic), c) there were known side effects in humans, d) there was enzymatic induction or inhibition (e.g., CYP450; glycoprotein P modulation), or e) log Kow > 4.5 and PEC > 10 ng L^{-1}. Application of these criteria identified approximately one-third of the pharmaceuticals and metabolites as priorities.

The California Water Resources Control Board, through SCCWRP, convened a study panel to prepare a monitoring strategy for CECs in California's aquatic ecosystem (Anderson et al., 2012). A risk-based approach was used to assess CECs for prioritization. The first step was to identify NOECs in fish and non-fish species based on a review of the literature and toxicity databases (EPA EcoTox and the MistraWikiPharma), and select priority compounds based on a NOEC < 0.1 mg L^{-1}. Sediment-based NOECs were determined only for compounds with occurrence data. The potential for human exposure through consumption of freshwater, or antibiotic resistance based on published minimum inhibitory concentrations was also considered. Eighty-two compounds were identified in this initial evaluation. The second step was to collect occurrence data (in WWTP effluent, receiving waters, sediments, and biological tissues). In the third step, compounds were screened through the determination of a risk-based monitoring trigger quotient (MTQ), which is the ratio of environmental concentrations to NOECs. An MTQ > 1 results in inclusion in the final priority list. This exercise was performed for three different exposure scenarios: a WWTP effluent-dominated inland freshwater receiving water, a coastal embayment receiving WWTP effluent and stormwater, and an offshore discharge. Ten compounds were identified for the freshwater systems (17β-estradiol [E2] and estrone [E1; metabolite of E2]; bifenthrin, permethrin, and chlorpyrifos; and ibuprofen, bisphenol A, galaxolide, diclofenac, and triclosan). Eight of the ten compounds identified in freshwater scenario were also identified for monitoring in the marine embayment scenario.

Diamond et al. (2011) applied three different screening approaches in their efforts to prioritize CECs. The first approach considered only risk; the second approach considered risk, persistence, and bioaccumulation; and the third approach considered toxicity (i.e., independent of measured or predicted concentration). The risk-based approaches focused on compounds with measured environmental concentrations. Predicted or calculated concentrations based on production information were not used since not all high production chemicals reach the environment, and low production compounds may have high potential for impacts.

The risk-based approach ranked compounds according to a calculated hazard value (HV, for toxicity) or endocrine risk values (based on either a no effects level or probable effects level):

$$\text{HV} = \frac{\text{Maximum observed concentration}}{\text{Most sensitive predicted effects threshold (toxic or estrogenicity)}}$$

Compounds with a HV of greater than 1.0 are likely to cause adverse impacts; compounds with HV greater than 0.1 were considered priorities.

The second prioritization approach considered the HV, in addition to persistence and bioaccumulation potential. Persistence was estimated with US EPA's Persistent, Bioaccumulative, and Toxic Profiler (PBT Profiler; www.pbtprofiler.net). Bioaccumulation potential was estimated based on log K_{ow}. An overall priority score was determined by assigning from one to three points for each parameter (risk, P, and B; Appendix A) and summing points give a total rank score. Priority compounds were those which received a score of seven or higher and could, for example, include those with high persistence and bioaccumulation but low toxicity.

The third prioritization approach considered toxicity (not risk), persistence, and bioaccumulation; it is described in section 1.4.2. The results of each approach resulted in a different prioritized list, clearly illustrating that the method will influence the outcome. By category, natural and synthetic hormones made up the highest proportion of the compounds identified by risk-based approach, while pesticides made up the highest proportion of the second and third approaches (those that considered persistence and bioaccumulation potential for each compound).

1.4.1.2 Human Health

Several studies prioritized CECs based on the potential risk posed to human health through consumption of groundwater or surface water. Vulliet and Cren-Olive (2011) screened pharmaceuticals and hormones in groundwater and surface water to evaluate risk to human populations. They collected approximately 70 groundwater and 70 surface water samples in France and analyzed for a suite of compounds identified in Besse and Garric (2008). Risk was determined by calculating I_{70} values, which is the ratio of potential lifetime exposure (lifespan = 70 years, consumption = 2 L d^{-1}, dose = max. measured concentration) to the minimum daily therapeutic dose. For pharmaceuticals, the highest risk was presented by benzodiazepine, which still had a potential indirect exposure 125,000 times below the therapeutic dose. Three hormones (norethindrone, ethinylestradiol, and levonorgestrel) were detected at concentrations resulting in $I_{70} > 1$, indicating some potential for risk.

Schricks et al. (2010) screened a suite of 100 CECs for potential human health impacts by first establishing provisional drinking water guidelines, and then comparing the provisional guidelines to environmental concentrations detected in surface water or groundwater of the Rhine or Meusse river basins. Guidelines were established from (in order of priority): 1) existing statutory guideline values, 2) published Tolerable Daily Intake (TDI), Acceptable Daily Intake (ADI) or Reference Dose (RfD) values, 3) published lowest/no observable effects levels (LOEL, NOEL), or 4) other toxicological data. Compounds without effects data were not included in the screening. A Benchmark Quotient (BQ) was calculated by comparing the guideline value with the measured occurrence data; a BQ >0.1 indicated a priority compound. For the majority of the compounds there was a significant margin of safety between environmental concentrations and the provisional guidelines with 1,4-dioxane, carbamazepine, diuron, p,p'-sulfonyldiphenol, and PFOS/PFOA approaching the priority criteria.

Murray et al. (2010) evaluated 71 compounds within three broad classes of chemicals (industrials, pesticides, and PPCPs) to assess the relative risk to human health. Compounds were selected based on

frequency of reporting in the literature. Risk was determined by comparing reported ADI values to exposure via direct consumption of surface waters. Based on an assumed consumption threshold of 20 L d^{-1} (2 L d^{-1} with a safety factor of 10) perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), bis(2-ethylhexyl) phthalate, the hormones EE2, βE2, and E1, PPCPs carbamazepine, DEET, triclosan, and acetaminophen, and several pesticides (diazinon, methoxychlor, and dieldrin) were identified as priority compounds. They were unable to evaluate several compounds due to the lack of toxicity data.

As described above, there have been several efforts to prioritize CECs using risk- based approaches which require either MECs or PECs to assess exposure scenarios. There is, however, a paucity of such information (Roos et al., 2012). There are several other efforts that have performed prioritization work considering only compound specific properties, similar to the PBT approach in Diamond et al. (2011). These will be discussed in more detail, below.

1.4.2 Prioritization Based on Chemical Properties

Under the European Union chemical legislation (REACH), chemical compounds are evaluated based on persistence (P), bioaccumulation potential (B), and toxicity (T). Strempel et al. (2012) performed this evaluation for approximately 95,000 chemicals. Chemical properties were determined based on either measured values reported in the literature, or calculated utilizing EPA's EPI Suite: BIOWIN3 for the biodegradation half-lives under aerobic conditions; BCFBAF for bioconcentration factor (BCF), and ECOSAR for toxicity (the 96 h EC_{50} or LC_{50} for fish and 48 h EC_{50} or LC_{50} for *Daphnia*). Predicted values were compared to threshold values ($t_{½,soil}$ = 120 days, BCF = 2000; and chronic NOEC of 0.01 mg L^{-1} or an acute effect concentration of 0.1 mg L^{-1}). Sub-scores for P, B, and T were calculated relative to the threshold values (see Appendix A) and summed to determine a final ranking. Results indicated that 3.1% of all compounds (n=2930) were classified as PBT, while 61.3% did not exceed any threshold category. Fifty-seven of the PBT compounds were high production volume chemicals.

Howard and Muir have undertaken a series of studies to identify compounds of concern used in commerce (Howard & Muir, 2010), pharmaceuticals (Howard & Muir, 2011), or byproducts, impurities, and transformation products (Howard & Muir, 2013). In each case they compiled an extensive list of compounds from published governmental databases (e.g., Canadian Domestic Substance List, U.S. EPA Toxic Substances Control Act [TSCA] Inventory Update Rule database, U.S. FDA. Drugs@FDA data files, etc.) and evaluated the potential for persistence and bioaccumulation of the individual compounds; measures of toxicity were not included. Persistence and bioaccumulation were based on QSAR modeling in the EPI Suite software. The KOWWIN program was used to estimate log K_{ow} and the BCFBAF program was used to determine bioconcentration factors (BCF). BIOWIN was used to estimate persistence. A compound was judged as being potentially bioaccumulative if log K_{ow} > 3. Persistent compounds were those with the BIOWIN output of less than 0.5 (50% probability that biodegradation will not be fast); or where chemical structure suggested persistence (e.g., highly halogenated, highly branched, nitroaromatic). In each case an extensive list of compounds was identified to help focus monitoring efforts.

As described above, Diamond et al. (2011) evaluated three prioritization schemes applying different selection criteria for each. Two of the approaches included an element of risk while the third focused

solely physical/chemical properties (toxicity, persistence, and bioaccumulation), but not occurrence. Persistence was determined with the US EPA PBT profiler, bioaccumulation predicted from log K_{ow}, and toxicity was based on structure activity relationships predicted through US EPA's ECOSAR modeling program (http://www.epa.gov/oppt/newchems/tools/21ecosar.htm). A score was determined according to the value of each parameter (Appendix A) and summed to give a total rank score. Importantly, the resulting ranking was markedly different from this approach compared to the other two described.

Sanderson et al. (2004) utilized QSAR modeling (US EPA EPIWIN) to estimate EC50 values for algae, daphnid, and fish for a group of 2986 pharmaceuticals. The EC50 values were converted to a HQ based on an EC50/PNEC safety factor of 1000 and assumed environmental concentration of 1 µg L^{-1} in order to identify groups of priority compounds. Results suggested that paraffins and anionic surfactants had highest predicted toxicity. Treatability of compounds was also estimated through the US EPA STPWIN model. These values were not used to estimate or adjust PECs.

1.4.3 Other Approaches

Kumar and Xagoraraki (2010) developed a ranking system for PCPPs and EDCs in surface waters and drinking water based on four criteria: occurrence, treatment potential, ecological effects, and human health effects. The ranking was performed by calculating a utility function for each of the criteria and then combining the utility function values based on a weighting scheme. For example, the occurrence criteria is determined by:

$$Uo = 0.5\left(\frac{df}{100}\right) + 0.5\left(\frac{C - C_{min}}{C_{max} - C_{min}}\right)$$

where: df = detection frequency and C, C_{max}, and C_{min}, are the measured, maximum, and minimum environmental concentrations.

The utility function for each criteria range from 0 to 1 and allow incorporation of qualitative and quantitative data into the ranking scheme. Weighting is used to combine unit scores of each criterion into an overall ranking. The ranking scheme was applied to a suite of 100 PCPPs and EDCs in order to identify a list of 20 priority compounds. The list of 20 varied depending on the individual criteria as well as the system or water of interest suggesting that the results of the ranking exercise will vary according to local scenarios.

de Voogt et al. (2009) performed a review of several existing prioritization processes for pharmaceutically active compounds based on an extensive set of criteria. They reviewed 25 different publications, covering 153 compounds and applied 17 unique evaluation criteria. They chose to focus on seven criteria for a focused re-evaluation. The criteria were: regulation (i.e., appearance on regulatory list); consumption/sales; physiochemical properties; occurrence in waters (e.g., surface water, groundwater, drinking or wastewater); toxicity/ecotoxicity; degradability/persistence; and resistance to treatment. The compounds were separated into three priority classes based on their frequency of mention in the documents reviewed and the number of criteria each satisfied. High priority chemicals included carbamazepine, sulfamethoxazole, diclofenac, ibuprofen, naproxen, bezafibrate, atenolol, ciprofloxacin, erythromycin, and gemfibrozil. Results of de Voogt's work were

used to create a high-priority list of compounds for WWTP effluent and biosolid monitoring by the Washington State Department of Ecology (Lubliner, Redding, & Ragsdale, 2010).

1.4.4 Literature Review – CEC occurrence data

A suite of regional projects provide information on the occurrence of CECs in various compartments, including wastewater (Hope, Pillsbury, & Boling, 2012; Lubliner et al., 2010; Morace, 2012), freshwater (Dougherty, Swarzenski, Dinicola, & Reinhard, 2010; Rounds, Doyle, Edwards, & Furlong, 2009), marine water (Keil, Salemme, Forrest, Neibauer, & Logsdon, 2011), sediments (Long, Dutch, Weakland, Chandramouli, & Benskin, 2013), and biota (da Silva et al., 2013); other investigations are underway. A summary of results is presented in Table 2. These studies provide a strong base of monitoring information on the occurrence of CECs and allow some predicative capabilities about the occurrence of CECs in general:

- Many CECs are present at low levels (<100 ng L^{-1}) in marine waters of Puget Sound. Conservative and highly used consumer products are nearly ubiquitous, while more labile compounds are regularly detected.
- CECs are also detected in lowland streams. Concentrations and detection frequencies are more variable compared to marine waters.
- Limited CECs are present in marine sediments. Detection frequency is low, even in urban bays.
- WWTPs are effective at removing some but not all CECs. Advanced treatment processes may be more effective at CEC removal compared to standard secondary treatment systems.
- Synthetic hormones have not been detected in fish bile. Other EDCs (e.g., bisphenol A and E2), however, have been detected.

There also remain many fundamental data gaps in regional occurrence information. Indeed, a major objective of this current work is to develop a meaningful and rational process by which these gaps, particularly with regard to compounds of highest concern, are addressed. In addition to specific or groups of compounds, there are some environmental compartments which may be of interest due to potential exposures but lack monitoring data. These include:

- rivers and marine waters proximate to WWTP outfalls;
- lowland streams;
- stormwater outfalls;
- livestock handling operations; and
- surface waters receiving runoff from areas of biosolids application.

1.4.5 Literature Review - Summary

- As demonstrated above, there are a wide variety of approaches can be used to prioritize monitoring of CECs in the environment. The method chosen will impact the suite of compounds identified as priorities.
- Measured or reported data will likely be limiting in the application of a prioritization scheme. The use of “action categories” can be a way to allow prioritization of compounds with sufficient information, while identifying research needs for those without (von der Ohe et al., 2011).

- Risk based approaches (i.e., comparing a measure of occurrence with a measure of toxicity) have demonstrated promise (Diamond et al., 2011; Roos et al., 2012).
- Measured environmental concentration data may be limited. The use of predicted environmental concentration data should account for fate and transport processes, including losses through WWTPs. Not accounting for fate and transport will likely lead to poor estimations of environmental concentrations and unrealistic prioritization outcomes (Dong et al., 2013)
- Environmental toxicity information may be limited to only a few receptors or exposure scenarios. It may be possible to utilize other toxicological measures to estimate potential ecological impacts (Dong et al., 2013; Kumar & Xagoraraki, 2010)
- Conceptual exposure scenarios may help refine sets of compounds for consideration.

2 IDENTIFY CONCEPTUAL MODELS.

A conceptual model can be used to explicitly identify relationships between human activities and environmental impacts. The exercise of developing a conceptual model can: 1) highlight source and exposure pathways that have the potential to cause the highest degree of impact, either to humans or to the environment, and 2) improve estimates of CEC distribution among aqueous, particulate, sediment, vapor, or biological compartments. With respect to the prioritization of monitoring of CECs, conceptual models can define areas of interest for focused investigation.

Anderson et al. (2012) utilized a pressure framework to identify three priority exposure scenarios to focus monitoring. These included an effluent-dominated inland waterway, a coastal embayment receiving WWTP discharge and stormwater, and an ocean discharge of WWTP effluent. Others have developed prioritization schemes based on specific exposure scenarios including sources (e.g., human pharmaceuticals), pathways (e.g., WWTP effluent), and exposure (e.g., dissolved phase in aquatic environment) (Besse & Garric, 2008). Others have evaluated similarly specific exposure scenarios (Dong et al., 2013; Drewes et al., 2013; Kumar & Xagoraraki, 2010; Munoz et al., 2008; Murray et al., 2010). There is generally a lack of extensive discussion on the use of conceptual exposure models in these studies, though their implicit use likely resulted in the identification of a given scenario.

Conceptual models have been developed for Puget Sound to support coordinated ecosystem recovery efforts using Miradi software (version 4.1). A pressure framework was developed based on a regional pressure taxonomy (Stiles & Redman, 2013). From this framework, a conceptual model was developed to provide an overview of the sources of contaminants to the aquatic food web. It is specific to the freshwater system and associated food web, but can be easily adapted to focus on the marine system and associated food web (Figure 2).

Several conceptual models focusing on contaminant fate and transport have been developed to depict transference of contaminants through the marine system, marine food web, and to the freshwater and terrestrial systems. Overall, the models are general and the strength of each connection depends on the physiochemical properties of a compound or suite of compounds. CECs have a variety of accumulative properties due to varying mechanisms for metabolism and varying degrees of solubility in the water column. Thus, no single model can be created to show movement of CECs through a food web since they are specific to the system of interest, i.e., Puget Sound.

The generalized model (Figure 3) shows linkages between different sources of compounds, how they enter and travel through the food web. Modifications to exposure pathways can be made to represent a different significance of a particular pathway for a specific compound.

Generalized models can be modified according to compound-specific properties. For example, a model could be created to elaborate on sources, fate, and transport of a suite of CECs that are hydrophobic and undergo some level of metabolism within organisms. Hydrophobic compounds associate more-strongly with sediments compared to water. As a result, organisms that spend a greater portion of their life cycle in the benthic environment will accumulate a higher contaminant load. Compounds that are readily metabolized are not biomagnified in the food web. A fraction of the compounds are water

soluble, and may be taken up by plankton and aquatic plants. The detritus loop also plays a role in primary exposure. The secondary route of exposure is consumption of benthic organisms.

2.1 Conceptual Model - Recommendation/Next Step

It is recommended that the generalized pressure and fate and transport conceptual models be utilized to develop versions for specific sources and associated compound groups, and that these specific models be utilized to focus and communicate recommendations for monitoring. Models could include human health exposure from freshwater.

.

3 DEFINE THE PRIORITIZATION PROCESS.

The need for a process to prioritize CECs and biological endpoints for monitoring has been demonstrated (Boxall et al., 2012; von der Ohe et al., 2011); there are thousands of compounds with a likelihood of occurrence and limited resources for monitoring, characterization, or evaluation. As previously discussed, a prioritization process should include scientific/technical evaluation, an independent review, and stakeholder involvement. There are many decision points and a robust stakeholder involvement program can offer significant opportunities for review and to strengthen the decision process. This section will focus on the scientific and technical decision points.

A fundamental, framing objective of this exercise is the reduction or elimination of the potential for environmental harm due to the occurrence of anthropogenic compounds. As such, any prioritization process identified should include a consideration of risk (e.g., exposure and biological response) (Drewes et al., 2013; Roos et al., 2012; von der Ohe et al., 2011). A discussion of the risk-based prioritization approach is presented in section 3.2.

The quality of any such evaluation is dependent on the quality of data (occurrence and toxicity) upon which key factors are determined. Quality information on many CECs is, by definition, lacking. As such, it is recommended that a categorization step be performed on the compounds under consideration based on the extent and quality of information available. This step is discussed in section 3.1.

Further, it is recommended that the prioritization process includes consideration of biological endpoints where observations of ecological impacts (e.g., endocrine disruption, feminization, etc.) inform and focus chemical monitoring; an impact is noted and followed by an investigation of potential causative agents. A discussion is included in section 3.7.

3.1 Compound Prioritization - Categorization

A risk-based prioritization process must be based on reliable and accurate occurrence and effects data Otherwise the outcome may be meaningless. There is extensive data for some compounds while a complete lack of for others. A rational prioritization program should give consideration to the extent and quality of information available for compounds of interest, including that for occurrence and toxicity. This has been acknowledged elsewhere. von der Ohe et al. (2011) and Dulio and von der Ohe (2013) recommend an initial screening step where compounds are categorized based on the extent of knowledge of exposure and effects. Final prioritization would only be made for compounds with sufficient information, with a recommendation of further research for those without. Drewes et al. (2013) acknowledged the existence of “unknown unknowns” - compounds for which there was neither occurrence nor toxicological information – and recommended that these not be included in any prioritization scheme until reliable measurements or estimates could be made. Kumar and Xagoraraki (2010) calculated data gap scores to quantify and compare the uncertainty of various parameters (e.g., occurrence, magnitude, etc.) for individual compounds. The data gaps and priority rankings were determined independently and so a compound could have both a high uncertainty and a high priority ranking.

Others have chosen not to perform a categorization step, but have either selected an initial candidate list that includes only compounds with existing data or have used surrogate measurements to estimate exposure or effects. As a management-support evaluation, one of the objectives of this exercise is to identify follow-up activities for consideration (monitoring, ecotoxicological research, analytical method development, etc.), which is consistent with the idea of explicitly categorizing compounds based on available data. It is recommended that categorization be an integral part of the prioritization process. A potential approach is shown in Figure 1, where individual compounds could be evaluated with a decision tree resulting in several distinct groups clearly categorized for follow-up action.

3.1.1 Management Categories

Table 3 lists recommended management categories, consistent with the decision tree shown in Figure 1. As shown, follow-on activities can be identified for each group based on measures of the extent and quality of supporting data. For example, compounds in Category 1 (sufficient occurrence and ecotoxicity data, potential risk) or Category 2 (lack occurrence data, sufficient ecotoxicity data, unknown risk) could be selected for inclusion in a monitoring program based on the results of a prioritization exercise (section 3.2), while compounds in Category 6 (sufficient occurrence and ecotoxicity data, no potential risk) can be removed from future monitoring programs as they are unlikely to cause harm. Compounds in the other groups will require investment in fundamental research prior to deciding whether or not to include them in a monitoring program. Category 3 compounds lack ecotoxicity data and therefore some measure of their potential harm/outcome should be determined prior to monitoring. For Category 4 compounds, current analytical methods are not sufficient to measure the compounds in the environment at levels that are anticipated to cause harm. As such, there should be investment in analytical method development. Category 5 compounds lack information on impacts and there is little analytical capacity to determine the extent or magnitude of occurrence. These information gaps should be filled prior to their inclusion in any monitoring program.

The theoretical, long-term outcome of this categorization exercise is that all compounds will either end up in Category 1 (sufficient occurrence and ecotoxicity data, potential risk) or Category 6 (sufficient occurrence and ecotoxicity data, no potential risk). Those posing a potential risk will be subject to a management or control measure (e.g., water quality standards, chemical action plan, labeling restrictions, etc.) and continued monitoring, while those not posing a risk can be categorized as such. Investments will be made to fill knowledge gaps associated with compounds in the other groups (i.e., those which lack ecotoxicity data or sufficient analytical methods), allowing a full, risk-based evaluation. The risk-based evaluation will inform on the final status (i.e., pose risk or not) of the compounds under investigation allowing them to be placed into Category 1 or 6. This process can aid in the definition of a long-term investment strategy.

3.1.2 Management Category Decision Criteria

Classifying CECs into management categories requires establishing criteria to determine if available data are sufficient and reliable. Others, for example, have suggested that an ecotoxicological evaluation be based on laboratory studies for at least three trophic levels, e.g., algae (*Selenastrum capricornutum*), a cladoceran (*Daphnia magna*) and the fathead minnow (*Pimephales promelas*), to be considered sufficiently reliable to support further classification (von der Ohe et al., 2011). Similarly, sufficient

occurrence data has been defined by having measurable concentrations at a minimum of 20 different sites.

With regard to the sufficiency of occurrence data, it is important to have actual measurements to determine exposure concentrations to environmental receptors at a given location. It is not necessary, however, that a given evaluation effort measures concentrations of a specific compound at every location. Similarities in use and behavior patterns and sources allow the transference of information gained in one system to be reasonably well transferred to another. For example, there are ample measurements of CECs in WWTP effluent (Hope et al., 2012; Luo et al., 2014; Michael et al., 2013; Miege, Choubert, Ribeiro, Eusebe, & Coquery, 2009; Pal, Gin, Lin, & Reinhard, 2010) and such information could be used to inform categorization, so long as consideration of data quality and use patterns (e.g., between countries) are included.

With regard to the sufficiency of effects data, it is recommended that effects and/or impacts be determined based on experimental data and that is documented in the published literature. There are several approaches for developing a suitable effects level (Hahn et al., 2014). As such it is imperative to document decision points associated with, among other things, the species and ecosystems of interest, the effects and species of concern, and the use of safety factors. The trophic level approach outlined in (von der Ohe et al., 2011) can be adopted for local application.

3.2 Compound Prioritization – Risk Based Characterization

The categorization exercise will identify groups of compounds with sufficient data to allow for prioritization based on potential to cause environmental harm. Compounds in Category 2 (insufficient occurrence data, sufficient ecotoxicity data, unknown risk) could also be included for consideration in an environmental monitoring program, though they would not be prioritized through a risk based process. Compounds in the other groups would not be included in a risk based prioritization due to the lack of sufficient data.

A risk-based approach compares a measure of occurrence of a given compound with a measure of potential impact. In the simplest method, compounds with occurrence levels greater than impact levels are considered priorities for follow up. The resulting quotient has been described variously as a risk quotient (RQ), monitoring trigger quotient (MTQ), risk value (RV), or benchmark quotient (BQ). Similar measures have also been devised strictly for human exposures. In general terms, the risk quotient is calculated by:

$$\text{Risk Quotient} = \frac{\text{Occurrence Concentration}}{\text{Toxicity Threshold}}$$

Priorities are identified by those compounds displaying the highest quotient of risk and generally include all compounds with a risk quotient value > 1.0. Sufficient safety factors are included to account for potential uncertainties.

It is recommended that a risk quotient (or equivalent) be utilized to prioritize compounds with sufficient occurrence and toxicity information.

3.3 Compound Prioritization – Hazard Based Characterization

Advances in analytical techniques have allowed the identification of anthropogenic compounds in the environment at part per billion levels and below (Kolpin et al., 2002), many of which had not previously been observed. The implication is that there remain a large number of compounds that occur at comparable levels but have not yet been detected or reported. In order to account for this, it is recommended that the prioritization list includes compounds that have toxicity data indicating a PNEC < 0.1 μg L^{-1}, including those without occurrence data (Category 2). The highest priority compounds identified in this step will be those with the lowest PNEC.

3.4 Determination of occurrence levels and toxicological threshold

To determine absolute or relative risk, measures of occurrence and toxicity are needed. Various measures have been used; a brief discussion of these is presented below.

3.4.1 Predicted vs. Measured Environmental Concentrations

Measured environmental concentrations are the preferred method of estimating environmental occurrence of a given compound though available data may be limited (Anderson et al., 2012; Roos et al., 2012). MECs may lack sufficient coverage to adequately characterize spatial and temporal variations and, further, the range of parameters may be limited. Quality sampling programs can be expensive. Advances in instrumentation make broadscan analysis possible which provide information on a wide range of compounds in a single sampling effort. However, even with sufficient time and budget, there remain analytical challenges. Despite cost and complexities, it may be necessary to collect environmental data through sampling (even in cases where a modeling approach is preferred) in order to verify model outputs.

Data sets describing environmental measurements in other locations can be used to inform on local conditions. However, prior to utilizing data it is important to note considerations in sampling program design and implementation (C. Ort, Lawrence, Reungoat, & Mueller, 2010; Christoph Ort, Lawrence, Rieckermann, & Joss, 2010), regional differences in chemical use (Curtis et al., 2006), and physical characteristics which impact fate and transport, all of which can influence whether measurements accurately depict the environment of interest, whether they are transferrable, and whether compounds are susceptible to similar environmental processes. Careful consideration is required before adopting external data sets.

In additional to MECs, several approaches for determining a PEC have been developed (Appendix A). Carlsson et al. (2006) estimated PEC based on sales data, dosing, and assumed dilution factors. Estimates were later refined to incorporate partitioning and degradation through a WWTP, though the accuracy of the model for CECs was not discussed. Besse and Garric (2008) followed a similar approach; however, they did not account for degradation. Others have used modeling (e.g., USEPA EPI Suite) based on a compound's physical and chemical properties to estimate losses and environmental exposures (Cooper, Siewicki, & Phillips, 2008; Sanderson et al., 2004). The validity of such an approach has been questioned (Tunkel, Mayo, Austin, Hickerson, & Howard, 2005); some biodegradation models can provide qualitative or quantitative predictions for some compounds, though the user needs to be

aware of the appropriate model domain prior to application. Not all models have predictive capability for all compounds. An evaluation of Biowin models to predict the biodegradability of pharmaceuticals (which are necessary parameters for fate and transport modeling) found that they performed poorly (Rucker & Kummerer, 2012).

Pistocchi et al. (2010) reviewed the state of spatially explicit chemical fate and transport modeling, summarizing approaches taken with multiple box models, numerical solutions of simultaneous advection–dispersion equations, and meta-models. All models require information on the physical–chemical properties of the compounds of interest, the environmental conditions where the model is applied, and factors related to emissions and releases of the compounds to the environment. While remote sensing has increased availability and accuracy of data describing environmental conditions (e.g., landscapes, spatial and temporal weather patterns, etc.), there remains a paucity of information on the physical-chemical properties and, in particular, emissions, which make accurate modeling difficult to achieve. In any case, models require validation prior to acceptance, which relies on actual observations and environmental data.

There are currently a limited number of environmental fate and transport models available for the Puget Sound region. The Washington State Department of Ecology has combined a box model to estimate spatial and temporal patterns in circulation (Babson, Kawase, & MacCready, 2006) to develop the Puget Sound Regional Toxics Model, a mass balance model of contaminant fate and transport to investigate responses to management scenarios for the control of PCBs. A revision of the model to evaluate PAHs, PBDEs, and selected metals is ongoing.

The use of MECs is preferred over PECs. There are currently a few data sets generally describing the presence of a selected number of CECs in the Puget Sound (see Section 1.4.4). Additional monitoring should be focused on areas that may experience high exposures to inputs of CECs (near WWTP outfalls in rivers and the Puget Sound, CSO outfalls, etc.).

The use of a statistical measure of MEC to represent potential exposure scenario in a given environment is recommended. A 95th percentile of measured data (or equivalent) may be used to represent a higher end of potential environmental occurrences without the consideration of outliers. External (i.e., non-local) data may be used to augment data sets after careful consideration of suitability.

3.4.2 Ecotoxicity Evaluation

A risk based evaluation requires estimates of exposures and effects. Effects measures can be associated with acute or chronic toxicity, endocrine disruption, carcinogenic effects, mutagenesis, and/or teratogenicity. Compounds that bioaccumulate, biomagnify, or are otherwise persistent, are often classified as having a higher potential to cause adverse impacts. Analogous to occurrence, effects estimates can be based on modeled or experimentally determined outcomes. For example, Diamond et al. (2011), utilized predicted chronic toxicity thresholds for fish, *Daphnia*, and algae determined from ECOSAR and PBT profiler, and an estrogenic activity derived from a Food and Drug Administration database (http://edkb.fda.gov/). Kumar and Xagoraraki (2010) utilized published acute measure LC_{50} for aquatic indicator species, such as fish, daphnids, and algae to rank effects. They also allowed for the incorporation of other measures of health impacts such as evidence of risk during pregnancy or

evidence of carcinogenicity, mutagenicity, or impairment to fertility. The risk score was determined by reports in the literature; if any study indicated that a compound was carcinogenic, for example, the given compound would increase its risk rating through a weighted determination of unit functions (Appendix A). Others have used information that is not strictly ecotoxological to screen for the potential to cause harm to non-target organisms such as side effects in humans, enzymatic induction or inhibition, or glycoprotein P modulation (Besse & Garric, 2008). The proper method for incorporating such information into a risk assessment has been identified as a significant research need (Boxall et al., 2012). In addition, concentrations of compounds associated with the promotion of antibiotic resistance has also been used as a criteria for prioritization (Anderson et al., 2012).

von der Ohe (2011) estimated toxicity through the determination of a PNEC based on experimentally-determined or modeled values. Experimentally determined PNECs were either from existing risk assessments or published LC_{50} values for standard test organisms corrected with a safety factor. In cases where there was no toxicity data, the PNEC was estimated using a k-nearest neighbor read-across methodology based on experimental data from similar compounds, or estimated from the octanol-water partitioning coefficient when data for similar compounds was not available. When more than one PNEC was available, the lowest was utilized in the determination to evaluate risk. It is important to note that the authors specifically categorized compounds with insufficient toxicity data as needing a rigorous effects assessment and did not consider the use of modeled toxicity to be sufficiently robust for final classification/categorization.

Fick et al. (2010) developed a critical exposure concentrations, which is the concentration of a pharmaceutical in water expected to cause a response in fish based on the therapeutic level in humans and a bioconcentration factor. A drug that is measured in the aquatic environment above the critical exposure concentration is considered a priority. This approach is based on the assumption that drugs will act on the same targets in humans and fish; the validity of this assumption has been questioned (Rand-Weaver et al., 2013).

The use of models/QSARs to determine toxicity thresholds can be problematic. de Roode et al. (2006) evaluated the ability of four QSARs to predict toxicity for 170 compounds and found that they are not suitable as stand-alone tools to produce ecotoxicological data. As with fate and transport modeling, consideration of chemical domain is important, and new substances may fall outside the domains. The OECD has published several guidelines for model validation and use. QSARs should have a defined endpoint, clear algorithm, clearly defined domain, clear statistical measures of predictive capability, and mechanistic interpretation, if possible (Cherkasov et al., 2013). Only the results of a well-validated model should be utilized in a prioritization scheme.

There remain many important questions associated with characterizations of effects associated with CECs in the environment (see Boxall et al, 2012, for an excellent review). A meaningful prioritization scheme should account for these and associated uncertainties to avoid misclassification or the production of nonsensical results.

With regard to utilizing effects thresholds, it is important to ensure that relevant exposure/receptor relationship be considered, which can be achieved through the application of conceptual exposure frameworks as described above (Section 2). Potential impacts on ecological receptors can be included

though the use of PNEC values; the use of human health exposure measures could be appropriate in other exposure scenarios. When available, an Adverse Outcome Pathway (AOP; see below) process can provide additional refinements by specifically estimating the threshold environmental concentration likely to cause target organ concentrations of concern. Thus, it formally considers bioavailability and target tissue levels, which may not be included in the PNEC process.

3.5 Prioritize biological endpoints

As clearly demonstrated in the literature review (Section 1.4), there are many different approaches and factors to consider in the development of a prioritization scheme for monitoring of CECs in the environment. Several approaches incorporate biological impacts through a risk-based evaluation whereby those compounds most likely to cause ecological impacts would be those most-closely monitored. Identified limitations include the fact that overall biological risk may not be accurately estimated by consideration of individual compounds. Further, monitoring for individual compounds can be a daunting prospect due to the sheer numbers in the environment. An alternative prioritization approach would be through effects-directed analysis, where analytical work is driven by the presence of a biological impact such as endocrine disruption. Monitoring would focus on areas of concern identified through a biological assay, supported by directed analytical work to identify the causative agents (Brack, 2011). Likewise, Johnson et al. (2010) proposed biotic measures of effects as an important consideration in contaminant monitoring programs. The rationale is that the priority driver ought to be the reduction of harm and not necessarily the characterization of the occurrence of benign compounds; the occurrence of caffeine at the ng L^{-1} level can be informative (e.g., (Buerge, Poiger, Müller, & Buser, 2003) but is unlikely to result in significant environmental impacts. A process summary is shown in Figure 4.

Biological impacts have been identified in several different ways including the evaluation of biomarkers (e.g., vitellogenin (Hinck et al., 2006; L. L. Johnson et al., 2008)), acute toxicity assays, and a range of surrogate systems. For example, the Yeast Estrogen Screen (YES) and Estrogen Receptor mediated Chemical Activated LUciferase gene eXpression (ER-CALUX) are in vitro surrogate methods that have been applied to evaluate the estrogenic activity of a given sample based on receptor activation. Similar assays exist to evaluate other endocrine disruption pathways (e.g., progesterone activity), specific toxicity (e.g., Aryl hydrocarbon receptor activation), or genotoxicity. The in vitro assays focus on a specific impact or pathway and, as such, it is important to ensure that they are reflective of the processes of the organisms of interest. An adverse outcome pathway (AOP) framework can be a valuable approach to link specific responses identified in screening assays to impacts on an individual or population scale (Hutchinson, Lyons, Thain, & Law, 2013). The AOP approach is meant to utilize information on specific modes of action (that may be shared between species) to guide the prediction of adverse outcomes at a biological level of organization through quantitative linkages with population models (Ankley et al., 2010; Kramer et al., 2011). Because the health of populations is a primary driver of environmental regulation and ecosystem-restoration programs, the AOP framework may be an informative method of focusing monitoring of CECs in the environment by highlighting those CEC that have highest potential to cause a population risk.

There are significant challenges to using AOPs in a prioritization framework (e.g., there are few complete AOPs linking measured biochemical exposure-responses to population outcomes, there is natural variability between populations which lends uncertainty to predictive relationships and multi-generational adaptation may alter response pathways, etc. (Kramer et al., 2011)). These challenges, though, are not specific to the AOP process and are common to much of the work associated with monitoring and evaluating trace compounds in the environment. Ongoing research in the region and elsewhere is strengthening our ability to apply AOPs in risk assessment and prioritization processes. Examples of the interest and growth in AOPs is the recent launch of websites and WIKI programs by the US EPA (http://www.epa.gov/research/priorities/docs/aop-wiki.pdf) and the European Union (http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm), which are designed to facilitate creation of new AOPs.

3.5.1 Biological Endpoints - Recommendations/Next Steps

- Use existing monitoring data to identify potential modes of toxic action (e.g. mutagenic / carcinogenic, estrogenic) associated with CECs in Puget Sound
- Prioritize modes of action based on likelihood of impacts on fish and other aquatic animals
- Identify biological endpoints that are diagnostic for specific modes of toxic action
- Assess feasibility of measuring selected biological endpoints in Puget Sound relevant species
- Recommend specific biological endpoints for monitoring

3.6 Other Considerations

The steps described above will result in the identification of a suite of compounds or biological endpoints for ecosystem monitoring. There are other considerations which may influence the final selection. These could include costs, opportunities for management response, etc.

3.7 Summary - Identifying Priority CECs and biological monitoring

The prioritization process consists of several steps and includes consideration of the calculated risk, the potential to cause risk, and observations driven by biological endpoints. Approaches utilizing calculated or potential risk focus on individual compounds and use information related to those specific compounds to focus a monitoring campaign. Biological endpoints, on the other hand, focus on observed conditions in biota in an ecosystem of interest to drive monitoring through knowledge of endpoints, pathways, and potential causative agents. It is imperative to approach the prioritization of CECs from both ends of the exposure-response spectrum. This includes focusing on compounds believed to impose a risk on human health or the environment with the intent of monitoring to discover whether the potential risk is real, as well as using observed biological responses to identify compounds that may be responsible.

The compound-focused aspect of prioritization will:

1. Categorize compounds based on sufficiency of occurrence and toxicity data;

2. For those compounds with sufficient occurrence and toxicity data;
    a. Prioritize compounds anticipated to present risk for monitoring;
    b. Remove compounds anticipated to present insignificant risk from further consideration;
3. For those compounds with sufficient toxicity data;
    a. Prioritize compounds with PNEC < 0.1 µg L^{-1} for monitoring;
4. Consider investment in fundamental research (analytical method development or ecotoxicity evaluation) for other compounds.

The biological endpoint aspect of prioritization can serve to identify the presence of causative agents. In cases where the AOP/exposure-response has been identified and is understood, biological monitoring efforts can be used to prioritize CECs for monitoring. In many cases, however, the cause-effect relationship is not clearly known and monitoring key biological endpoints can give important information on biological condition. The change of expression of an endpoint may be reflective of management actions (e.g., bioinfiltration systems appear to reduce the expression of toxicity associated with stormwater exposure) without explicitly identifying the contaminant of interest and, as such, can demonstrate progress towards ecological restoration. Biological monitoring may give a more holistic evaluation of risk compared to monitoring of specific compounds, CECs or otherwise.

4 RECOMMENDATIONS FOR NEXT STEPS

Based on the findings of this review the following recommendations and next steps are presented for consideration:

- Develop focus sheet describing examples of regional investigations on the occurrence and impacts of CECs in the Pacific Northwest. The intent of developing the worksheet is to raise the awareness of policy makers regarding CECs. The focus sheet will be developed in conjunction with the Columbia River Toxics Reduction Workgroup, which has been conducting a parallel process to the one for Puget Sound. This focus sheet will present regional examples of impacts caused by CECs in the Northwest.
- Secure funding to implement next steps in the process of developing a target list of CECs for Puget Sound monitoring.
- Develop a pressure, fate, and transport conceptual model to identify specific scenarios to focus monitoring efforts. Models could also include human health impacts associated with exposure via CECs in freshwater pathways. Candidate conceptual models have been identified; the selection of a final set of conceptual models should be done when applying the prioritization process.
- Categorization should be performed (prior to prioritization) to evaluate whether there is sufficient occurrence or toxicity information for a given compound. A decision tree format can be used to categorize all compounds, clearly identifying follow up activities.
    - Prioritization should only be applied to compounds for which there is sufficient occurrence and toxicity data.
    - Additional priority compounds can be identified as those with toxicity data supporting the conclusion that the PNEC < 0.1 $\mu g\ L^{-1}$.
    - Investments in analytical method development or ecotoxocity evaluation should be made for compounds for which there are not sufficient data.
- The prioritization process should be risk-based and based on a comparison of exposure levels versus effects levels.
    - Occurrence data should be measured, not modeled, unless the model has been verified for performance for the environment and compound in question. Data should be of sufficient quality and quantity to determine the 95th percentile confidence interval.
    - Toxicity data should be represented as a PNEC based on experimental results on organisms representing at least three trophic levels. Toxicity data should not be obtained through QSAR modeling unless the models have been verified to be representative for the compound in question.
- The use of biological endpoints should be an integral part of the CEC monitoring and prioritization program; the following steps should be considered:

    - Identify biological endpoints that are diagnostic for specific modes of toxic action
    - Assess feasibility of measuring selected biological endpoints in Puget Sound relevant species
    - Rely on existing monitoring data, begin to identify potential modes of toxic action (e.g. mutagenic / carcinogenic, estrogenic) associated with contaminants occurring in Puget Sound
    - Prioritize modes of action based on likelihood of impacting fish and other aquatic animals

- This process has been developed within the Puget Sound Ecosystem Monitoring Program Toxics (PSEMP) Workgroup, and in conjunction with the Columbia River Toxics Reduction Working Group in order to increase transparency and stakeholder involvement. This involvement will continue through the refinement and application of the CEC prioritization process. An advisory process should be develop to review the proposed process for identifying CECs. This should include ultimate end-users of the process, and incorporate knowledge and concerns across the region.
- The next step in developing a target list of CECs for monitoring for Puget Sound would be to apply the risk based approach recommended to existing information in Puget Sound. The outcome of this effort would then be subjected to expert peer and stakeholder review.

TABLES

	Southern California Coastal Waters Research Project (SCCWRP)	San Francisco Estuary Institute: Regional Monitoring Program	Oregon Department of Environmental Quality	Washington Department of Ecology
Compounds of Interest	CECs with no regulatory limits	Defined chemicals based on science, usage, PBT	CECs with no regulatory limits. Compounds partially defined by legislative process.	Not rule making but investigatory monitoring
Media	Exposure scenarios including WWTP effluent in rivers and estuaries and marine sediments	Estuary and marine water	Relevant media for each chemical group	
Prioritization	Selected for monitoring if the CEC exceeded risk-based monitoring quotient	Tiered prioritization based on risk and management	Usage, stakeholder review, political (chemicals with friends), available benchmarks and cost	Define chemicals based on usage (TRI) and PBT
End-Points	Moving toward biological screening tools	Highest prioritization based on biological thresholds, detection in apex predators, and unknown sources	Available benchmarks	Available benchmarks
Transparency	Stakeholder and technical review panels	Technical panel members reviewed chemical classifications	Agency reporting and review	PSEMP working groups
Leverage – additional groups or resources involved in program		Leverage stakeholder process including NIST, universities, etc.		PSEMP and other programs

Table 1. Summary of selected points from review of regional programs that have performed an evaluation and/or prioritization of Contaminants of Emerging Concern in the environment. In general, each program made decisions concerning factors listed on left column which impacted the implementation of the monitoring program.

Year	Analytes	Matrix	Site Description	Summary	Methods	Reference
2014	25 anthropogenic CECs	Freshwater WWTP effluent	20 sites with range of septic system impacts	Selected compounds with hiogh frequency of occurrence can be associated with septic system impacts	1 L water sample SPE LC/MS	James, C.A., Miller-Schultze, J.P., and Ultican, S. Contaminants of Emerging Concern and their Use as Tracers of Bacterial Pollution, *in preparation*
2014	25 anthropogenic CECs	Marine Water	Sanpshot of 40 samples in Puget Sound. 20 samples at Foss for time series.	Snapshot - range of concentrations nad detection frequecies. Some correltions between conservative compounds. TIme series - limited correlations	1 L water sample SPE LC/MS	Miller-Schulze, J.P., Gipe, A., and Overman, D. Contaminants of Emerging Concern in Puget Sound: A Comparison of Spatial and Temporal Levels and Occurrence, *in preparation*
2013	EDCs: 17β-estradiol (E2), estrone (E1), estriol (E3), and 17α-ethynylestradiol (EE2), bisphenol A (BPA), octylphenol (OP) and nonyphenol (NP)	Fish bile	Male and female English sole from 10 locations	EE2, OP and NP were below LOQ. BPA was frequently detected. E1, E2, E3 were higher is fish bile from urban and near-urban sites.	Fish bile extraction and processing SPE LC/MS	Associated Ref: da Silva, D. A. M.; Buzitis, J.; Reichert, W. L.; West, J. E.; O'Neill, S. M.; Johnson, L. L.; Collier, T. K.; Ylitalo, G. M., Endocrine disrupting chemicals in fish bile: A rapid method of analysis using English sole (Parophrys vetulus) from Puget Sound, WA, USA. Chemosphere 2013, 92 (11), 1550-1556.
2013	119 PPCPs and 13 perfluoroalkyl substances (PFASs)	Marine Sediments	30 sites in Bellingham Bay 10 sites throughout Puget Sound	14 of 119 PPCPs and 3 of 13 PFASs were abpve LOQ. Diphenhydramine was most frequently detected (87.5%). Triclocarban was detected in 35.0% of the samples. PFASs were detected in 2.5% of analyses.	EPA Method 1694 (LC/MS)	Long, E. R.; Dutch, M.; Weakland, S.; Chandramouli, B.; Benskin, J. P., Quantification of pharmaceuticals, personal care products, and perfluoroalkyl substances in the marine sediments of Puget Sound, Washington, USA. Environmental Toxicology and Chemistry 2013, 32 (8), 1701-1710.
2013	119 PPCPs and 13 perfluoroalkyl substances (PFASs)	Marine Sediments	30 sites in Elliot Bay	13 of 119 PPCPs and 3 of 13 PFASs were above LOQ. Triclocarban, diphenhydramine, and triamterene were detecetd > 50%. PFASs were detected in 6.9% of analyses.	EPA Method 1694 (LC/MS)	Dutch, M.; Weakland, S.; Partridge, V.; Welch, K., Pharmaceuticals, personal care products, and perfluoroalkyl substances in Elliott Bay sediments: 2013 data summary. Washington State Department of Ecology publication no. 14030xx. *in draft* .
2012	118 PPCPs and 27 hormones and sterols	WWTP (tertiary) effluent Groundwater	3 reclaimed water facilities and groundwater at recharge sites	73 of 145 compounds detected in reclaimed water. 15 compounds detected in groundwater at lower concentrations than reclaimed water. Carbamazepine, meprobamate, and sulfamethoxazole were consistently detected in reclaimed water and groundwater.	PPCPs EPA 1694 Hormones EPA 1698	Johnson A and P. Marti. 2012. Pharmaceuticals, personal care products, hormones, and sterols detected in process water and groundwater at three reclaimed water treatment plants. Publication 12-03-032. Washington State Department of Ecology, Olympia, WA.
2011	37 compounds - 15 anthropogenic, 8 suspected anthropogenic, 14 mixed source.	Marine Water	Puget Sound (n=66) and Barkley Sound (n=22)	Most chemcials were detected more frequently and at a hgher range of concentrations in Puget Sound compared to Barkley Sound, suggesting anthropogenic impact.	1-2.5 L Water Samples SPE GC/MS	Keil, R.; Salemme, K.; Forrest, B.; Neibauer, J.; Logsdon, M., Differential presence of anthropogenic compounds dissolved in the marine waters of Puget Sound, WA and Barkley Sound, BC. Marine Pollution Bulletin 2011, 62 (11), 2404-2411.
2011	Vitellogenin levels in juvenile salmon	Fish plasma and serum	6 sites (urban and non-urban) in Puget Sound	Method development. Fish from 2 of 3 urban sites had elevated VTG levels compared to non-urban	Developed ELISA for VTG	and L.L. Johnson. 2011. Development of an enzyme-linked immunosorbent assay for quantifying vitellogenin in Pacific salmon and assessment of field exposure to environmental estrogens. Environ Toxicol Chem 30:477–486.
2010	406 compounds total 118 persistent defined by SB737 PPCPs, pesticides, industrial intermediaries, metals	WWTP effluent	52 WWTPs in Oregon with discharge > 1 MGD	114 compounds detcted above the LOQ.	15 methods were used to capture suite of analytes.	Hope, B. K.; Pillsbury, L.; Boling, B., A state-wide survey in Oregon (USA) of trace metals and organic chemicals in municipal effluent. Science of the Total Environment 2012, 417, 263-272.
2010	13 perfluoroalkyl acids	Freshwater WWTP effluent Fish tissue Osprey eggs	14 surface waters throughout Washington. Three rivers and one lake in Puget Sound watershed. Two sites along Columbia river.	Total PFC ranged from 1.11-185 (median = 7.47) ng/L in spring, and <0.9-170 (median = 3.60) ng/L in fall. At least one PFC was detected in all but 2 samples.	Water 1 L sample SPE UPLC/MS/MS	Furl, C. and C. Meredith. 2010. Perfluorinated compounds in Washington rivers and lakes. Publication 10-03-034. Washington State Department of Ecology, Olympia, WA, USA.

Table 2: Regional studies investigating the occurrence of Contaminants of Emerging Concern in the aquatic environment, wastewater, and stormwater

Year	Analytes	Matrix	Site Description	Summary	Methods	Reference
2008 - 2010	WWTP effluent: 210 compounds (PPCPs, PCBs, PBDEs, legacy compounds, pesticides, Hg, and estrogenicity) Stormwater: PCBs, PBDEs, organochlorine compounds, PAHs, pesticides, trace elements, Hg, and oil and	WWTP effluent Stormwater	WWTP and sotmrwtaer collected at 9 cities along Columbia River.	Sampling performed in nine cities. In WWTP-effluent, 53% of compounds were detected with DF generally >80%. Similar patterns of detection detected among the WWTPs. In stormwater, 58% of analytes detected. Stormwater was heterogeneous.	GC/MS as described	Morace, J. L. Reconnaissance of contaminants in selected wastewater-treatment-plant effluent and stormwater runoff entering the Columbia River, Columbia River Basin, Washington and Oregon, 2008–10: USGS Scientific Investigations Report 2012–5068; U.S. Geological Survey: Reston, VA, 2012.
2008	172 organic compounds (PPCPs, hormones, steroids, semi-volatile organics)	WWTP influent WWTP effluent Biosolids	5 WWTPs total. 2 secondary treatment and 3 tertiary treatment.	One sample collected at influent, effluent, and biosolids at each site. There was a wide range of occurrence and removal. Some compounds were only detected in biosolids.	EPA Method 1694 (HPLC/MS/MS) EPA Method 1698 (GC/MS) EPA Method 8270d	Lubliner, B.; Redding, M.; Ragsdale, D. Pharmaceuticals and Personal Care Products in Municipal Wastewater and Their Removal by Nutrient Treatment Technologies. Publication Number 10-03-004.; Washington State Department of Ecology: Olympia, WA, 2010.
2008	Xenoestrogen exposure through vitellogenin measurements in bottom fish.	english sole	16 sites in Puget Sound. 8 urban, 5 near-urban, and 3 non-urban.	Significant levels of vitellogenin were found in male fish from several urban sites compared to non-urban.		S.M. O'Neill, J. West, and T.K. Collier. 2008. Xenoestrogen exposure and effects in English sole (Parophrys vetulus) from Puget Sound,WA. Aquat Toxicol 88:29–38.
2007	25 compounds (PPCPs, flame retardants, herbacides)	Surface Water Groundwater	8 creek sites 3 shallow groundwater	12 of 25 compounds were detected at least once. Only 3 compounds were detected in more than one sample.	1-2 L Water Sample SPE POCIS passive samplers LC/MS	Dougherty, J. A.; Swarzenski, P. W.; Dinicola, R. S.; Reinhard, M., Occurrence of Herbicides and Pharmaceutical and Personal Care Products in Surface Water and Groundwater around Liberty Bay, Puget Sound, Washington. Journal of Environmental Quality 2010, 39 (4), 1173-1180.
2007	20 pharmaceuticals. 13 antidepressants. 61 anthropogenic waste indicator compounds.	River bed sediments	Nine sites in Columbia river. Five sites in Willamette river. Two sites in Tualatin river. Seven sites in tributaries or slough.	Reconnaissance study Pharmeceutical compounds detected at 13/14 tributary sites, and 4/9 Columbia R. sites. 16 of 33 compounds were detected. At least 2 Anthropogenic Waste Indicators detected at every site. Detected compounds included EDCs.	Accelerated solvent extraction. LC-MS/MS GC-MS	Nilsen E.B., R.R. Rosenbauer, E.T. Furlong, M.R. Burkhardt, S.I. Werner, I. Greaser, and M. Noriega. 2007. Pharmaceuticals, personal care products and anthropogenic waste indicators detected in streambed sediments of the lower Columbia River and selected tributaries. Proceedings from 6th International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals inWater. Costa Mesa, CA: National Grround Water Association. p. 15. (Paper
2004	24 PPCPs	Freshwater WWTP effluent	Tertiary WWTP effluent from Sequim and Sunland development and nearby creeks and groundwater	Reconnaissance study 16 of 24 coumpounds detected in WWTP efflunet. Only caffeine, nicotine, and metformin were consistently detected well and creek samples.	1 L water sample. SPE HPLC/MS	screening analysis for pharmaceuticals in wastewater treatment plant effluents, wells, and creeks in the Sequim-Dungeness Area. Publication 04-03-051. Washington State Department of Ecology, Olympia, WA, USA.
2002	21 pharmaceuticals and metabolites	Surface Water	10 site in urban stream representing gradient of development	6 of 21 compounds detected.	1 L water sample SPE LC/MS	Rounds, S.A., Doyle, M.C., Edwards, P.M., and Furlong, E.T., 2009, Reconnaissance of pharmaceutical chemicals in urban streams of the Tualatin River basin, Oregon, 2002: U.S. Geological Survey Scientific Investigations Report 2009–5119, 22 p.

Table 2. Regional studies investigating the occurrence of Contaminants of Emerging Concern in the aquatic environment, wastewater, and stormwater

Category	Occurrence Data	Ecotoxicity Data	Potential Risk?	Management Action
1	+	+	Y	Priority Compounds – Include in monitoring. Highest priority compounds would be those with highest risk quotient.
6	+	+	N	No further action
3	+	-	?	Develop measure of ecotoxicity
2	-	+	?	Develop monitoring program. Can prioritize compounds in this category through hazard assessment – focus on those with lowest effects levels
4	-	+	?	Develop analytical methods (if lacking),
5	-	-	?	Require both analytical and effects investigation

Table 3. Proposed categorization scheme for Contaminants of Emerging Concern (CECs) based on availability of environmental monitoring data or experimental ecotoxicity data. A "+" indicates there is sufficient data for evaluation. A "-"indicates there is not sufficient data to carry out an evaluation. The potential risk is determined based on the calculation of a risk quotient.

FIGURES

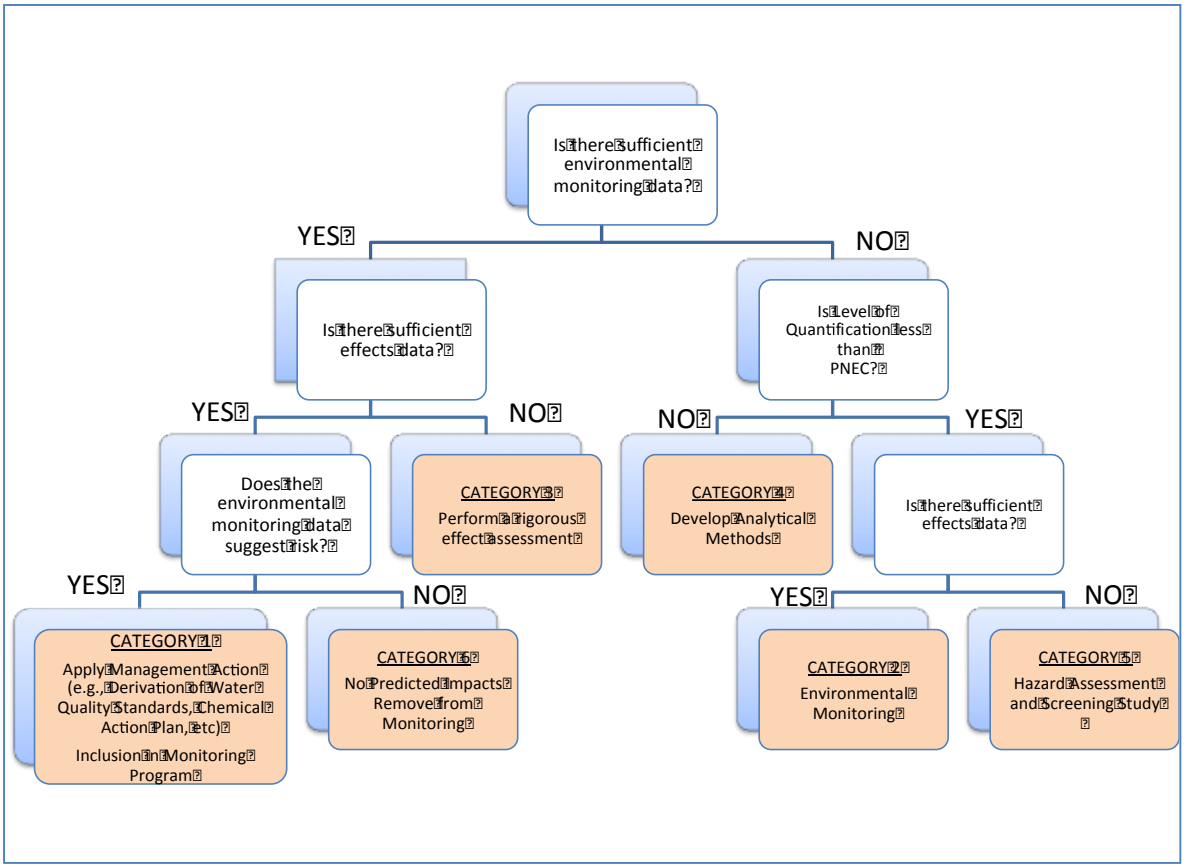


Figure 1. Proposed decision tree to categorize and group Contaminants of Emerging Concerns for follow up actions. All compounds of interest can be categorized according to the decision tree. Compounds with sufficient data to allow for a full risk-based evaluation will be in Category 1 or Category 6. Those lacking will be assigned another category. Investment in monitoring, effects assessments, and/or analytical method development will allow the eventual re-categorization of compounds into Category 1 or Category 6. Adapted from von der Ohe et al (2012).

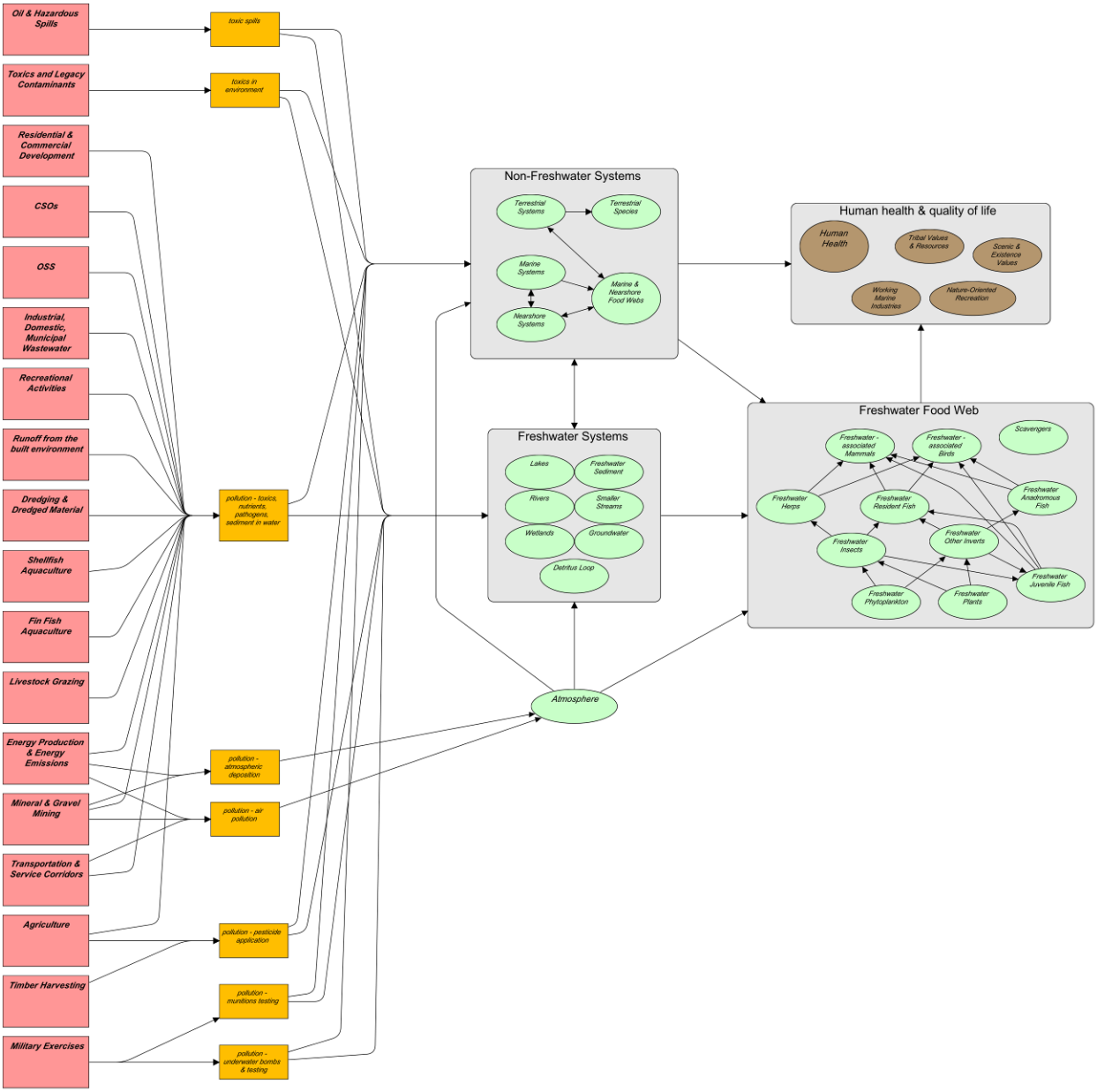


Figure 2. Pressures-driven model detailing potential sources of contaminants to Puget Sound, the compounds associated with a given source, and transport pathway from source to ecosystem and food web.

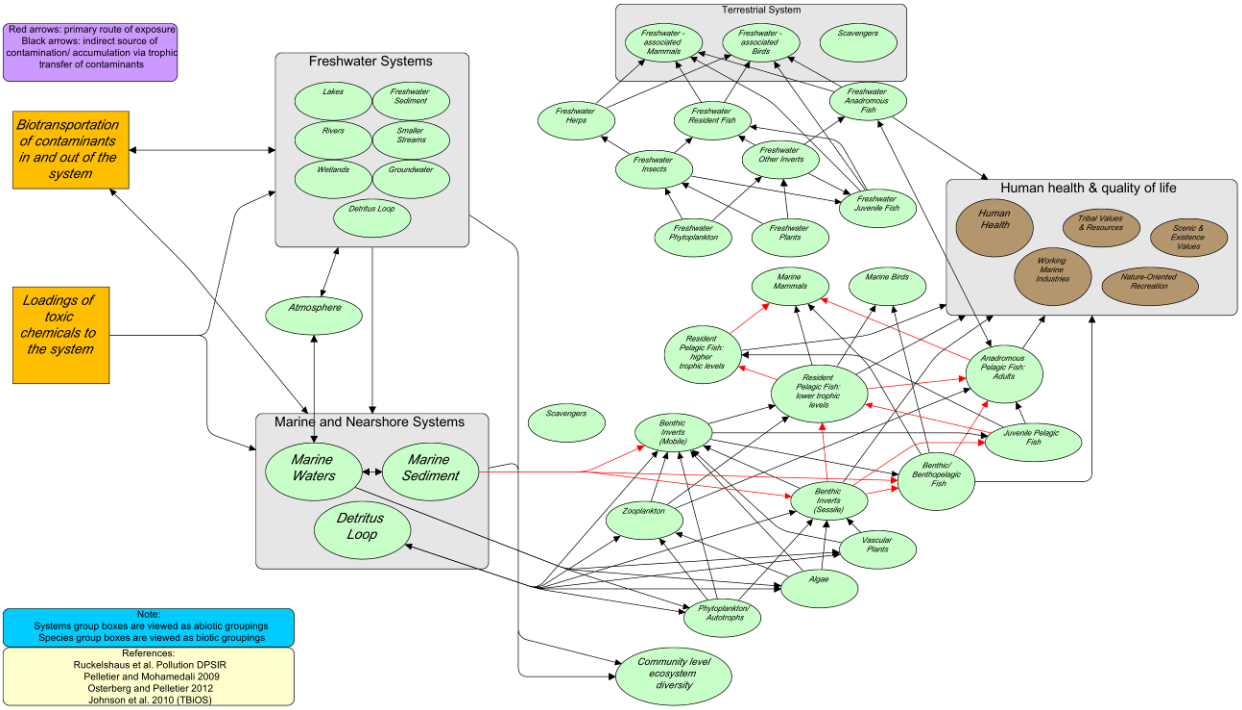


Figure 3. Conceptual fate and transport model for bioaccumulative chemicals in Puget Sound. Note that the loadings and sources are general. Information on loading to a given ecosystem can be obtained by combining the fate and transport model shown here with a Pressure Framework (Figure 2).

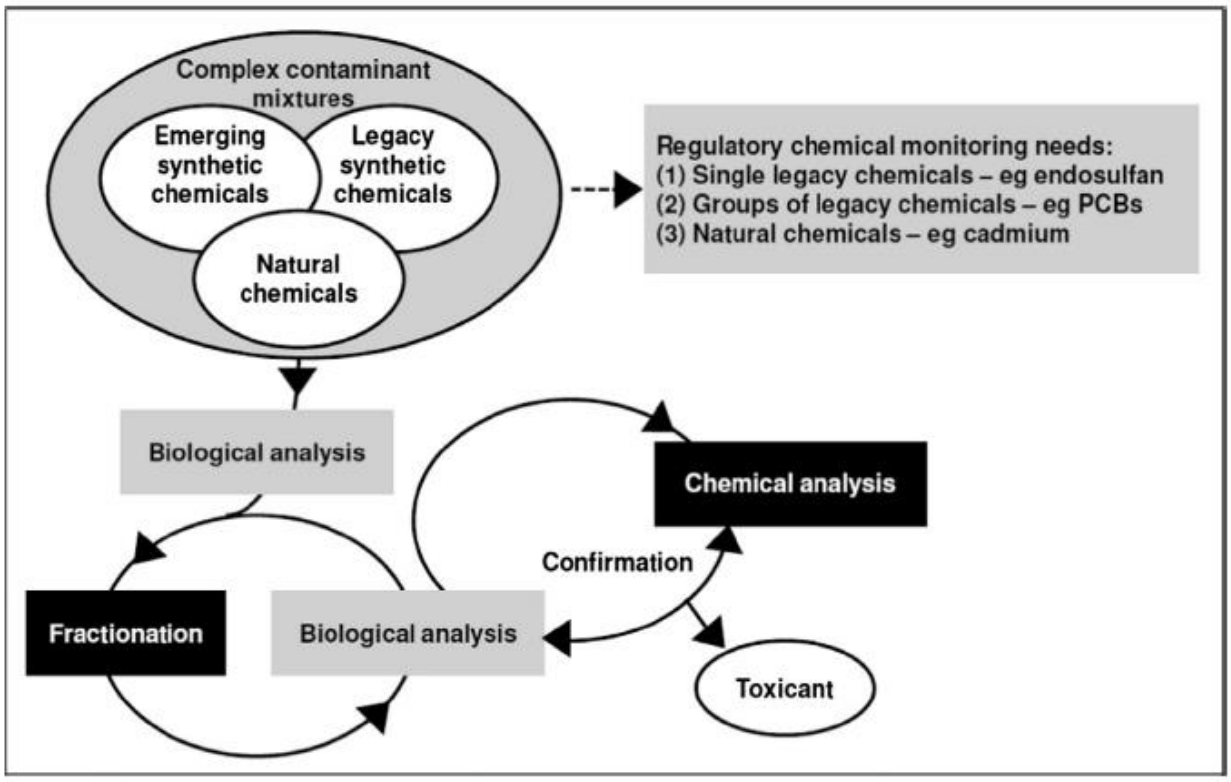


Figure 4. Schematic of biological effects-directed analysis with chemical monitoring to focus investigation and identification of priority chemicals (adapted from (Hutchinson et al., 2013))

LIST OF ABBREVIATIONS

- ADI – Acceptable Daily Intake
- AOP – Adverse Outcome Pathways
- B – Bioaccumulation
- BQ – Benchmark Quotient
- CEC – Contaminants of Emerging Concern
- EC_{50} - Half maximal effective concentration. Concentration that induces a response level halfway between the baseline and maximum
- HV – Hazard Value
- IC_{50} – The half maximal inhibitory concentration. Concentration that inhibits a given biological process by half
- K_{ow} – Octanol Water partitioning coefficient
- LC_{50} –Half lethal concentration. Concentration that kills 50% of biological subjects following exposure.
- LD_{50} –Half lethal dose. Dose that kills 50% of biological subjects following exposure.
- LOAEL - Lowest Observed Adverse Effect Level
- LOEC – Lowest Observable Effects Concentration
- LOEL – Lowest Observable Effects Level
- MEC – Measured Environmental Concentrations
- MTQ – Monitoring Trigger Quotient
- NOEL – No Observable Effects Level
- P – Persistence
- PEC – Predicted Environmental Concentration
- PNEC – Predicted No Effects Concentration
- PPCP – Pharmaceutical and Personal Care Products
- PSEMP – Puget Sound Ecosystem Monitoring Program
- QSAR – Quantitative Structure Activity Relationship
- RfD – Reference Dose
- RQ – Risk Quotient
- RV – Risk Value
- T – Toxicity
- TL – Toxic Loading
- TDI – Tolerable Daily Intake
- WWTP – Wastewater Treatment Plant

REFERENCES

Anderson, P. D., Denslow, N. D., Drewes, J. E., Olivieri, A. W., Schlenk, D., Scott, G. I., & Snyder, S. A. (2012). Monitoring Strategies for Chemicals of Emerging Concern (CECs) in California's Aquatic Ecosystems. Costa Mesa, CA: California Water Resources Control Board and Southern California Coastal Water Research Project.

Ankley, G. T., Bennett, R. S., Erickson, R. J., Hoff, D. J., Hornung, M. W., Johnson, R. D., . . . Villeneuve, D. L. (2010). ADVERSE OUTCOME PATHWAYS: A CONCEPTUAL FRAMEWORK TO SUPPORT ECOTOXICOLOGY RESEARCH AND RISK ASSESSMENT. *Environmental Toxicology and Chemistry, 29*(3), 730-741. doi: 10.1002/etc.34

Arnot, J. A., & Mackay, D. (2008). Policies for chemical hazard and risk priority setting: Can persistence, bioaccumulation, toxicity, and quantity information be combined? *Environmental Science & Technology, 42*(13), 4648-4654. doi: 10.1021/es800106g

Babson, A. L., Kawase, A., & MacCready, P. (2006). Seasonal and interannual variability in the circulation of Puget Sound, Washington: A box model study. *Atmosphere-Ocean, 44*(1), 29-45. doi: 10.3137/ao.440103

Besse, J. P., & Garric, J. (2008). Human pharmaceuticals in surface waters implementation of a prioritization methodology and application to the French situation. *Toxicology Letters, 176*(2), 104-123. doi: 10.1016/j.toxlet.2007.10.012

Boxall, A. B. A., Rudd, M. A., Brooks, B. W., Caldwell, D. J., Choi, K., Hickmann, S., . . . Van Der Kraak, G. (2012). Pharmaceuticals and Personal Care Products in the Environment: What Are the Big Questions? *Environmental Health Perspectives, 120*(9), 1221-1229. doi: 10.1289/ehp.1104477

Brack, W. (2011). *Effect-directed analysis of complex environmental contamination*. Berlin; Heidelberg; New York: Springer.

Buerge, I. J., Poiger, T., Müller, M. D., & Buser, H.-R. (2003). Caffeine, an Anthropogenic Marker for Wastewater Contamination of Surface Waters. *Environmental Science & Technology, 37*(4), 691-700. doi: 10.1021/es020125z

Carlsson, C., Johansson, A. K., Alvan, G., Bergman, K., & Kuhler, T. (2006). Are pharmaceuticals potent environmental pollutants? Part I: Environmental risk assessments of selected active pharmaceutical ingredients. *Science of the Total Environment, 364*(1-3), 67-87. doi: 10.1016/j.scitotenv.2005.06.035

Cherkasov, A., Muratov, E. N., Fourches, D., Varnek, A., Baskin, I. I., Cronin, M., . . . Tropsha, A. (2013). QSAR Modeling: Where Have You Been? Where Are You Going To? *Journal of Medicinal Chemistry, 57*(12), 4977-5010. doi: 10.1021/jm4004285

Cooper, E. R., Siewicki, T. C., & Phillips, K. (2008). Preliminary risk assessment database and risk ranking of pharmaceuticals in the environment. *Science of the Total Environment, 398*(1–3), 26-33. doi: http://dx.doi.org/10.1016/j.scitotenv.2008.02.061

Curtis, L. H., Stoddard, J., Radeva, J. I., Hutchison, S., Dans, P. E., Wright, A., . . . Schulman, K. A. (2006). Geographic Variation in the Prescription of Schedule II Opioid Analgesics among Outpatients in the United States. *Health Services Research, 41*(3p1), 837-855. doi: 10.1111/j.1475-6773.2006.00511.x

da Silva, D. A. M., Buzitis, J., Reichert, W. L., West, J. E., O'Neill, S. M., Johnson, L. L., . . . Ylitalo, G. M. (2013). Endocrine disrupting chemicals in fish bile: A rapid method of analysis using English sole (Parophrys vetulus) from Puget Sound, WA, USA. *Chemosphere, 92*(11), 1550-1556. doi: 10.1016/j.chemosphere.2013.04.027

De Roode, D., Hoekzema, C., de Vries-Buitenweg, S., van de Waart, B., & Van der Hoeven, J. (2006). QSARs in ecotoxicological risk assessment. *Regulatory Toxicology and Pharmacology, 45*(1), 24-35. doi: 10.1016/j.yrtph.2006.01.012

de Voogt, P., Janex-Habibi, M. L., Sacher, F., Puijker, L., & Mons, M. (2009). Development of a common priority list of pharmaceuticals relevant for the water cycle. *Water Science and Technology, 59*(1), 39-46. doi: 10.2166/wst.2009.764

Diamond, J. M., Latimer, H. A., Munkittrick, K. R., Thornton, K. W., Bartell, S. M., & Kidd, K. A. (2011). Prioritizing Contaminants of Emerging Concern for Ecological Screening Assessments. *Environmental Toxicology and Chemistry, 30*(11), 2385-2394. doi: 10.1002/etc.667

Dong, Z., Senn, D. B., Moran, R. E., & Shine, J. P. (2013). Prioritizing environmental risk of prescription pharmaceuticals. *Regulatory Toxicology and Pharmacology, 65*(1), 60-67. doi: 10.1016/j.yrtph.2012.07.003

Dougherty, J. A., Swarzenski, P. W., Dinicola, R. S., & Reinhard, M. (2010). Occurrence of Herbicides and Pharmaceutical and Personal Care Products in Surface Water and Groundwater around Liberty Bay, Puget Sound, Washington. *Journal of Environmental Quality, 39*(4), 1173-1180. doi: 10.2134/jeq.2009.0189

Drewes, J. E., Anderson, P., Denslow, N., Olivieri, A., Schlenk, D., Snyder, S. A., & Maruya, K. A. (2013). Designing monitoring programs for chemicals of emerging concern in potable reuse - what to include and what not to include? *Water Science and Technology, 67*(2), 433-439. doi: 10.2166/wst.2012.520

Dulio, V., & von der Ohe, P. C. (2013). NORMAN Prioritisation framework for emerging substances. Verneuil-en-Halatte, France: NORMAN Association.

Fick, J., Lindberg, R. H., Tysklind, M., & Larsson, D. G. J. (2010). Predicted critical environmental concentrations for 500 pharmaceuticals. *Regulatory Toxicology and Pharmacology, 58*(3), 516-523. doi: 10.1016/j.yrtph.2010.08.025

Gotz, C. W., Stamm, C., Fenner, K., Singer, H., Scharer, M., & Hollender, J. (2010). Targeting aquatic microcontaminants for monitoring: exposure categorization and application to the Swiss situation. *Environmental Science and Pollution Research, 17*(2), 341-354. doi: 10.1007/s11356-009-0167-8

Hahn, T., Diamond, J., Dobson, S., Howe, P., Kielhorn, J., Koennecker, G., . . . Stauber, J. L. (2014). Predicted no effect concentration derivation as a significant source of variability in environmental hazard assessments of chemicals in aquatic systems: An international analysis. *Integrated Environmental Assessment and Management, 10*(1), 30-36. doi: 10.1002/ieam.1473

Hinck, J. E., Schmitt, C. J., Blazer, V. S., Denslow, N. D., Bartish, T. M., Anderson, P. J., . . . Tillitt, D. E. (2006). Environmental contaminants and biomarker responses in fish from the Columbia River and its tributaries: Spatial and temporal trends. *Science of the Total Environment, 366*(2-3), 549-578. doi: 10.1016/j.scitotenv.2005.11.008

Hope, B. K., Pillsbury, L., & Boling, B. (2012). A state-wide survey in Oregon (USA) of trace metals and organic chemicals in municipal effluent. *Science of the Total Environment, 417*, 263-272. doi: 10.1016/j.scitotenv.2011.12.028

Howard, P. H., & Muir, D. C. G. (2010). Identifying New Persistent and Bioaccumulative Organics Among Chemicals in Commerce. *Environmental Science & Technology, 44*(7), 2277-2285. doi: 10.1021/es903383a

Howard, P. H., & Muir, D. C. G. (2011). Identifying New Persistent and Bioaccumulative Organics Among Chemicals in Commerce II: Pharmaceuticals. *Environmental Science & Technology, 45*(16), 6938-6946. doi: 10.1021/es201196x

Howard, P. H., & Muir, D. C. G. (2013). Identifying New Persistent and Bioaccumulative Organics Among Chemicals in Commerce. III: Byproducts, Impurities, and Transformation Products. *Environmental Science & Technology, 47*(10), 5259-5266. doi: 10.1021/es4004075

Hutchinson, T. H., Lyons, B. P., Thain, J. E., & Law, R. J. (2013). Evaluating legacy contaminants and emerging chemicals in marine environments using adverse outcome pathways and biological effects-directed analysis. *Mar Pollut Bull, 74*(2), 517-525. doi: 10.1016/j.marpolbul.2013.06.012

International Joint Commission. (2009). Work Group Report on Great Lakes Chemicals of Emerging Concern, Special Publication 2009-01 *Great Lakes Water Quality Agreement Priorities 2007-09 Series*. Windsor, Ontario, Canada.: IJC

Johnson, L., Bravo, C., O'Neill, S., West, J., Myers, M. S., Ylitalo, G., . . . Collier, T. (2010). A Toxics-Focused Biological Observing System for Puget Sound. Olympia, WA: Washington State Department fo Ecology.

Johnson, L. L., Lomax, D. P., Myers, M. S., Olson, O. P., Sol, S. Y., O'Neill, S. M., . . . Collier, T. K. (2008). Xenoestrogen exposure and effects in English sole (Parophrys vetulus) from Puget Sound, WA. *Aquatic Toxicology, 88*(1), 29-38. doi: 10.1016/j.aquatox.2008.03.001

Keil, R., Salemme, K., Forrest, B., Neibauer, J., & Logsdon, M. (2011). Differential presence of anthropogenic compounds dissolved in the marine waters of Puget Sound, WA and Barkley Sound, BC. *Marine Pollution Bulletin, 62*(11), 2404-2411. doi: http://dx.doi.org/10.1016/j.marpolbul.2011.08.029

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, E. M., Zaugg, S. D., Barber, L. B., & Buxton, H. T. (2002). Pharmaceuticals, hormones, and other organic wastewater contaminants in US streams, 1999-2000: A national reconnaissance. *Environmental Science & Technology, 36*(6), 1202-1211. doi: 10.1021/es011055j

Kramer, V. J., Etterson, M. A., Hecker, M., Murphy, C. A., Roesijadi, G., Spade, D. J., . . . Ankley, G. T. (2011). ADVERSE OUTCOME PATHWAYS AND ECOLOGICAL RISK ASSESSMENT BRIDGING TO POPULATION-LEVEL EFFECTS. *Environmental Toxicology and Chemistry, 30*(1), 64-76. doi: 10.1002/etc.375

Kumar, A., & Xagoraraki, I. (2010). Pharmaceuticals, personal care products and endocrine-disrupting chemicals in U.S. surface and finished drinking waters: A proposed ranking system. *Science of the Total Environment, 408*(23), 5972-5989. doi: 10.1016/j.scitotenv.2010.08.048

Long, E. R., Dutch, M., Weakland, S., Chandramouli, B., & Benskin, J. P. (2013). Quantification of pharmaceuticals, personal care products, and perfluoroalkyl substances in the marine sediments of Puget Sound, Washington, USA. *Environmental Toxicology and Chemistry, 32*(8), 1701-1710. doi: 10.1002/etc.2281

Lubliner, B., Redding, M., & Ragsdale, D. (2010). Pharmaceuticals and Personal Care Products in Municipal Wastewater and Their Removal by Nutrient Treatment Technologies. Publication Number 10-03-004. Olympia, WA: Washington State Department of Ecology.

Luo, Y. L., Guo, W. S., Ngo, H. H., Nghiem, L. D., Hai, F. I., Zhang, J., . . . Wang, X. C. C. (2014). A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. *Science of the Total Environment, 473*, 619-641. doi: 10.1016/j.scitotenv.2013.12.065

Michael, I., Rizzo, L., McArdell, C. S., Manaia, C. M., Merlin, C., Schwartz, T., . . . Fatta-Kassinos, D. (2013). Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: A review. *Water Research, 47*(3), 957-995. doi: 10.1016/j.watres.2012.11.027

Miege, C., Choubert, J. M., Ribeiro, L., Eusebe, M., & Coquery, M. (2009). Fate of pharmaceuticals and personal care products in wastewater treatment plants - Conception of a database and first results. *Environmental Pollution, 157*(5), 1721-1726. doi: 10.1016/j.envpol.2008.11.045

Morace, J. L. (2012). Reconnaissance of contaminants in selected wastewater-treatment-plant effluent and stormwater runoff entering the Columbia River, Columbia River Basin, Washington and Oregon, 2008–10: USGS Scientific Investigations Report 2012–5068. Reston, VA: U.S. Geological Survey.

Munoz, I., Gomez, M. J., Molina-Diaz, A., Huijbregts, M. A. J., Fernandez-Alba, A. R., & Garcia-Calvo, E. (2008). Ranking potential impacts of priority and emerging pollutants in urban wastewater through life cycle impact assessment. *Chemosphere, 74*(1), 37-44. doi: 10.1016/j.chemosphere.2008.09.029

Murray, K. E., Thomas, S. M., & Bodour, A. A. (2010). Prioritizing research for trace pollutants and emerging contaminants in the freshwater environment. *Environmental Pollution, 158*(12), 3462-3471. doi: 10.1016/j.envpol.2010.08.009

Ort, C., Lawrence, M. G., Reungoat, J., & Mueller, J. F. (2010). Sampling for PPCPs in Wastewater Systems: Comparison of Different Sampling Modes and Optimization Strategies. *Environmental Science & Technology, 44*(16), 6289-6296. doi: 10.1021/es100778d

Ort, C., Lawrence, M. G., Rieckermann, J., & Joss, A. (2010). Sampling for Pharmaceuticals and Personal Care Products (PPCPs) and Illicit Drugs in Wastewater Systems: Are Your Conclusions Valid? A Critical Review. *Environmental Science & Technology, 44*(16), 6024-6035. doi: 10.1021/es100779n

Pal, A., Gin, K. Y. H., Lin, A. Y. C., & Reinhard, M. (2010). Impacts of emerging organic contaminants on freshwater resources: Review of recent occurrences, sources, fate and effects. *Science of the Total Environment, 408*(24), 6062-6069. doi: 10.1016/j.scitotenv.2010.09.026

Pistocchi, A., Sarigiannis, D. A., & Vizcaino, P. (2010). Spatially explicit multimedia fate models for pollutants in Europe: State of the art and perspectives. *Science of the Total Environment, 408*(18), 3817-3830. doi: 10.1016/j.scitotenv.2009.10.046

Rand-Weaver, M., Margiotta-Casaluci, L., Patel, A., Panter, G. H., Owen, S. F., & Sumpter, J. P. (2013). The Read-Across Hypothesis and Environmental Risk Assessment of Pharmaceuticals. *Environmental Science & Technology, 47*(20), 11384-11395. doi: 10.1021/es402065a

Roos, V., Gunnarsson, L., Fick, J., Larsson, D. G. J., & Ruden, C. (2012). Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection. *Science of the Total Environment, 421*, 102-110. doi: 10.1016/j.scitotenv.2012.01.039

Rounds, S. A., Doyle, M. C., Edwards, P. M., & Furlong, E. T. (2009). Reconnaissance of pharmaceutical chemicals in urban streams of the Tualatin River basin, OR, 2002. USGS Scientific Investigations Report 2009–5119. Reston, VA: U.S. Geological Survey.

Rucker, C., & Kummerer, K. (2012). Modeling and predicting aquatic aerobic biodegradation - a review from a user's perspective. *Green Chemistry, 14*(4), 875-887. doi: 10.1039/c2gc16267a

Sanderson, H., Johnson, D. J., Reitsma, T., Brain, R. A., Wilson, C. J., & Solomon, K. R. (2004). Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Regulatory Toxicology and Pharmacology, 39*(2), 158-183. doi: http://dx.doi.org/10.1016/j.yrtph.2003.12.006

Schriks, M., Heringa, M. B., van der Kooi, M. M. E., de Voogt, P., & van Wezel, A. P. (2010). Toxicological relevance of emerging contaminants for drinking water quality. *Water Research, 44*(2), 461-476. doi: 10.1016/j.watres.2009.08.023

Stiles, K., & Redman, S. (2013). 2013 Puget Sound Partnership Pressure Taxonomy Working Paper. Tacoma, WA: Puget Sond Partnership.

Strempel, S., Scheringer, M., Ng, C. A., & Hungerbühler, K. (2012). Screening for PBT Chemicals among the "Existing" and "New" Chemicals of the EU. *Environmental Science & Technology, 46*(11), 5680-5687. doi: 10.1021/es3002713

Tunkel, J., Mayo, K., Austin, C., Hickerson, A., & Howard, P. (2005). Practical considerations on the use of predictive models for regulatory purposes. *Environmental Science & Technology, 39*(7), 2188-2199. doi: 10.1021/es049220t

von der Ohe, P. C., Dulio, V., Slobodnik, J., De Deckere, E., Kühne, R., Ebert, R.-U., . . . Brack, W. (2011). A new risk assessment approach for the prioritization of 500 classical and emerging organic microcontaminants as potential river basin specific pollutants under the European Water

Framework Directive. *Science of the Total Environment, 409*(11), 2064-2077. doi: http://dx.doi.org/10.1016/j.scitotenv.2011.01.054

Vulliet, E., & Cren-Olive, C. (2011). Screening of pharmaceuticals and hormones at the regional scale, in surface and groundwaters intended to human consumption. *Environmental Pollution, 159*(10), 2929-2934. doi: 10.1016/j.envpol.2011.04.033

APPENDIX A – CEC PRIORITIZATION LITERATURE REVIEW SUMMARY

This appendix presents a brief summary of published prioritization efforts. For each paper, the following was recorded:

- Summary
- Compound group – the chemicals of interest which were included in the study
- Determination of Environmental Concentration – a summary of the method used to determine the environmental concentration, either measured or predicted
- Endpoint – the receptor of interest
- Impact Measure – the measure by which the impact of exposure was quantified.
- Evaluation Measure – the measure that was used to quantify the level of potential impact
- Prioritization Benchmark – the method or level that was used to determine if a compound was a priority

Summaries are included below.

Reference:
Dong et al. (2013)

Summary:
Prioritization of pharmaceuticals based on predicted occurrence (by # of prescriptions, metabolism, and WWTP removal) and environmental toxicity

Compound Group:
200 most-prescribed pharmaceuticals in US

Determination of Environmental Concentration
Predicted

Endpoint
Aquatic environment

Impact Measure

$$\text{Toxic Load (TL)} = \frac{\text{Mass Loading}}{\text{Toxicity Threshold}}$$

Mass Loading = P x u x e x d

- P = mass of compound prescribed per year (kg/yr)
- u = fraction of compound utilized by consumer (assume = 1)
- e = fraction of compound excreted
- d = fraction of compound discharged from WWTP

Toxicity Threshold - 12 endpoints considered:

(1) Adult Minimum Initial Dose,
(2) Human LOAEL (Lowest-Observed-Adverse-Effect-Level),
(3) Rat LD50 (lethal dose for 50% of test population),
(4) Rat LOAEL,
(5) Mouse LD50,
(6) Mouse LOAEL,
(7) Algae 96-h EC50 (concentration at which 50% of test population exhibit toxic effect)
(8) Algae Chronic Value (ChV, concentration showing no significant toxic effect during a 30-day exposure period),
(9) Daphnid 48-h LC50 (lethal concentration for 50% of test population),
(10) Daphnid Chronic Value,
(11) Fish 96-h LC50, and
(12) Fish Chronic Value.

Evaluation Measure

$$PS_{ij} = \frac{logTL_{ij} - \overline{logTL_j}}{Std(logTL_j)}$$

TLij = toxic load of compound I on endpoint J
TLj = mean toxic load of all compounds on endpoint j

Prioritization Benchmark
Higher PS → higher priority

Reference:
Howard and Muir (2013)

Summary:
Identification of compounds of interested based on persistence and bioaccumulation potential - byproducts, impurities, and transformation products

Compound Group:
Started with 610 P&B compounds from Howard and Muir (2010) and applied University of Minnesota Biocatalysts/Biodegradation Database Pathway Prediction System

Determination of Environmental Concentration
NA

Endpoint
NA

Impact Measure
NA

Evaluation Measure
Bioaccumulation potential, log Kow, and biodegradability per EPI Suite software "

Prioritization Benchmark
Bioaccumulation - log Kow>3
Persistence - BIOWIN1 or BIOWWIN5 models output < 0.5 (50% probability that biodegradation will not be fast); or chemical structure suggest persistence using the (e.g., highly halogenated, highly branched, nitroaromatic)

Reference:
Anderson et al. (2012)

Summary:
Assess CECs with highest potential to cause impact in California receiving waters

Compound Group:
CECs with occurrence information reported in literature or in monitoring programs. Also included compounds with NOEC < 0.1 mg/L.

Determination of Environmental Concentration
Measured - obtained from literature review

Endpoint
Human
Ecotoxicological

Impact Measure
No Observable Effects Concentrations (NOEC) from the literature

Evaluation Measure
MTQ (monitoring trigger quotient) = Max Environmental Concentration/NOEC

Prioritization Benchmark
MTQ > 1.0

Reference:
Roos et al. (2012)

Summary:
Evaluate nine prioritization schemes in terms of ranking and input data. Found considerable variation in ranking results. Recommended improved exposure data

Compound Group:
582 active pharmaceutical ingredients available in Sweden

Determination of Environmental Concentration
Varied

Endpoint

Impact Measure

Evaluation Measure

Prioritization Benchmark

Reference:
Strempel et al. (2012)

Summary:
Screening of compounds based on predicted P, B, and T properties compared to the threshold values published in EU REACH program.

Compound Group:
~95,000 chemicals. Also to 2576 high production volume chemicals and 2781 "new" chemicals to compare properties of replacement compounds

Determination of Environmental Concentration
Measured where available. Predicted based on EPA EPI suite

Endpoint
Aquatic organisms

Impact Measure
Persistence - half-life measured or calculated in BIOWIN3
Bioaccumulation - measured or calculated with BCFBAF
Toxicity - measured or ECOSAR

Evaluation Measure

$$PBT = \sum \frac{\min\left\{\frac{t_{1/2}}{120}, 1\right\}}{3} + \frac{\min\left\{\frac{BCF}{2000}, 1\right\}}{3} + \frac{\min\left\{\frac{NOEC_{chronic}}{0.01\ mg/L}, \frac{LC_{50}}{0.1\ mg/L}, \frac{EC_{50}}{0.1\ mg/L}, 1\right\}}{3}$$

where:

$t_{1/2}$ - degradation half-life in soil
BCF - bioconcentration factor
$NOEC_{chronic}$ - chronic no observable effects concentration
LC50 - acute lethal concentration to 50% of test subjects
EC50 - acute effective concentration for 50% of test subjects

Prioritization Benchmark
PBT = 1, persistent, bioconcentrating, and toxic
PBT = (0.333, 1) compounds with one or more PBT threshold exceedance
PBT = [0, 0.333) nonpersistent, nonbioconcentrating, and nontoxic

Reference:
Diamond et al. (2011) – Method 1

Summary:
Evaluated three different methods: 1) risk only based on measured concentrations; 2) risk, persistence, and bioaccumulation; and 3) toxicity, persistence, and bioaccumulation

Compound Group:
517 CECs which occur in US surface waters

Determination of Environmental Concentration
Measured/Occurrence Database

Endpoint
Aquatic organisms

Impact Measure
Method 1:
Risk - Compare measured environmental concentrations with predicted chronic or estrogenic effects from EPA ECOSAR and PBT profiler.

Evaluation Measure

Prioritization Benchmark
Method 1:
risk > 0.1 => priority compound

Reference:
Diamond et al. (2011) – Method 2

Summary:
Evaluated three different methods: 1) risk only based on measured concentrations; 2) risk, persistence, and bioaccumulation; and 3) toxicity, persistence, and bioaccumulation

Compound Group:
517 CECs which occur in US surface waters

Determination of Environmental Concentration
Measured/Occurrence Database

Endpoint
Aquatic organisms

Impact Measure
Risk - Compare measured environmental concentrations with predicted chronic or estrogenic effects from EPA ECOSAR and PBT profiler.
Bioaccumulation - log Kow
Persistence - Predicted degradation in water" "

Evaluation Measure
Risk
risk > 0.1 = 3 points
0.01 > risk > 0.1 = 2 points
risk < 0.01 = 1 point

Persistence
t1/2 > 180 days = 3 points
180 days > t1/2 > 60 days = 2 points
t1/2 < 60 days = 1 point

Bioaccumulation
log Kow > 5 = 3 points
3 > log Kow > 5 = 2 points
log Kow < 3 = 1 point

Prioritization Benchmark
Σ (Risk + Persistence + Bioaccumulation) > 7 →priority compound

Reference:
Diamond et al. (2011) – Method 3

Summary:
Evaluated three different methods: 1) risk only based on measured concentrations; 2) risk, persistence, and bioaccumulation; and 3) toxicity, persistence, and bioaccumulation

Compound Group:
517 CECs which occur in US surface waters

Determination of Environmental Concentration
Measured/Occurrence Database

Endpoint
Aquatic organisms

Impact Measure
Toxicity - Predicted chronic or estrogenic effects from EPA ECOAR and PBT profiler
Bioaccumulation - log Kow
Persistence - Predicted degradation in water" "

Evaluation Measure
Toxicity
< 0.01 mg/L = 3 points
0.01 < toxicity < 1 mg/L = 2 points
> 1 mg/L = 1 point

Persistence
t1/2 > 180 days = 3 points
180 days > t1/2 > 60 days = 2 points
t1/2 < 60 days = 1 point

Bioaccumulation
log Kow > 5 = 3 points
3 > log Kow > 5 = 2 points
log Kow < 3 = 1 point

Prioritization Benchmark
Σ (Risk + Persistence + Bioaccumulation) > 7 →priority compound

Reference:
Howard and Muir (2011)

Summary:
Identification of compounds of interested based on persistence and bioaccumulation potential - pharmaceuticals

Compound Group:
Approximately 2700 drugs identified by the U.S. Food and Drug Administration includes prescription and over-the-counter drugs in addition to top 300 Rx prescriptions

Determination of Environmental Concentration
NA

Endpoint
NA

Impact Measure
NA

Evaluation Measure
Bioaccumulation potential, log Kow, and biodegradability per EPI Suite software "

Prioritization Benchmark
Bioaccumulation - log Kow>3
Persistence - BIOWIN1 or BIOWWIN5 models output < 0.5 (50% probability that biodegradation will not be fast); or chemical structure suggest persistence using the (e.g., highly halogenated, highly branched, nitroaromatic)

Reference:
von der Ohe et al. (2011)

Summary:
Step 1 - categorize CECs based on occurrence and toxicity data.
Step 2 - (for those with sufficient information) prioritize CEC for each category

Compound Group:
500 compounds identified in environmental measurements

Determination of Environmental Concentration
Measured. Data obtained in measurements in Elbe, Scheldt, Danube, and Llobregat river basins.

Endpoint
Aquatic Environment

Impact Measure
Predicted No Effects Concentration (PNEC):
Lowest of:

1) $PNEC_{acute}$
2) $PNEC_{chronic}$
3) P-PNEC - LC_{50}/1000

Evaluation Measure

1) Frequency of Exceedance - number of times that MEC>lowest PNEC
2) Extent of Exceedance = MEC95/lowest PNEC, scaled from 0-1
    a) 1 - 10, 0.1 points,
    b) 10 - 100, 0.2 points,
    c) 100 - 1000, 0.5 points,
    d) >1000, 1 point

PR = frequency of exceedance value + extent of exceedance

Prioritization Benchmark
PR = priority ranking

Reference:
Vulliet and Cren-Olive (2011)

Summary:
Evaluate priority list of compounds (from Besse and Garric) in surface and groundwater intended for human consumption

Compound Group:
52 pharmaceuticals and hormones

Determination of Environmental Concentration
Measured

Endpoint
Humans

Impact Measure
Lifetime dose to humans

Evaluation Measure
I70 = total consumption based on consumption of water (2 L/d) with compound at maximum environmental concentration for 70 years

Prioritization Benchmark
I70 > daily therapeutic dose (TD) = priority compound

Reference:
Fick et al. (2010)

Summary:
Determined Critical Environmental Concentration (CEC) in water based on fish plasma model. Levels above CEC are expected to cause pharmacological response in fish.

Compound Group:
500 pharmaceuticals

Determination of Environmental Concentration
NA

Endpoint
Aquatic organisms (fish)

Impact Measure

$$\boldsymbol{Critical\ Environmental\ Concentration} = \frac{\boldsymbol{HTPC}}{\boldsymbol{CR} \times \boldsymbol{P_{blood:water}}}$$

HTPC = human therapeutic plasma concentration
CR = critical ratio. Effects conc. in fish vs effects conc. in humans.
Pblood:water = partitioning between water and blood (based on Kow)

Critical Environmental Concentration is based on steady state partitioning from water to fish plasma. Assumption was that pharmacological response in fish would occur at same plasma concentration as observed in humans

Evaluation Measure

Prioritization Benchmark
Ranked list based on Critical Environmental Concentration.

Reference:
Gotz et al. (2010)

Summary:
Occurrence-based ranking. Identified 7 exposure categories according to potential to occur in surface waters based on physical-chemical properties and input dynamics

Compound Group:
250 compounds based on EU Water Framework Directive and had been measured in Swiss surface waters

Determination of Environmental Concentration
Predicted based on water-soil distribution, degradation time, and input

Endpoint
NA

Impact Measure
NA

Evaluation Measure
Distribution in water phase: equilibrium partitioning coefficients
Persistence:

- $t_{1/2}$ < 1 day = readily degradable
- $t_{1/2}$ > 1 day, BIOWIN: moderately persistent --> moderately persistent
- $t_{1/2}$ > 1 day, BIOWIN: highly persistent --> highly persistent

Input: continuous or complex

Prioritization Benchmark

Exposure category	Distribution into water phase	Persistence	Input dynamics	Potential to occur in surface waters[a]
I	≥10%	High	Continuous	Very high
II	≥10%	High	Complex	Very high
III	≥10%	Moderate	Continuous	High
IV	≥10%	Moderate	Complex	High
V	<10%	nc	nc	Moderate–low
VI	≥10%	Low	nc	Moderate–low
VII	One of the attributes above is not known			Unknown

Categories I-IV are generally relevant for surface water quality and should be considered for further monitoring or risk assessment

Reference:
Howard and Muir (2010)

Summary:
Identification of compounds of interested based on persistence and bioaccumulation potential - chemicals of commerce

Compound Group:
22 000 commercial chemicals from the Canadian Domestic Substances List and EP Toxic Substances Control Act Inventory Update Rule

Determination of Environmental Concentration
NA

Endpoint
NA

Impact Measure
NA

Evaluation Measure
Bioaccumulation potential, log Kow, and biodegradability per EPI Suite software "

Prioritization Benchmark
Bioaccumulation - log Kow>3
Persistence - BIOWIN1 or BIOWWIN5 models output < 0.5 (50% probability that biodegradation will not be fast); or chemical structure suggest persistence using the (e.g., highly halogenated, highly branched, nitroaromatic)

Reference:
Kumar and Xagoraraki (2010)

Summary:
Apply multi-criteria rank scheme for EDCs and PCPPs in surface water and drinking water

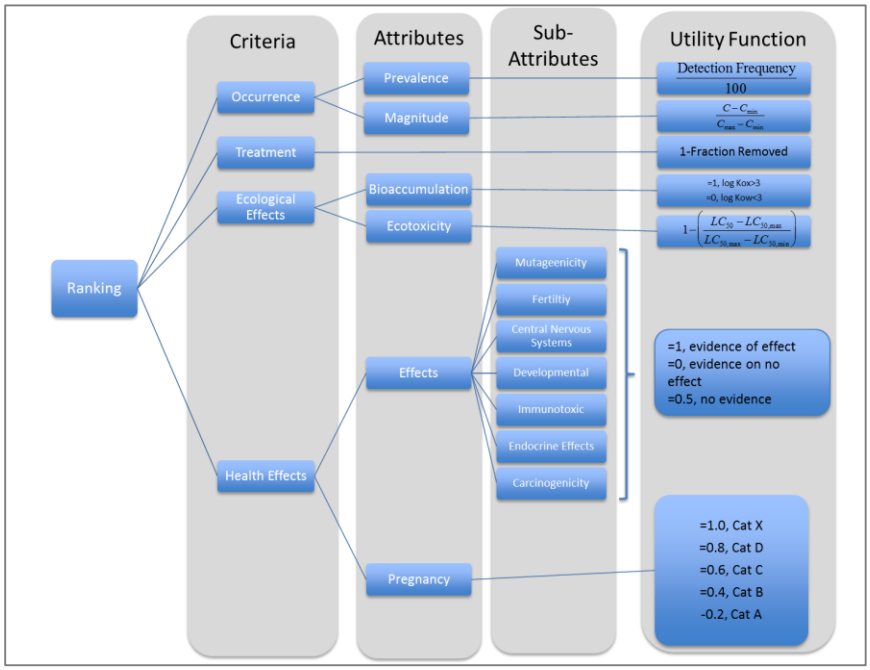
Compound Group:
100 PCPPs and EDCs

Determination of Environmental Concentration
Measured

Endpoint
Human
Eco toxicological

Impact Measure
Weighted sum of ranking criteria: occurrence, treatment, ecological effects, and health effects.

Evaluation Measure
The value of each of the criteria is based on the determination of specific utility functions. And a weighting scheme. For example, the value of Occurrence is the average of the utility function for prevalence and magnitude, as shown below. Values of each criteria are added to determine ranking.



Prioritization Benchmark
Based on final ranking value.

Reference:
Murray et al. (2010)

Summary:
Assess human risk due to direct consumption of freshwater.

Compound Group:
71 CECs

Determination of Environmental Concentration
Measured - Obtained from literature review

Endpoint
Human Acceptable Daily Intake (ADI) from direct consumption

Impact Measure

Evaluation Measure

Prioritization Benchmark
Exceedance of ADI based on maximum environmental concentration and assumed consumption of 2 to 200 L/d

Reference:
Schriks et al. (2010)

Summary:
Evaluated potential impact to human health based on surface water measurements.

Compound Group:
100 compounds of interest

Determination of Environmental Concentration
Measured - Rhine and Meusse rivers

Endpoint
Humans

Impact Measure
Reference dose based on chronic exposure
Established guideline value based on:

1) existing guideline
2) published Tolerable Daily Intake (TDI), Acceptable Daily Intake (ADI) or Reference Dose (RfD) values,
3) published lowest/no observable effects levels (LOEL, NOEL), or
4) other toxicological data.

Evaluation Measure

$$\text{Benchmark Quotient (BQ)} = \frac{\text{Environmental Occurrence}}{\text{Reference Dose}}$$

Prioritization Benchmark
BQ > 0.1 = priority compound

Reference:
de Voogt et al. (2009)

Summary:
Prioritization of pharmaceutically active compounds based on literature review

Compound Group:
153 pharmaceutically active compounds

Determination of Environmental Concentration
NA

Endpoint
Human
Ecotoxicology

Impact Measure

Evaluation Measure
Prioritization is based on number of criteria shown to be met during review of 20 documents. Criteria are:

1. Regulation,
2. Consumption/Sales
3. Physicochemcial properties
4. Human and Ecotoxicity
5. Occurrence
6. Degradability/persistence
7. Resistance to treatment

Prioritization Benchmark
High Priority - mentioned in 5+ documents and fulfil 4 of 7 criteria
Priority - mentioned in 3+ documents and fulfil more than 2 criteria
Low Priority - mentioned in 2 document and fulfil more than 2 criteria

Reference:
Arnot and Mackay (2008)

Summary:
Utilize RAIDAR mass-balance, equilibrium model to estimate concentration in biota. Risk is evaluated by comparing to impact threshold concentration

Compound Group:
200 Canadian Domestic Substances List (DSL) chemicals
12 UN listed POPs

Determination of Environmental Concentration
Calculated based on environmental emissions (EA)

Endpoint
Defined by selection of biota

Impact Measure
Ct = defined based on end point of interest
Cu is determined based on mass-balance modelling (RAIDAR)

Evaluation Measure
RAF = (Cu/Ct)*(Ea/Eu)
RAF = risk assessment factor;
Cu = predicted unit concentration; Ct = toxic threshold concentration; Ea = actual emission; Eu = unit emissions"

Prioritization Benchmark

Reference:
Besse and Garric (2008)

Summary:
Evaluate the potential of human pharmaceuticals in surface waters on non-target organisms in France.

Compound Group:
Human pharmaceuticals (120 parent compounds + 30 metabolites)

Determination of Environmental Concentration

$$PEC = \frac{\text{Consumption} \times F_{excreta}}{WW_{inhab} \times \text{pop} \times \text{dil} \times 365}$$

Consumption - total quantity of pharmaceutical consumed;
$F_{excreta}$ – unmetabolized fraction excreted, if known
WW_{inhab} - per capita wastewater production (200 l/d)
pop - watershed population
dil - dilution factor (10)

Endpoint
Aquatic organisms

Impact Measure
Potential environmental risk. Considered multiple potential endpoints via effects criteria.

Evaluation Measure

Prioritization Benchmark
Compounds are included as priorities if any of the below is true:
1) Exposure criteria:
    a) PEC > 100 ng/L
2) Effects Criteria:
    a) Chronic No Observable Effects Concentration (NOEC) < 10 µg/L
    b) Specific Mechanism of Action (e.g., alter serotonin reuptake, estrogenic activity, antibiotic)
    c) Known side-effects in humans
    d) Enzymatic induction or inhibition (e.g., CYP450)
    e) Glycoprotein P modulation
    f) log Kow > 4.5 and PEC > 10 ng/L

Reference:
Munoz et al. (2008)

Summary:
Modeled the human and ecotoxicological risk from WWTP effluent. Exposure scenarios either discharge to aquatic environment or WWTP effluent used in crop irrigation.

Compound Group:
98 frequently detected pollutants in Spain

Determination of Environmental Concentration
Measured WWTP

Endpoint
Human

Impact Measure
Environmental toxicity estimated with PNECs –
1) literature, 2) EPA Ecotox database, and EPA ECOSAR
Human toxicity estimated with ADI - 1) literature, or 2) EPA IRIS database

Evaluation Measure
Marine aquatic ecotoxicity potential (MAETP) of substances emitted to seawater calculated with USES-LCA model.
Human toxicity potential (HTP) of substances emitted to soil calculated with EDIP97

Prioritization Benchmark
Modeling allows calculation of relative potential impacts.

Reference:
Carlsson et al. (2006)

Summary:
Environmental risk of active pharmaceutical agents

Compound Group:
27 common pharmaceuticals in Sweden

Determination of Environmental Concentration

$$PEC = \frac{DOSE_{ai} \times F_{pen}}{WW_{inhab} \times dil \times 100}$$

$DOSE_{ai}$ - maximum daily dose;
F_{pen} - market penetration (1%);
WW_{inhab} - per capita wastewater use (200 L/day);
dil - dilution (10)

If PEC > 0.01 µg/L a refined PEC determined with Simple Treat WWTP modelling.

Endpoint
Environmental

Impact Measure
Predicted No Effects Concentration (PNEC):
Lowest of:

1) (LC50-, EC50-, or IC50-value)/1000
2) Chronic NOEC (single species)/100
3) Chronic NOEC (two trophic levels)/50
4) Chronic NOEC (three trophic levels)/10

Evaluation Measure
Risk Quotient (RQ) = PEC/PNEC

Prioritization Benchmark
RQ > 1 = priority compound

Reference:
Sanderson et al. (2004)

Summary:
Hazard assessment of pharmaceuticals in surface waters based on predicted toxicity, treatability, and bioaccumulation potential

Compound Group:
2986 pharmaceuticals

Determination of Environmental Concentration
Assumed 1 µg/L in surface waters

Endpoint
Aquatic organisms

Impact Measure
Toxicity predicted via ECOSAR
PNEC = predicted EC50/1000

Evaluation Measure
Toxicity: Hazard quotient (HQ) = 1 µg/L / PNEC
Treatability: Predicted based on STPWIN program
Bioaccumulation potential: Log Kow (predicted via KOWWIN program)

Prioritization Benchmark
Ranked List