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Submitted via email: keithm@sccwrp.org

Re: Comments on Draft Final Report Monitoring Strategies for Constituents of Emerging Concern (CECs) in Recycled Water: Recommendations of a Science Advisory Panel (January 31, 2018)

Dear Dr. Maruya,

The Alkylphenols & Ethoxylates Research Council (APERC) appreciates this opportunity to comment on the Science Advisory Panel (SAP) Draft Final Report entitled "Monitoring Strategies for Constituents of Emerging Concern (CECs) in Recycled Water: Recommendations of a Science Advisory Panel (January 31, 2018)". APERC is a North American organization whose mission is to promote the safe use of alkylphenols (APs), alkylphenol ethoxylates (APEs), including nonylphenol (NP), which is one of the CECs addressed in the SAP report, through science-based research within the framework of responsible chemical management. For more than twenty-five years, APERC and its member companies have been actively engaged in the conduct and review of studies on the environmental fate, occurrence and toxicological effects of these compounds.[1]

APERC found the SAP report and recommendation to be well-founded in science and appropriate for its purpose, which is to provide a framework for CEC monitoring in recycled water in California that is protective of human health. APERC supports the methodology developed by the SAP for a highly conservative, risk-based framework to prioritize and monitor CECs in potable and non-potable recycled water. The SAP relies on 90th percentile

[1] Members of the Alkylphenols & Ethoxylates Research Council are The Dow Chemical Company; SI Group, Inc.; and Dover Chemical Company.

concentrations of the distribution of CECs based on monitoring data collected by water reuse facilities in California to establish Measured Environmental Concentrations (MECs) for the framework. The use of 90th percentile concentrations was selected by the SAP as a conservative approach due to data sets for individual CECs that were limited and in many cases highly variable. The SAP also updated conservative Monitoring Trigger Levels (MTLs) based on toxicological information gathered from various sources giving greatest priority to drinking water thresholds developed by the State of California and US EPA. The SAP screened 489 CECs using updated MECs and MTLs to calculate MEC/MTL ratios. While emphasizing that a MEC/MTL ratio of greater than 1 does not represent an immediate threat to public health, the SAP relies on the MEC/MTL ratios to provide a valid basis to prioritize CEC for monitoring.

APERC provides the following comments in support of this highly conservative risk-based monitoring framework.

- **The Monitoring Trigger Level (MTL) of 110 µg/L, which was derived for NP is well supported by four high-quality, multi-generation rat studies that address all life stages and include reproductive and developmental endpoints.**

MTLs are monitoring trigger levels that the SAP conservatively based on existing Acceptable Daily Intake (ADI) values, Reference Doses (RfDs) or Predicted No Effect Concentrations (PNECs) for human health from various governmental sources.

The MTL for NP was lowered from 500 µg/L in the previous 2010 SAP report to 110 µg/L in the drat 2018 SAP report. In the draft 2018 SAP report the MTL for NP was revised based on a Health Reference Level (HRL) of 105 µg/L NP calculated by US EPA in its Fourth Candidate Chemical List (CCL4) Information Sheets in 2016. [2] The US EPA HRL is based on a No Observed Adverse Effect Level (NOAEL) of 15 mg/kg-bw that EPA cited from a 2014 World Health Organization (WHO) report, which in turn cited a European Commission (EC) 2002 Risk Assessment Report for NP. [3,4] The primary source of the NOAEL of 15 mg/kg-day for NP is a study conducted by the US National Toxicology Program (NTP) that was reported by Chapin et al., 1999. [5,6]

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[2] US EPA Office of Water (2016, November). Contaminant Information Sheets for the Final Fourth Contaminant Candidate List (CCL4). EPA 815-R-16-003.
[3] World Health Organization, International Programme on Chemical Safety (WHO IPCS). (2004). Integrated Risk Assessment: Nonylphenol Case Study.
[4] European Commission (EC). 2002. European Union Risk-Assessment Report Vol.10, 2002 on 4-nonylphenol (branched) and nonylphenol, European Chemicals Bureau, Joint Research Centre, European Commission, Ispra, Italy, ISBN 92-827-801.
[5] National Toxicology Program (NTP). 1997. NTP Report # RACB94021. Nonylphenol: Multigenerational Reproductive Effects in Sprague-Dawley Rats when Exposed to Nonylphenol (CASRN: 84852-15-3) in the Diet. Report Date: September 2, 1997. Available at URL: http://ntp.niehs.nih.gov/.

As reported by Osimitz et al, 2015 four multi-generation reproductive toxicology studies in rats have been reported for NP, the latter studies building on or clarifying the findings of the earlier studies and all support the NOAEL selected by both US EPA and the SAP. [7] The earliest was the three-generation study conducted by the National Toxicology Program (NTP) and reported by Chapin et al. 1999 mentioned above. Then Nagao et al., 2001 published a two-generation reproductive study. [8] As a follow-up to Chapin et al., 1999, Tyl et al., 2006 conducted a three-generation study at the identical dietary levels of 0, 20, 200, 650, and 2000 ppm NP. [9] The results confirmed the conclusions of Chapin et al, 1999 and Nagao et al, 2001 that NP is not a selective reproductive toxicant with a NOAEL of > 15 mg/kg-bw/day for reproductive toxicity. It also provided a NOAEL for male rat kidney toxicity of 15 mg/kg-bw/day.

The most extensive study of reproductive toxicology of NP was a five-generation study that was performed by the National Center for Toxicological Research (NCTR, 2009) at dietary doses of 25, 200, and 750 ppm. The NCTR five-generation rat study found a NOAEL for reproductive effects of 750 ppm (the highest dose tested: 51 and 80 mg/kg for males and females, respectively) and 200 ppm (~15 mg/kg-bw in males) for kidney effects. [10]

The consistent findings of these four high-quality multi-generation rat studies using NP, all with NOAELs at approximately 15 mg/kg-day, address all life stages and include reproductive and developmental endpoints and provide additional support that the MTL derived for NP in the draft 2018 SAP report is protective of human health.

- **Based on data presented in the SAP draft report, MEC/MTL ratios for NP can be estimated as approximately $1x10^{-3}$, which is significantly less than 1 and supportive of a low priority for monitoring in recycled water; however, the transparency of the SAP report would benefit by providing complete monitoring data for all the CECs in an appendix to the report.**

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[6] Chapin, R.E., Delaney, J., Wang, Y., Lanning, L., Davis, B., Collins, B., Mintz, N., & Wolfe, G. (1999). The effects of 4-nonylphenol in rats: A multigeneration reproduction study. Toxicological Sciences, 52, 80-91

[7] Osimitz, T., Droege, W., Driver, J. (2015). Human Risk Assessment for Nonylphenol. Human and Ecological Risk Assessment. , 21(7), 1903-1919

[8] Nagao, T., Wada, K., Marumo, H., Yoshimura, S., & Ono, H. (2001). Reproductive effects of nonylphenol in rats after gavage administration: A two-generation study. Reproductive Toxicology, 15 (3), 293-315.

[9] Tyl, R.W., Myers, C.B., Marr, M.C., Castillo, N.P., Seely, J.C., Sloan, C.S., Veselica, M.M., Joiner, R.L., Van Miller, J.P., & Simon, G.S. (2006). Three-generation evaluation of dietary para-nonylphenol in CD (Sprague-Dawley) rats. Toxicological Sciences, 92, 295-310.

[10] National Center for Toxicological Research (NCTR). (2009). Para-Nonylphenol: Evaluation of Reproductive Effects over Multiple Generations. Study Report #(E0213501). Available at URL: http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR

Since monitoring data for some of the CECs were relatively scarce and, in many cases, highly variable for individual CECs in 2010, the Panel at that time selected the 90th percentile of the distribution of CEC concentrations reported in California as a conservative MEC screening value. The 2018 Panel compared MECs for individual CECs from the 2010 report to utility data for the period 2008 to 2017. The MECs for NP in 2010 (~110-120 ng/L) and 2018 (~120-130 ng/L) that were used in this report can be estimated from Figure 4.1 on page 33 of the Draft 2018 SAP report. Based on this the MEC/MTL ratios for NP for both periods can be estimated as approximately $1x10^{-3}$, which is significantly less than 1 and supports low concern for human risk and a lesser need to conduct ongoing monitoring. This presentation of the MEC data in the draft 2018 SAP report is very useful; however, APERC recommends that the SAP consider including the data tables from which the MECs were drawn in an appendix to the report for even greater transparency.

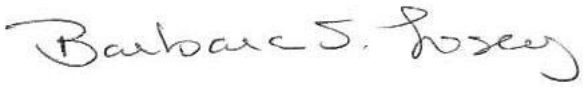
- **APERC supports the SAP's recommendation for the role of bioanalytical methods to assess the relevance of unknown CECs as described in Section 7 of the draft report, particularly the Panel's recommendation that "assay endpoints under consideration (see Table 7.2) be mechanistically linked to apical endpoints of toxicity (e.g., cancer, development, immune dysfunction, reproduction) rather than to non-specific biological responses."**

The SAP draft report points out that while the Panel's risk-based framework is clearly effective in identifying CECs for which pertinent data are available, the framework cannot capture all contaminants that may be present in recycled water. To help identify such compounds that may occur in recycled water and their potential, if any, to affect human health, APERC supports the SAP's view that bioanalytical screening methods can be an important tool whose value and applicability as screening tools needs to be explored as recommended in the SAP draft report (see Figure ES.1) . The Panel specifically recommends that the Estrogen Receptor alpha (ER-α) and the Aryl hydrocarbon Receptor (AhR) bioassays be used to respectively assess estrogenic and dioxin-like biological activities in recycled water "since these two *in vitro* bioassays each have clear adverse outcome pathways that allow specific molecular responses to be adequately standardized for screening recycled water quality at potable reuse projects". APERC supports using bioanalytical assays that are adequately validated by international bodies and have been linked to apical endpoints of toxicity. APERC also supports the value of incorporating appropriate QA/QC samples in bioanalytical assays (*i.e.* matrix spikes as well as those mentioned in EPA methods) and the importance of making the appropriate, concurrent measures of cell viability. If significant effects on cell viability are observed in the bioassay (i.e. > 20%), then this would be an indication of non-specific effects, and the specific receptor results in the bioassay should not be considered valid. APERC also supports the view that available research and approaches to relate observed *in vitro* bioanalytical assay results to effects that can be

expected to occur *in vivo* should be incorporated into the conduct and interpretation of bioassays, when available.

In summary, APERC commends the SAP for its work to develop a practical, risk-based framework for monitoring CECs in recycled water.

Regards,



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