Peer Review of the Final Report Entitled,
Monitoring Strategies for Chemicals of Emerging Concerns (CECs) in Recycled Water: Recommendations of a Science Advisory Panel

Convened by the California State Water Resources Board

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1 Preface

The format of this peer review will follow the issues outlined in the document listed as Attachment 2, “Scientific Issues to be Addressed by Peer Reviewers”. In the document entitled, “Cal/EPA External Scientific Peer Review Guidelines, April 2010 Addendum” each peer reviewer is advised to address each topic insofar as her/his expertise allows.

2 General Comments

The organization and presentation of the topics covered in the Final Report, *Monitoring Strategies for Chemicals of Emerging Concerns (CECs) in Recycled Water,* (Final Report) was thoughtfully and comprehensively presented. The document was well organized and the topics were presented in a logical and rational manner. It is my opinion that the Science Advisory Panel met the goals of the State Water Resources Control Board and the California EPA.

3 Peer Review of the Scientific Issues

3.1 Sufficiency of Potential Water Contaminant Lists of CECs

The adequacy of defining a list of potential chemicals of emerging concern (CECs) is founded on the process of screening the universe of chemicals. For a chemical-by-chemical model, defining the universe of CECs relevant to water recycling in a broad and transparent process is essential. The Final Report described a rigorous method to derive the list of health-relevant CECs and performance indicator CECs. The process included three primary sources:

1. U.S. EPA Contaminant Candidate List 3 (CCL3),
2. U.S. EPA Unregulated Contaminant Monitoring Regulation Program,
3. California Department of Public Health non-CCL List of Compounds.

3.1.1 Contaminant Candidate List 3 (CCL3)

The CCL3 is a list generated by the U.S. EPA of agents that are not currently subject to national primary drinking water regulations, that are known or anticipated to occur in public water systems, and which may require regulation under the Safe Drinking Water Act [1, 2]. The SDWA was passed by the 93rd Congress in 1974 to protect public health by regulating the nation’s public drinking water supply and was amended in 1986 and 1996. The law requires actions to protect drinking water and its sources. The Safe Drinking Water Act authorizes the U.S. EPA to set national health-based standards for drinking water to protect against contaminants that may be found in drinking water. The U.S. EPA implemented process expanded the evaluations used for previous CCLs and was based on substantial expert input and recommendations from the National Academy of Science's National Research Council and the National Drinking Water Advisory Council. The central steps of the CCL3 selection approach included the following process: 1) The identification of a universe of potential drinking water contaminants in which the U.S. EPA considered approximately 7,500 potential chemical and microbial contaminants. 2) The employment of a screening criterion that identified approximately 600 for further evaluation based on the potential of the contaminant to occur in public water systems and have possible public health concerns. 3) From this list the U.S. EPA chose 116 contaminants to include on the CCL based on detailed occurrence information and health effects and expert judgment. From this list the U.S. EPA considered the best available data and information and the final CCL3 includes 104 chemicals or chemical groups and 12 microbiological contaminants.

3.1.2 U.S. EPA Unregulated Contaminant Monitoring Regulation Program

The U.S. EPA established and employs the Unregulated Contaminant Monitoring program to collect data for drinking water contaminants for which there are no health-based standards set under the Safe Drinking Water Act [3]. Every five years EPA reviews the list of contaminants, largely based on the Contaminant Candidate List. This Final Report agreed that the Unregulated Contaminant Monitoring program follows the CCL3, it also contains additional compounds of interest along with methods for their detection.

3.1.3 California Department of Public Health non-CCL List of Compounds

The state of California has the authority to uphold the Safe Drinking Water Act and enforce all federal standards. However, the Safe Drinking Water Act permits states to enforce additional or more stringent regulations upon water contaminants [2]. The Division of Drinking Water and Environmental Management in the California Department of Public Health enforces both federal and state drinking water regulations. The state regulations encompass contaminants regulated in California but not by the U.S. EPA, a list of unregulated contaminants requiring monitoring in drinking water, and a series of notification levels for 29 unregulated contaminants. This additional level of regulation by the state of California for drinking water contaminants substantially enhances the safety of drinking water and the generation of recycled water for recharge.

3.1.4 Evaluation of the Process to Ensure the Sufficiency of the List of CECs

The use of the state of California enhanced drinking water contaminant regulations in consort with the U.S. EPA CCL3 and the U.S. EPA Unregulated Contaminant Monitoring provide for a robust, analytical and codified set of regulations based on the best science and public input. This reviewer considers the sufficiency of potential water contaminant lists of CECs to be well considered, rational, science based and adequate to meet the requirements as outlined in the Final Report.

Although the process to identify water contaminant lists of CECs is sufficient, it may be advised to consider the impact of complex mixtures of contaminants upon the environment and public health. This issue is addressed by the 1996 amendments to the Safe Drinking Water Act. Specifically the 1996 amendment stated:

> "Develop new approaches to the study of complex mixtures, such as mixtures found in drinking water, especially to determine the prospects

for synergistic or antagonistic interactions that may affect the shape of the dose-response relationship of the individual chemicals and microbes, and to examine non-cancer endpoints and infectious diseases, and susceptible individuals and subpopulations."

The development of regulations for recycled water based on single chemical analyses cannot account for synergistic or antagonistic interactions and thus reduces the breadth of the regulatory scheme for source water to drinking water plants.

3.2 Appropriateness of the Approach for selecting CECs of Toxicological Relevance to Monitor for Recycled Water Uses

3.2.1 Compilation of CEC Occurrence Data for Municipal Recycled Water in California

3.2.1.1 Approach for Determining the Toxicological Relevance of CECs in Recycled Water to Human Health

The principle of the screen process is direct and straightforward: empirical environmental measurements or predicted levels (MECs, PECs) of CECs for a specific water reuse scenario are compared to the monitoring trigger levels (MTLs) generated for a specific water use program. The process proposed in the Final Report is the Exposure Screening MEC/MCL method (Figure 3.2.1.1). A foundation of this methodology is the development of accurate MTLs for each water reuse scenario. The MTLs were derived as either drinking water standards from federal or state agencies and peer-reviewed publications with the goal that they be sufficiently low such that human health risks were kept to a minimum.

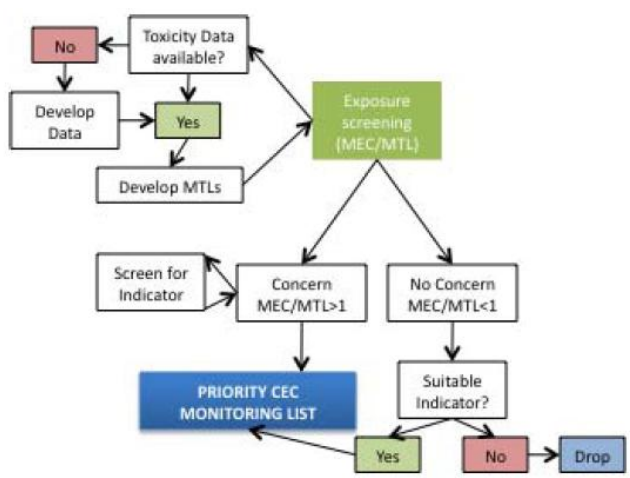

Figure 3.2.1.1 Exposure Screening MEC/MCL method of CECs with relevance in recycled water (from Final Report).

3.2.1.1.1 Comments on the Approach for Determining the Toxicological Relevance of CECs

1. The Panel recognized that CECs that have established benchmarks could be used for MTLs. However they noted that each benchmark could be developed using a diversity of assumptions and calculations.
2. Those CECs that have been listed in regulations usually have a rather rigorous foundation for their listing.
3. The real difficulty in using recommendations and regulations from federal and state agencies as well as from the peer-reviewed literature is that only CECs that are known will be listed. The universe of unknown chemical agents present now or generated in the future is not included in the system. Thus a MEC/MTL ratio cannot be easily derived.

3.2.1.2 Approach for Determining CECs Measured Environmental Concentration Occurrence

The use of the survey of sampling locations, analytical methods and treatment processes for water reuse practices in California was well described in the Final Report. The generation of MECs to MTLs from samples representing water quality after secondary and tertiary treatment as representative wastewater effluent quality for aquifer recharge was a reasonable approach to evaluate the process.

3.2.1.2.1 Comments on the Approach for Determining CECs Measured Environmental Concentration Occurrence

1. After exposure screening (MEC/MTL) the decision point was established as relevance for a CEC to be added to a proposed monitoring list as MEC/MTL>1 (concern and a candidate for listing); MEC/MTL<1 (no concern and not a candidate for listing). This approach is based on the available science, it provides an objective metric (albeit somewhat arbitrary) and the platform for decision is uniform, transparent and consistent. In general the approach is adequate for determining CECs measured environmental concentration occurrence concentration.
2. I have a moderate concern about the division between the approaches for recycled water devoted to potable recharge of aquifers versus landscaping and irrigation use. In Table 5.1, 17β-estradiol has a MEC/MTL value of 9.33 for potable reuse. This is clearly a signal for concern and a candidate for monitoring. However, for irrigation use, the MEC/MTL value is 0.93. Since this MEC/MTL value is <1 it would be categorized as no concern. Yet landscaping workers and irrigation workers, as a select population, could be exposed to this agent via ingestion, inhalation of the water vapor and skin exposure.
3. The recommendations to gather additional MEC data for CECs in California are well reasoned in the Final Report and are adequate.

3.2.2 Assignment of a Toxicologically Relevant Concentration Level (MTL) to individual CECs for each Recycled Water Exposure Scenario

The Final Report contains MTLs for ground water recharge from drinking water benchmarks from the U.S. EPA, California Department of Public Health and the Australian Environmental Protection and Heritage Council, two papers published in the scientific literature (Schwab et al. 2005; Schriks et al. 2010) [4, 5], and two peer-reviewed foundation final reports [6, 7]. The Panel used the drinking water benchmarks that were presented in Appendix J of the Final Report. Should multiple benchmarks be available for a compound, the Panel selected MTL values based on a prioritized ranking listed below.

- First priority, drinking water benchmarks developed by the California Department of Public Health.
- Second priority, drinking water benchmarks developed by a regulatory agency (U.S. EPA CCL benchmark).
- Third priority, the lowest drinking water benchmark from the peer reviewed literature.

3.2.2.1 Comments on the Development of MTLs for CECs for Recycled Waters

1. It is interesting that of the CECs evaluated only caffeine and triclosan of the non-CCL3 chemicals exceeded a ratio of “1”. It would be an interesting exercise to see the MTL values generated using the Schriks et al method [5] for the U.S. EPA regulated drinking water disinfection byproducts (chloroform, bromodichloromethane, chlorodibromomethane, bromoform, bromoacetic acid, chloroacetic acid, dibromoacetic acid, dichloroacetic acid, trichloroacetic acid, bromate, chlorite) [8]. Would these agents be assigned to the priority CECs monitoring list? This would be a good test of the resolving power of the system since the levels of these agents are analyzed in drinking water and they have a record of toxicology [9].
2. I am impressed that the Panel commented on the diversity of responses for CECs in which there are several benchmark levels. Their approach is inherently conservative and oriented toward the protection of the public health.
3. Attention should be given to the limitations of any scheme to develop MTLs especially for recycled waters based on limited knowledge. An example from a class of pharmaceutical contaminants in drinking water is the X-ray contrast agents, such as Iopamidol (Appendix J, Final Report). In the Final report for this single pharmaceutical contaminant the benchmark from the Australian Guidelines for Water Recycling www.scew.gov.au lists a drinking water guideline of 4.0×10^5 ng/L. In Schriks et al 2010 a provisional guideline value of 4.2×10^8 ng/L [5] is listed. They emphasize a very low level of toxicity of these pharmaceutical water contaminants as non-genotoxic agents (Figure 3.2.2.1). From their section entitled “Major Conclusions” Schriks et al states: “From a toxicological point of view iodinated contrast media as present in drinking water, such as

amidotrizoic acid, iopamidol, iohexol and iopromide, are not a direct concern for human health."

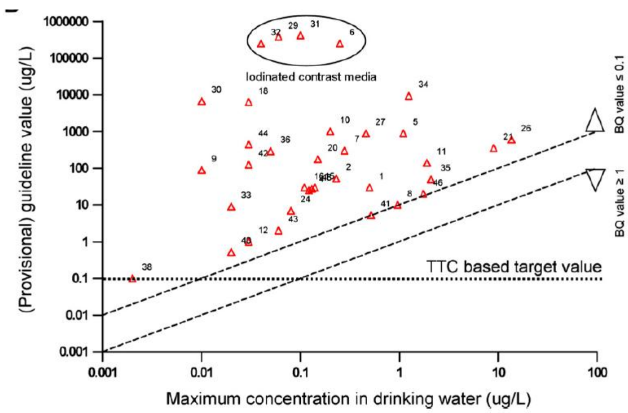

Figure 3.2.2.1 Drinking water provisional guideline values. Benchmark Quotient (BQ) thresholds are indicated with dashed lines. Threshold of Toxicological Concern (TTC) based target value for non-genotoxic compounds (0.1 mg/L) is indicated with a dotted line. Taken from Schriks et al 2010 [5].

However, new information demonstrated that iopamidol in source water that is disinfected with chlorine or chloramines reacts with natural organic material in the water and generates highly genotoxic iodinated DBPs [10]. In this case the conservative approach discussed in the Final Report may overlook the possible public health concerns of an important category of pharmaceutical CECs as being "non-toxic".

3.2.3 Comparison of the MEC to the MTL

After the measured environmental concentration or the predicted environmental concentration is determined the calculation of (MEC/MTL) provides a decision point of relevance for a CEC to be added to a proposed monitoring list as MEC/MTL>1 (concern and a candidate for listing); MEC/MTL<1 (no concern and not a candidate for listing). The comparison of the MEC to the MTL as a screening methodology for CECs to identify a list for monitoring was illustrated in Figure 4.1 in the Final Report. This approach is based on the available science, it provides an objective metric (albeit somewhat arbitrary) and the platform for decision is uniform, transparent and consistent.

3.2.3.1 Comments on the Comparison of the MEC to MTL

1. The MECs for specific CECs are generated from analytical data from water samples. These empirical measurements have high confidence levels. The Panel decided to use the 90th MECs and this provides an enhanced higher level of protection for the public health.

2. The MTL values are compilations derived from a variety of different toxicological databases and the application of uncertainty factors. This value is less robust than the MEC value. However, in my opinion the process, in general is science-based, consistent and transparent.
3. A routine updating on the data that is generated for the MTLs is important. A consistent and transparent incorporation of *in vitro* cellular based toxicity data would enhance the MTLs comparability.
4. My major concern is that there is no measurement for the possible adverse public health impacts of complex mixtures or for the impact of the unknown CECs. What if the forcing factors in the global toxicity of a recycled water are not the part of the known CEC universe?

3.2.4 Evaluation of Robust Analytical Method Availability

3.2.4.1 Comments on the Availability of Analytical Methods

This component of the Final Report is outside my expertise and I have no comments in this area.

3.2.5 Comments on the Lack of Use of Biological Assays for the Evaluation of Recycled Water Samples

Section 6 of the Final Report, *Screening Unknown CECs in Recycled Water to Assess Exposure*, provides a brief, yet cogent review on the issues of using biological and/or bioanalytical assays to evaluate CECs for toxic characteristics. In the case of unknown CECs, approaches for chemical analyses and identification may simply be inadequate. Micro-pollutants and contaminants in recycled water constitute a complex mixture and the chemical-by-chemical approach provides information on agents in which we have at least some knowledge. Section 6 of the Final Report is skewed to evaluating individual CECs at least in the future with bioassays. It is true that *in vitro* assays have limitations that may prevent adequate prediction of toxic responses in animal or human models. However, *in vivo* assays suffer from this limitation with the additional problem of low resolving power for a variety of endpoints. Extrapolation of animal to human risk assessment is not an exact science, thus the need for high uncertainty factors. Section 6 argues for the use of high throughput assays to focus on mode of action responses for CECs and perhaps recycled water samples. Clearly these high throughput assays hold a promise for rapid screening. To limit such bioassays to individual CECs is questionable. The Final report provides only minor guidance to the employment of bioassays in the analyses of recycled water in terms of unknown CECs. The Final report does mention that *in vitro* assays provide insight to detect and measure the impact of complex mixtures and for possible synergistic, additive and antagonistic interactions of chemical components. Even if *in vitro* assays are not employed for direct risk assessment of recycled waters, concentrated chemical fractions of recycled water could be screened for global effects such as chronic cellular cytotoxicity, genotoxicity, endocrine disruptors and other toxic effects of concern. A standard concentrated water sample control could be defined and used to compare concentrated recycled water. Using this approach recycled water samples could be rank-ordered to compare the levels of toxicity observed from a series of recycled water samples. This approach could be used to identify recycled water operations that generate the most toxic water samples and the offending chemical components could be identified. Comparing the relative toxicity among different recycled water processes could provide biologically-mediated optimization of recycling water plants. The use of bioassays to systematically evaluate complex water samples has been successfully applied to the analyses of drinking water [11], and swimming and recreational pool waters [12-15]. Finally, a central supporting document in this Final Report is the Safe Drinking Water Act [2]. The 1996 amendment to the Safe Drinking Water Act applied a focus on the need to consider the impact of and the study of complex mixtures, such as mixtures found in drinking water. Unfortunately this Final Report does not adequately address this area.

3.3 Determination of Initial MTLs for Landscape Irrigation

The Final Report states that the same assumptions to derive the MTLs for potable water use were used for the MTLs for landscape irrigation except that the water ingestion rate was based on an incidental ingestion fraction of 1% of the daily water intake. With this ingestion rate for irrigated water use, the MTLs for irrigated water are 100 times greater than those used for potable reuse.

3.3.1 Comments on MTLs for Landscape Irrigation

1. The ingestion level for recycled water is essentially an uncertainty factor and the Final Report should state this fact. The ingestion level value is 20 mL per day or 1% of daily potable water consumption. This ingestion value is similar to the hourly ingestion rate for adults while in swimming pools.
2. My concern is for a subset of the general population, field workers, landscapers and outdoor recreational staff who may be exposed to much higher equivalent levels than 20 mL per day ingestion. If they are exposed to the spray irrigation they may be at risk for exposure by not only ingestion but also inhalation and skin absorption as is the case with some DBPs [16].
3. Also I wonder if there is information about consumption of irrigation water by migrant workers or temporary field workers and others. If there is a history of, or a custom of consuming water used for irrigation, then this subpopulation may be at higher risk that is not accounted for by the current method of determining MTLs for landscape irrigation.
4. A final comment is that the Final Report uses irrigation recycled water for landscaping. Would these MTLs also be applied to agricultural irrigation scenarios?

3.4 Adequacy of the Selected Performance Indicator CECs

Within section 8 of the Final Report the Panel defined an indicator compound as individual CECs that occur in recycled water that represent physiological and biodegradable characteristics of trace organics that are relevant to the fate and transport during treatment. These agents represent a metric of contaminant removal by water treatment technologies (chlorine, photochemical reactions, ozone etc.) for use as indicators in potable and irrigation recycled water. These health-based indicator and performance-based indicator compounds were chosen to represent agents not currently identified (unknowns) and new, synthetic compounds that may enter the environment in the future. The foundation of the metric is that the absence or removal of an indicator CEC during a treatment process would indicate the absence or removal of unidentified compounds with similar properties. The adequacy of a treatment regime upon the agents listed in Final Report Table 8.2 would be followed by determining the differential in the concentration of the indicator agent before and after operating conditions of a treatment plant. The health-based or performance-based indicator efficiency of removal would be determined using the general formula $\Delta Y = [Y_{in} - Y_{out}]/Y_{in}$. The panel recommended that the ΔY for selected indicator compounds be monitored for each unit process on a semiannual/annual timeframe.

3.4.1 Comments on the Selected Performance Indicator CECs

1. The general approach for the measurement of the efficiency of sentinel agents before and after the processing of recycled water is reasonable. However, the principle that the absence or removal of an indicator CEC during a treatment process would indicate the absence or removal of unidentified compounds with similar properties, is the strength and the weakness of the approach. It is difficult to ensure that observing the reduction of an indicator agent will ensure simultaneous reduction of the toxicity of unknown CECs that may be present in recycled water.
2. Consider the antimicrobial agent, triclosan, which is on the list of the health-based indicator CECs presented in Final Report Table 8.2. Using the approach presented in the report, a reduction of >90% is expected by a treatment plant. Yet the degradation products may be more toxic than the parent CEC itself. It was reported that reactions between triclosan and free chlorine are rapid at pH values typically encountered in drinking waters and lead to the production of several deleterious products. These degradation products include, 5,6-dichloro-2-(2,4-dichlorophenoy)phenol, 4,5-dichloro-2-(2,4-dichlorophenoxy)-phenol, 4,5,6-trichloro-(2,4-dichlorophenoxy)phenol, 2,4,6-trichlorophenol, and 2,4-dichlorophenol [17]. Treating triclosan with chloramines leads to the generation of 5,6-dichloro-2-(2,4-dichlorophenoxy)phenol, 4,5-dichloro-2-(2,4-dichlorophenoxy)phenol, and 4,5,6-trichloro-2-(2,4-dichlorophenoxy)phenol as well as chloroform, a federally regulated DBP [18]. With UV treatment methods triclosan is converted into 2,8-dichlorodibenzo-p-dioxin [19]. Using triclosan as an example, the possibility exists that a treatment method will effectively remove this indicator CEC but the degradation byproducts may express toxicity in excess of the parent CEC.
3. Again focusing on the principle that the absence or removal of an indicator CEC during a treatment process would indicate the absence or removal of unidentified compounds with similar properties one may ask the question if a similar CEC can predict the adverse effects of a chemically related compound. Consider the pharmaceutical agent, iopromide, which is on the list of the performance-based indicator CECs presented in Final Report Table 8.2. Using the approach presented in the report, a reduction of >90%

is expected by a treatment plant. Iopromide is an X-ray contrast agent and is related to another X-ray contrast pharmaceutical, iopamidol. However, these very similar pharmaceutical water contaminants react differently when treated with free chlorine or with chloramines in natural source waters. When iopamidol is treated with chlorine or chloramines in the presence of NOM the generation of highly toxic iodinated DBPs was detected. Yet when iopromide was treated under the same conditions no such reaction was detected (Figure 3.4.1) [10]. Thus in this case the response of the performance-based indicator CEC did not predict the response of a highly similar pharmaceutical water contaminant.

Iopamidol
62883-00-5
776.85 Da

Iopromide
73334-07-3
790.87 Da

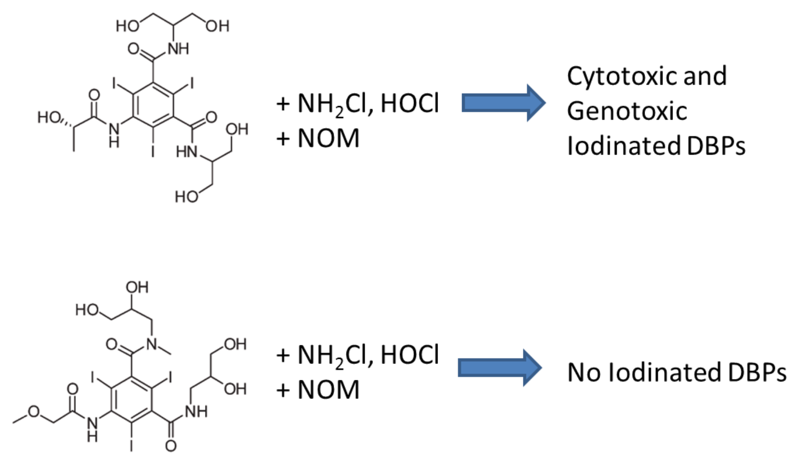

Figure 3.4.1 Comparison of the generation of iodinated DBPs by iopamidol or iopromide in source waters after treatment with chlorine or chloramines.

This is presented as a caution to indicate the limitations of the principle that the removal of an indicator agent will reflect the response of related compounds.

4. I suggest that an additional process be considered to complement the indicator chemical approach to determine the efficiency between the influent and effluent of a treatment plant process. The number of unknown agents in the feed recycled water may well be very high and these agents may provide the forcing function for health risks. By using global *in vitro* cell based toxicity assays one could apply a similar formula to measure the reduction of Toxicity (T) of the water ($\Delta T = [T_{in} - T_{out}]/T_{in}$). Influent water could be concentrated by activated carbon, XAD or liquid/liquid extraction. The concentrated organic fraction would be diluted in an appropriate cell medium and *in vitro* assays using mammalian cells for cytotoxicity, genotoxicity and endocrine function could be conducted to measure the reduction in global toxicity associated with the treatment process. This would further ensure that the treatment process would not generate byproducts that may pose a public health concern.

3.5 Adequacy of the Selected Surrogates for Monitoring Treatment Process Performance

This approach is to determine changes of a bulk parameter that can measure the performance of individual unit treatment processes or operations in removing organic agents from the recycled water. The principle is that a poor or less than expected reduction of global metrics such as COD, TOX, TOC, conductivity etc., would be an indicator that a treatment process also fails to remove or reduce CECs.

3.5.1 Comments on the use of Surrogates for Monitoring Treatment Process Performance

1. This component of the Final Report is outside my expertise and I have no comments on this area.

3.6 Validity of Expected Percent Removal of Surrogates and Performance Indicator CECs for a Treatment Process

Based on the literature, the Final Report lists estimates of removal levels for CECs for treatment scenarios.

3.6.1 Comments on the Comparison of the Levels of Removal of Surrogates and Performance Indicator CECs for a Treatment Process

1. This component of the Final Report is outside my expertise and I have no comments for this area.

3.7 Appropriateness of Tiered Risk Quotient Thresholds and Corresponding Degree of Response for Evaluating Monitoring Results for Health-Based CECs in Recycled Water

The Final Report describes a multi-tiered methodology to interpret the data from the recycled water project monitoring for health-based CECs. Using the data the Final Report describes additional actions based on the monitoring results. The reduction of risk for CECs with limited toxicological information is based on the use of a 10^5-fold safety factor. Should the MEC/MTL level exceed 1 then a series of actions are implemented that involve consultation among the recharge agency and the California Department of Public Health and the relevant Regional Water Quality Control Board. The tiered approach has five levels; (i) with 25% MEC/MTL < 0.1, (ii) 1 <MEC/MTL <10, (iii) 10 < MEC/MTL <100, (iv) 100 < MEC/MTL < 1000, and (v) MEC/MTL > 1000. This design permits increasing increments of concern, consultation, consistent and prescribed action, and control by the appropriate regulatory agencies.

3.7.1 Comments on the Use of Tiered Risk Quotient Thresholds and Corresponding Degree of Response for Evaluating Monitoring Results for Health-Based CECs in Recycled Water

1. After establishing a level of concern based on a ratio of MEC/MTL = 1 this tiered method to assign priority and process is consistent, rational and transparent.
2. If violations of the MEC/MTL = 1 ratio become extreme (levels iv and v) after what was considered an acceptable water treatment process, one wonders what could be the impact of the unknown, unknown agents in the recycled water. Some overall toxicity metric of the recycled water and comparison against some standard may be appropriate and necessary.
3. The tiered risk quotient thresholds provide a universal standard for individual CECs and indicator agents, but do not address the adverse biological impact of CEC or byproduct mixtures at any tiered level.
4. The information on the toxicity of individual CECs should be upgraded on a regular basis and the MEC/MTL ratio recalculated. I am concerned that a level of concern could be eliminated merely by altering the MTL value.

3.8 Adequacy of Monitoring Frequencies for CECs and Surrogates and the Phased Monitoring Approach

The Final Report lists a proposed monitoring program to assess CEC and surrogate parameters in recycled water. The monitoring approach is phased in that it uses an investigative program for incremental information-gathering on CECs before and after recycled water treatment.

3.8.1 Comments on the Monitoring Frequencies for CECs and Surrogates and the Phased Monitoring Approach

1. This component of the Final Report is outside my expertise and I have no comments on this area.

3.9 Additional Consideration for the Peer Reviews

The Panel presented an alternative “preferred” method for deriving MTL values using a screening level that was based on allowable daily intakes. Section 4 of the Final Report was to find and implement an approach to estimate the relative toxicity of CECs and to establish a predicted no effect concentration (PNEC) or to derive a threshold of toxicological concern (TTC). The route for screening CECs that have the potential for toxicological relevance was to use the predicted or measured environmental concentration of the CECs at the point of monitoring and compare these levels with the monitoring trigger levels for each water reuse scenario. The calculation of the monitoring trigger level for each CEC is essential for the screening process to identify toxic CECs. As an alternative approach the Panel reviewed one system to systematically and uniformly evaluate each CEC based on the approach by Snyder et al [20]. This approach, although it requires a series of assumptions, is rational, science driven and, importantly, consistent. This will provide a level field of comparison for each CEC. The process based on the Snyder et al report to determine a monitoring trigger level was described in the Final Report and illustrated below (Figure 3.9).

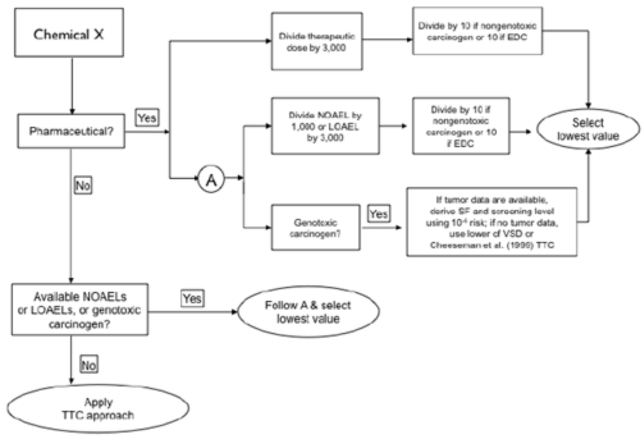

Figure 3.9. The decision tree for determining the predicted no effect level for CECs (from the Final Report, derived from Snyder et al., 2010).

3.9.1 Comments on the Alternative Method for Deriving MTL Values

1. The Snyder et al reference is a final report submitted to the Water Reuse Foundation [20]; has this report been published by a reputable peer-reviewed scientific journal? I find that a review by an established and respected journal tends to be more rigorous than that usually devoted to a final report for a foundation. Nevertheless, the use of a rational platform that is applied consistently to determine the threshold of toxicological concern and/or the predicted no effect concentration for the CECs is an important step in reducing the level of error associated with such literature-based calculations.
2. In step 1 of the process (page 31 of the Final Report), the CECs are based on the parental compounds. Research has emerged that demonstrate that source waters that were contaminated with pharmaceutical agents had degradation products more toxic than the parental pharmaceuticals [10, 21, 22]. Thus a CEC could be identified as having a low toxicity risk and not be monitored because of its measured environmental concentration below the monitoring trigger level. Yet, a reaction of the CEC with a disinfectant may generate a byproduct that is significantly more toxic than the parental contaminant. This chemical-by-chemical approach does not address these types of issues.
3. The use of the NOAEL to establish a base number for the application of the uncertainty factors is reasonable. Yet, the Final Report does not specifically list if this approach is

used only for *in vivo* or *in vitro* data. Should *in vitro* data be needed (especially for analytical comparative structure activity relationship information), how would the Panel recommend converting the concentration values (ppm, ppb, molar units etc.) to mg/kg/day units for application in this method to establish PNEC or TTC values?

4. The derivation of the monitoring trigger levels for potable water is rational, consistent and is adequate for the process.
5. I am concerned with the derivation of the monitoring trigger levels for landscape use. Although it may appear that removing the ingestion rate is applicable for the general public, I question if this could put landscape workers, at a heightened risk. Although non-potable landscaping water will be necessarily labeled, I wonder if the practice of drinking "from the hose" could be sufficiently curtailed amongst this exposure population.
6. The use of analytical chemical results for the baseline monitoring data for many CECs and the comparison of these levels to the MTLs as a first level in the decision tree in a monitoring program is an adequate method.
7. This method of evaluating the suitability of a recycled water stream for either potable water use via recharge or for landscape use ignores the contribution of the impact of mixtures. Unfortunately this has a low resolving power for identifying the forcing agents (unknown chemicals or chemicals with unknown toxic characteristics) in the overall toxicity of a recycled water stream as compared to some standard level of overall toxicity in a defined standard.

4 The Big Picture

4.1 Comments on Additional Scientific Issues that are Part of the Scientific Basis of the Proposed Rule

1. My greatest concern, as stated previously in this peer review, is the lack of incorporating the impact of complex mixtures in the methodology of establishing acceptable tolerances in the quality of recycled water for use in groundwater recharge and for landscape irrigation.
2. This lack of appropriate attention to the issue of the effects of chemical mixtures in the broad scheme of determining the potential health and environmental risks of treated recycled water contravenes the emphasis on mixtures stated in the Federal Safe Drinking Water Act.
3. It has been clear to toxicologists that the exposure to harmful agents is not an isolated event that occurs as single exposures. Yet the majority of toxicological research and the resulting regulation has focused on single chemical exposures [23-25].

4. In the arena of public health, exposure to a toxicant might potentially be altered by the presence of other toxic agents in which interactions can be additive, synergistic, or antagonistic [26].
5. Single-chemical approaches such as advocated in the Final Report can potentially miss yet-to-be characterized components and important biological effects resulting from chemical interactions [27].
6. Incorporating an evaluation of mixtures may provide more accurate descriptions of the potential risks of the chemicals present in recycled water before or after treatment processes.
7. As mentioned earlier in this peer review, the decision to monitor a CEC based on a MEC/MTL ratio is rational and importantly consistent. However, recycled water is a highly complex mixture of many chemical agents. The addition of treating recycled water to remove toxic agents may only increase the complexity of the mixture in that a multitude of byproducts may be generated. It may be useful for the California State Water Resources Control Board to consider adding *in vitro* global toxicity bioassays to enhance the breadth of their evaluation of the recycled waters. To-be-sure one cannot define health risks based on *in vitro* assays, yet an analytical, comparative analyses amongst a diversity of recycled waters (before and after treatment) would be an approach to rank order these samples. In addition these recycled water samples could be compared to a rank order of CEC-based recycled water data.
8. This *in vitro* cellular method has been used to analyze individual DBPs within a chemical class and compare the results to the U.S. EPA list of regulated DBPs [28]. Also concentrated water samples from diverse drinking water treatment processes, as well as from recreational pools have been analyzed and compared using *in vitro* cellular assays [11, 14]. It is not necessary to employ the specific cell lines or assays referenced above, but a host of specific cell lines could be used to measure chronic cytotoxicity, genotoxicity, or to analyze the metabolic activation of recycled water agents (human HepG2 cells) or to determine endocrine disruption activity (human breast cancer MCF-7 cells) [29].
9. Cell-based, global toxicity analyses of recycled water samples would require the concentration of chemicals present in these waters. No concentration process is perfect however, the most common water concentration methods include lyophilization, reverse osmosis, liquid-liquid extraction, activated carbon, XAD resin, and ion exchange [30]. Using resin-based concentration methods, an adequate sample of recycled water could be efficiently processed and concentrated for *in vitro* analyses.
10. The employment of *in vitro* bioassays of a concentrated recycled water sample would provide a baseline value for the entire mixture of contaminants in the recycled water before and after treatment. Also one could directly compare the overall toxicity of the recycled water sample to a known regulated standard such as a DBP regulated by the U.S. EPA (e.g. bromoacetic acid).

4.2 Comments on the Scientific Portion of the Proposed Rule Basis on Sound Scientific Knowledge, Methods and Practices

1. It is this reviewer's opinion that the Panel has generated an exemplary Final Report and that Appendix A reflects well the intent and foundation of the proposed rule on the use of recycled water in California.
2. The California State Water Resources Control Board, by establishing this Scientific Advisory Panel on monitoring strategies for CECs in recycled water, has taken a leadership position on this issue. This rule will serve as an example for the other states of the Union and, indeed, federal regulators.
3. The proposed rule is based on a scientific foundation that is transparent, consistent, grounded in the best science available and acknowledges and addresses the levels of uncertainty inherent with recycled water use. This is a good rule.

4.3 Does the Draft Amendment (Attachment A) Adequately Characterize and Implement the Panel's Recommendation for Monitoring for CECs in Recycled Water Use in Groundwater Recharge and Landscape Irrigation

1. Based on my reading and with my limited legal experience, the draft amendment provided in Attachment A adequately characterizes and implements the Scientific Advisory Panel's recommendations for monitoring CECs in recycled water for groundwater recharge and recycled water used for landscape irrigation.

References

1. U.S. Environmental Protection Agency, Drinking Water Contaminant Candidate List 3: Draft. *Federal Register* **2008,** *73*, (35), 9628-9654.
2. An Act to amend the Public Health Service Act to Assure that the public is provided with safe drinking water, and for other purposes. In *88 Stat. 1660 (1974)*, United States of America, 1974; Vol. 42 U.S.C. 300f.
3. U.S. Environmental Protection Agency Unregulated Contaminant Monitoring Program. http://water.epa.gov/lawsregs/rulesregs/sdwa/ucmr/
4. Schwab, B. W.; Hayes, E. P.; Fiori, J. M.; Mastrocco, F. J.; Roden, N. M.; Cragin, D.; Meyerhoff, R. D.; D'Aco, V. J.; Anderson, P. D., Human pharmaceuticals in US surface waters: a human health risk assessment. *Regul. Toxicol. Pharmacol.* **2005,** *42*, (3), 296-312.
5. Schriks, M.; Heringa, M. B.; van der Kooi, M. M.; de Voogt, P.; van Wezel, A. P., Toxicological relevance of emerging contaminants for drinking water quality. *Water Res.* **2010,** *44*, (2), 461-476.
6. Snyder, S. A.; Trenholm, R. A.; Snyder, E. M.; Bruce, G. M.; Pleus, R. C.; Hemming, J. D. C. *Toxicological relevance of EDCs and pharmaceuticals in drinking water*; AWWA Research Foundation: Denver, CO, 2008.
7. Cotruvo, J.; Bull, R.; Crook, J.; Whittaker, M. *Identifying health effects concerns of the water reuse industry and prioritizing research needs for nomination of chemicals for research to appropriate national and international agencies*; WaterReuse Research Foundation: Alexandria, VA, 2010.
8. U. S. Environmental Protection Agency, National primary drinking water regulations: Stage 2 disinfectants and disinfection byproducts rule. *Federal Register* **2006,** *71*, (2), 387-493.
9. Richardson, S. D.; Plewa, M. J.; Wagner, E. D.; Schoeny, R.; DeMarini, D. M., Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: A review and roadmap for research. *Mutat. Res.* **2007,** *636*, 178-242.
10. Duirk, S. E.; Lindell, C.; Cornelison, C.; Kormos, J. L.; Ternes, T. A.; Attene-Ramos, M. S.; Osiol, J.; Wagner, E. D.; Plewa, M. J.; Richardson, S. D., Formation of toxic iodinated disinfection by-products from compounds used in medical imaging. *Envion. Sci. Technol.* **2011,** *45*, 6845–6854.
11. Plewa, M. J.; Wagner, E. D.; Metz, D. H.; Kashinkunti, R.; Jamriska, K. J.; Meyer, M., Differential toxicity of drinking water disinfected with combinations of ultraviolet radiation and chlorine. *Environ. Sci. Technol.* **2012,** *In Press*.
12. Zwiener, C.; Richardson, S. D.; DeMarini, D. M.; Grummt, T.; Glauner, T.; Frimmel, F. H., Drowning in disinfection byproducts? Assessing swimming pool water. *Environ. Sci. Technol.* **2007,** *41*, (2), 363-372.
13. Kogevinas, M.; Villanueva, C. M.; Font-Ribera, L.; Liviac, D.; Bustamante, M.; Espinoza, F.; Nieuwenhuijsen, M. J.; Espinosa, A.; Fernandez, P.; DeMarini, D. M.; Grimalt, J. O.; Grummt, T.; Marcos, R., Genotoxic effects in swimmers exposed to disinfection by-products in Indoor swimming pools. *Environ.Health Perspect.* **2010,** *118*, (11), 1531-1537.

14. Liviac, D.; Wagner, E. D.; Mitch, W. A.; Altonji, M. J.; Plewa, M. J., Genotoxicity of water concentrates from recreational pools after various disinfection methods. *Environ. Sci. Technol.* **2010,** *44*, (9), 3527-3532.
15. Plewa, M. J.; Wagner, E. D.; Mitch, W. A., Comparative mammalian cell cytotoxicity of water concentrates from disinfected recreational pools. *Environ. Sci. Technol.* **2011,** *45*, 4159–4165.
16. Villanueva, C. M.; Gagniere, B.; Monfort, C.; Nieuwenhuijsen, M. J.; Cordier, S., Sources of variability in levels and exposure to trihalomethanes. *Environ. Res.* **2007,** *103*, (2), 211-220.
17. Rule, K. L.; Ebbett, V. R.; Vikesland, P. J., Formation of chloroform and chlorinated organics by free-chlorine-mediated oxidation of triclosan. *Environ. Sci. Technol.* **2005,** *39*, (9), 3176-3185.
18. Greyshock, A. E.; Vikesland, P. J., Triclosan reactivity in chloraminated waters. *Environ. Sci. Technol.* **2006,** *40*, (8), 2615-2622.
19. Latch, D. E.; Paker, J. L.; Arnold, W. A.; McNeill, K., Photochemical conversion of triclosan to 2,8-dichlorodibenzo-*p*-dioxin in aqueous solution. *J. Photochem. Photobiol.* **2003,** *158*, (1), 63-66.
20. Snyder, S. A.; Stanford, B. D.; Bruce, G. M.; Pleus, R. C.; Drewes, J. E. *Identifying hormonally active compounds, pharmaceuticals, and personal care product ingredients of health concern from potential presence in water intended for indirect potable reuse*; Alexandria, VA, 2010.
21. Schirmer, K.; Schirmer, M., Who is chasing whom? A call for a more integrated approach to reduce the load of micro-pollutants in the environment. *Water Sci. Technol.* **2008,** *57*, (1), 145-150.
22. Richardson, S. D.; Ternes, T. A., Water analysis: emerging contaminants and current issues. *Anal. Chem.* **2011,** *83*, (12), 4614-4648.
23. Groten, J. P., Mixtures and interactions. *Food Chem Toxicol* **2000,** *38*, (1 Suppl), S65-71.
24. Feron, V. J.; Cassee, F. R.; Groten, J. P.; van Vliet, P. W.; van Zorge, J. A., International issues on human health effects of exposure to chemical mixtures. *Environ. Health Perspect.* **2002,** *110 Suppl 6*, 893-899.
25. Feron, V. J.; Groten, J. P., Toxicological evaluation of chemical mixtures. *Food Chem.Toxicol.* **2002,** *40*, (6), 825-839.
26. Narotsky, M. G.; Best, D. S.; McDonald, A.; Godin, E. A.; Hunter, E. S., 3rd; Simmons, J. E., Pregnancy loss and eye malformations in offspring of F344 rats following gestational exposure to mixtures of regulated trihalomethanes and haloacetic acids. *Reprod. Toxicol.* **2011,** *31*, (1), 59-65.
27. Henschler, D.; Bolt, H. M.; Jonker, D.; Pieters, M. N.; Groten, J. P., Experimental designs and risk assessment in combination toxicology: panel discussion. *Food. Chem. Toxicol.* **1996,** *34*, (11-12), 1183-1185.
28. Plewa, M. J.; Wagner, E. D., *Mammalian Cell Cytotoxicity and Genotoxicity of Disinfection By-Products*. Water Research Foundation: Denver, CO, 2009; p 134.
29. Welshons, W. V.; Thayer, K. A.; Judy, B. M.; Taylor, J. A.; Curran, E. M.; vom Saal, F. S., Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. *Environ.Health Perspect.* **2003,** *111*, (8), 994-1006.

30. Jolley, R. L.; Suffet, I. H., Concentration Techniques for Isolating Organic Constituents in Environmental Water Samples. In *Organic Pollutants in Water: Sampling, Analysis, and Toxicity Testing*, Suffet, I. H.; Malaiyandi, M., Eds. Am. Chem. Soc.: 1987; pp 1-14.