Alkylphenols & Ethoxylates Research Council

Comments on

California Department of Toxic Substances Control

Discussion Draft (May 2018):

Product-Chemical Profile for Nonylphenol Ethoxylates in Laundry Detergents

Submitted to CalSafer.com June 20, 2018

The Alkylphenols & Ethoxylates Research Council (APERC) appreciates this opportunity to provide comment on the California Department of Toxic Substances Control (DTSC or the Department) Discussion Draft: Product-Chemical Profile for Nonylphenol Ethoxylates in Laundry Detergents (Discussion Draft). [1] APERC is a North American research-based trade association representing manufacturers of alkylphenols (APs) and their derivatives, including Nonylphenol (NP) and Nonylphenol Ethoxylates (NPEs). For more than twenty years, APERC and its member companies have been actively engaged in the conduct and review of the toxicological, environmental fate, occurrence and ecotoxicity of alkylphenol based chemistries. [2]

Executive Summary

APERC appreciates that DTSC clearly states in the Discussion Document that by proposing to list NPEs in commercial laundry detergents as Priority Product DTSC is not asserting that such products cannot be used safely. APERC also recognizes that the process to designate a Priority Product is not a conventional risk assessment. However, it is APERC's view that the approach taken in the Discussion Draft to assess environmental monitoring data for NP and other Nonylphenol Ethoxylate Degradants (NPEDs) is not sufficiently transparent or quantitative to support a conclusion that NPEs and/or their environmental degradation intermediates have the potential to pose "significant or widespread adverse impacts" to the aquatic environment in California from their use in laundry detergent, or from any use. Also, the Discussion Draft relies on some Guidelines, Standards and Criteria (GSC) that are not appropriate for use in the context of a Product-Chemical Profile under the California Safer Consumer Products (SCP) regulations.

It is important that Priority Product assessments conducted under the SCP regulations are anchored in a strong science-based understanding of the hazards and a quantifiable, verifiable and transparent analysis of exposures of Candidate Chemicals in California from their use in a Priority Product. This will ensure that DTSC focuses its resources and the resources of affected businesses on Candidate Chemicals and Priority Products that warrant the greatest priority due to their exposures and risk in California. Designation of a Priority Product under the SCP Regulations sets into motion a process that is significant and burdensome to both affected businesses and the Department. Therefore the regulations include a provision that states "it is necessary to ensure that the limited resources of DTSC, responsible entities, and other interested parties are focused on Product-Candidate Chemical combinations that are of high priority …"

[1] California Department of Toxic Substances Control (CA DTSC). (2018, May). Discussion Draft: Product-Chemical Profile for Nonylphenol Ethoxylates in Laundry Detergents.

[2] Members of APERC include: The Dow Chemical Company, SI Group, Inc., and Dover Chemical Corporation.

Selection of Priority Products should be focused on those that actually pose "significant or widespread adverse impacts" to the environment or human health in California, as required under ARTICLE 3 § Section 69503.2(a) of the CSP regulations.

APERC provides comments below recommending an approach that is more grounded in the principles of risk assessment and based on quantified assessment of the exposures to NP and NPED relative to GSCs that are most relevant to the SCP regulations. Additional comments address uncertainties inherent in the analytical methods used to measure NP that introduce a high degree of bias for false positive detections of NP in surface waters and indicate that available monitoring data tend to overstate the actual occurrence and concentrations of this compound in the environment. Other comments related to concerns raised in the Discussion Draft are provided,

Finally, while the Discussion Draft is clear that the proposal to make NPEs in laundry detergent a Priority Product is not based on human exposures and impacts, APERC provides additional comments below that support this approach as well as risk-based analyses that find very high Margins of Exposure (MOEs) and very low likelihood of adverse effects in humans from exposure to laundry workers and exposure to the general population via potable water reuse and consumption of contaminated shell fish. An aggregate risk assessment for human exposure to NP based on environmental monitoring data as well as on human biomonitoring data is also provided that finds reasonable certainty of no harm for source-specific and aggregate (based on biomonitoring) exposures to NP.

COMMENTS

1.0 The approach taken in the Discussion Draft to assess environmental monitoring data for NP and NPEDs is not sufficiently transparent or quantitative to support a conclusion that NPEs and/or their environmental degradation intermediates have the potential to pose "significant or widespread adverse impacts" to the aquatic environment in California.

The Discussion Draft summarizes monitoring data for NP and NPEDs in tables in Appendix E and acknowledges that concentrations of these compounds in the environments can range from non-detects to concentrations that exceed certain aquatic Guidelines, Standards and Criteria (GSC). As noted in comment 2.0 below, APERC does not view all of the GSC values used in the Discussion Draft as appropriate for use in this SCP process for scientific and/policy reasons. The Discussion Draft also notes that concentrations of these compounds can vary by an order of magnitude or more, particularly in effluent. The approach taken in the Discussion Draft is qualitative and reliant on some environmental monitoring data that are not sufficiently transparent for public comment. The qualitative approach taken to presenting and reviewing the exposure data is also not adequate to support a conclusion that NPEs and/or their environmental degradation intermediates have the potential to pose "significant or widespread adverse impacts" to the aquatic environment in California. Given the significant burden associated with regulation of a Priority Product under the Safer Consumer Products (SCP) regulations it is important that Product Profile assessments be anchored in a strong science-based understanding of the hazards

and a transparent, quantifiable and verifiable analysis of exposures of Candidate Chemicals in California from their use in a Priority Product.

1.1 The approach taken in the Discussion Draft is not sufficiently quantitative to conclude significant or widespread adverse impacts" to the aquatic environment in California; a risk-based statistical or probabilistic approach is more appropriate for the purpose of a Product Chemical Profile for NPEs in Laundry Detergent under the SCP regulations.

The Discussion Draft summarizes monitoring data in Appendix E in a tabular format. Table E1 lists available studies, years that sampling took place and the media analyzed. No quantitative results are provided. Tables E2 – E5 provide monitoring data from wastewater effluent, wastewater solids (biosolids), surface water and sediment. Results are provided as ranges with maximum, average and estimated values indicated where available. Also, where available number of samples (n) and percent detects from the studies are provided. Exceedance of one or more GSC is noted by footnote. It appears that exceedances are generally associated with the maximum values in a study. While, these tables indicate that there are instances in California and the United States where environmental concentrations of NPEs and NPEDs may exceed certain chronic GSC these exceedances need to be viewed in relation to the entire data set using a more statistical or probabilistic approach to quantify the potential for risk of significant or widespread adverse effects. An understanding of the geographic distribution of exceedances in California would also be more useful. APERC recommends an approach similar to that taken by Klecka et al, 2007, which developed a statistical understanding of exposures to alkylphenols and ethoxylates, including NP and NPED in U.S. surface waters. [3] In that paper, the statistical analysis found 67% of all analytes sampled between 1990 and 2005 were below their detection limit and that 99% of fresh surface waters are below the U.S. EPA WQC (6.6 μg/L) indicating the likelihood of exceeding this GSC was low even before market use trends that resulted in a decline in use of approximately 50% in the decade between 2005 and 2015. [4][5]

1.2 Transparency of Monitoring Data

The Discussion Draft references documents and/or data sets from the Los Angeles County Sanitation District (LACSD) and the State Water Board in its characterization of NPE concentrations in effluents. APERC was not able to locate these LACSD documents and/or associated data sets. APERC was able to find data via the California Environmental Data Exchange Network (CEDEN) as referenced in the State Water Board citations; however, it was unclear which filter terms were used to query the data cited in the Discussion Draft. As such, it was not clear which data were appropriate to review in the context of this Product-Chemical Profile. Therefore, APERC is concerned about a lack of transparency and accessibility of data in the Discussion Draft.

[3] Klecka, G., Zabik, J., Woodburn, K., Naylor, C., Staples, C., & Huntsman, B. (2007). Exposure analysis of C8- and C9-alkylphenols, alkylphenol ethoxylates, and their metabolites in surface water systems within the United States. Human and Ecological Risk Assessment, 13 (4), 792-822.
[4] Colin A. Houston & Associates, Inc. (2016, March). Surfactant Developments Newsletter. Aiken, SC, USA
[5] Colin A. Houston & Associates, Inc. (2007, June). Surfactant Developments Newsletter. Brewster, NY USA

2.0 Guidelines, Standards and Criteria should be evaluated for their appropriateness for use in the context of a Product-Chemical Profile under the California SCP regulations.

The Discussion Draft relies on a range of aquatic guidelines, standards or criteria (GSC) developed by other authoritative bodies to compare monitoring data in this Product Chemical Profile. GSC are environmental concentrations under which the authoritative bodies consider aquatic life protected from the effects of NPEs and/or NPEDs. The GSC are summarized in Table 3 of the Discussion Draft. It is APERC's view that not all GSC are appropriate for use in the context of a Product-Chemical Profile under the California SCP. Each GSC should be evaluated for its appropriateness from both a policy and scientific perspective. The basis for development and status of a GSC should be considered in deciding whether a GSC is applicable to this SCP process in California. As noted in the comments below, the U.S. EPA Water Quality Criteria for NP are appropriate from both a policy and scientific perspective for use in the context of a Product-Chemical Profile under the California SCP. The Canadian EQGs for NP/NPE, while not relevant from a regulatory policy perspective in the U.S., are appropriate from a scientific perspective for use in the context of a Product-Chemical Profile under the California SCP.

2.1 U.S. EPA Water Quality Criteria for NP

U.S. EPA developed Water Quality Criteria (WCQ) for NP based on a robust aquatic toxicity database for NP that included adverse effects observed in *in vivo* toxicity studies that characterize population level effects in the environment (*i.e*. effects on survival, growth and development, and reproduction) and consideration of acute to chronic ratios. [6,7] A review of more recent aquatic toxicity studies (17 freshwater species and 13 marine species) on NP, NP1EO and NP2EO that were available after US EPA developed the WQC for NP was conducted by Coady et al, 2010, which confirmed that these newer data also support that the US EPA chronic WQC for NP in freshwater and saltwater are protective of aquatic species. [8] While it is correct that the EPA WQC currently have no regulatory bearing in California they have been adopted by other states as Water Quality Standards under the Clean Water Act. U.S. EPA WQC are appropriate from both a regulatory policy and scientific perspective for use in the context of a Product-Chemical Profile under the California SCP.

2.2 Canadian Council of Ministers Environmental Quality Guidelines for NP/NPE

[6] US Environmental Protection Agency (US EPA). (2005). Aquatic life ambient water quality criteria - nonylphenol. Report 822-R-05-005. US Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/waterscience/criteria/nonylphenol/final-doc.pdf

[7] US Environmental Protection Agency (US EPA). (2006, February 23). Notice of availability of final aquatic life ambient water quality criteria for nonylphenol. Federal Register, 71 (36), 9337-9339. http://www.epa.gov/EPA-WATER/2006/February/Day-23/w2558.htm.

[8] Coady, K., Staples, C. Losey, B., and Klecka, G. (2010). A Hazard Assessment of Aggregate Exposure to Nonylphenol and Nonylphenol Mono- and Di-ethoxylates in the Aquatic Environment. *Human and Ecological Risk Assessment: An International Journal*. Volume 16, Issue 5, pgs 1066-1094

The Canadian Council of Ministers developed Environmental Quality Guidelines (EQGs) for NP, NP1EO and NP2EO based on the most sensitive, nonlethal-effect concentration in freshwater and marine species, and the application a safety factor to account for factors such as variation in toxicity between laboratory and field exposures. The freshwater chronic EQG (1.0 μg/L) on an NP-equivalent basis was based on a 91-day LOEC for growth endpoints in freshwater salmonids by Brooke, 1993, which was divided by an application factor of 10.[9] The marine chronic EQG (0.7μg/L) for NP was based on a 28-day mysid study by Ward and Boeri, 1991 in which a LOEC for effects on survival and reproduction was divided by a 10-fold application factor. [10]

The Canadian EQGs for NPEs use a toxic equivalency approach with a toxic equivalency factors (TEFs) of 0.5 (applied to concentrations of NP1EO and NP2EO) and 0.005 (applied to concentrations of NPneO n≥ 9, NP1EC and NP2EC) to account for co-exposure to these NPEDs. TEFs are values between 0 and 1, which are assigned to NP1EO and NP2EO to represent their toxicity relative to NP (assigned a value of 1.0), for which an abundant ecotoxicity database exists. The TEF values developed by Environment Canada were based on both acute and chronic studies for vertebrate and invertebrate aquatic species. To derive TEF values relative to NP, Environment Canada matched reported toxic concentrations of NP1EO and NP2EO with similar endpoints as for NP in the same species (and same laboratory if possible) and a TEF value was calculated for that substance. From all the available data, a mean TEF was calculated, with higher quality studies weighted more heavily than studies deemed of a lower quality. To obtain an aggregate Toxic Equivalence Quotient (TEQ), the concentration of each metabolite in the mixture is multiplied by its TEF value and then they are summed. This total TEQ is interpreted as an NP-equivalent concentration, since all the TEF values are calculated in reference to NP.

Additional toxicity data were also available for NP1EO and NP2EO in relation to NP since Environment Canada developed the TEF values for these compounds that support the Canadian TEF values for NP and NPEs. Coady et al (2010) conducted a review of these recent data, to further refine the assessment of potential aquatic effects from aggregate exposure to NP, NP1EO and NP2EO.[11] The studies reviewed encompassed a variety of species and endpoints (*i.e.*, population-level endpoints, behavioral endpoints, induction of biochemical markers, and alterations in cells within tissues) and showed an average TEF for NP1EO and NP2EO of 0.37. Coady et al (2010) also evaluated structure activity modeling, which predicted a TEF for NP1EO and NP2EO ranging from 0.46 to 0.53. The authors concluded "while a review of the current experimental data show that the TEF for NPE1 an NPE2 could be lowered to 0.37, the continued use of the original Canadian TEF of 0.5 will lead to a slight conservative bias in an aggregate hazard assessment". [12]

[9] Brooke, L.T. (1993a.). Acute and Chronic Toxicity of Nonylphenol to Ten Species of Aquatic Organisms. Report for U.S. EPA Contract No 68-C1-0034, Environmental Health Laboratory, University of Wisconsin-Superior, U.S. Environmental Protection Agency, Duluth, MN, USA.
[10] Ward, T.J. and Boeri, R.L. (1991, May 17). Chronic Toxicity of Nonylphenol to the Mysid, *Mysidopsis bahia.* EnviroSystems, Resource Analysts, Inc. Hampton, NH
[11] Coady, K. (2010).
[12] Coady, K. et al. (2010).

While not relevant to California from a regulatory perspective, the Canadian EQGs for NP/NPE are appropriate from a scientific perspective for use in the context of a Product-Chemical Profile under the California SCP.

2.3 Minnesota Pollution Control Agency Draft Support Document for Water Quality Standards for NP, NP1EO and NP2EO

The Minnesota Pollution Control Agency (MPCA) drafted a Technical Support Document for Water Quality Standards for Nonylphenol and Nonylphenol ethoxylates.[13] MPCA reviewed the data considered in the U.S. EPA Ambient Aquatic Life Water Quality Criteria (WQC) document for Nonylphenol (NP). [14] [15] In addition, MPCA considered additional, more recent data on both NP and NPEOs, including locally important species to develop draft Final Acute Value (FAV) and Chronic Standard (CS), which would serve as the basis for future proposed MN Water Quality Standards (WQSs). The Aquatic Life Summary Sheets (Table 3) in the MPCA Technical Support Document present the technical basis for the derivation of the Class 2 FAV (59.78 µg/L, rounded to 60 µg/L) and CS (and 7.4 µg/L) values for NP, NP1EO, and NP2EO. Additionally, a separate chronic value for cold water uses (Class 2a) of 2.4 µg/L was developed for the protection of cold-water fish. Also, in an effort to better reflect the freshwater focus of Minnesota criteria, the Acute to Chronic Ratio (ACR) for saltwater species, which was used in deriving the U.S. EPA WQC for NP, was not included in the derivation of the CS for Minnesota.

Unlike Canada, MPCA proposed a toxic equivalence basis that assumes NP1EO and NP2EO are equipotent to NP. In the Technical Support Document, MPCA considered additional studies on NP, NP1EO and NP2EO, which the Agency found "did not show NP to be considerably more toxic than NP1EO or NP2EO". [16] However, "considerably more toxic" is a subjective characterization. Adequate data exist to characterize the relative toxicity of NP1EO and NP2EO relative to NP and these have been demonstrated by Environment Canada and in the published peer-reviewed literature as described above. [17,18]

The MPCA Draft FAV and CS values for NP/NP1EO/NP2EO are not appropriate from a policy perspective for use in the context of a Product-Chemical Profile under the California SCP since they have not yet been finalized with consideration of public comments. The MPCA use of an equipotent TEF-based approach is not appropriate from a scientific perspective for use in the context of a Product-Chemical Profile under the California SCP due to the qualitative approach taken and the lack of consideration for existing data that support a TEF based approach consistent with that developed by Canada. .

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[13] Minnesotoa Pollution Control Agency. (2010, October 14). Draft 2008-2012 Triennial Water Quality Standards Review: Technical Support Document for Numeric Criteria for Nonylphenol and Ethoxylates

[14] US EPA, (2005).

[15] US EPA(2006, February 23). N

[16] MPCA. (2010, October 14).

[17] Environment Canada and Health Canada (EC and HC). (2001). Priority substances list assessment report for nonylphenol and its ethoxylates. ISBN: 0-662-29248-0. http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/nonylphenol/index-eng.php.

[18] Coady, K. (2010).

2.4 European Union Environmental Quality Standards for NP

The European Union developed Environmental Quality Standards (EQS) for NP based on the most sensitive endpoint in the dataset reviewed. The basis of the EU EQS was a toxicity study by Kopf, 1997 in the freshwater algae *Scenedesmus subspicatus*. [19] The PNEC for surface water was calculated by dividing the $EC_{10(Biomass)}$ by an assessment factor of 10. This assessment factor was justified by the fact that long-term NOECs from at least three species representing three trophic levels were available. Therefore, the NOEC for this freshwater alga provided the basis of the EQS value of 0.33 µg/L.

It is important to note that the Kopf, 1997 study was rejected for use by U.S. EPA in deriving WQC for NP because it did not meet the study quality criteria necessary to include it in a WQC derivation. Environment Canada and the Canadian Council of Ministers also did not rely on the Kopf, 1997 study. In addition, the EU EQS is based on an algal biomass endpoint, which according to current EU guidance on Information Requirements and Chemical Safety Assessment, is not the preferred algal endpoint, particularly for development of an EQS.[20] So, the current EU EQS for NP was developed based on an endpoint that would not be acceptable to the EU today from a study that does not meet the study quality requirements of the U.S. EPA. Therefore, it is APERC's view that the EU EQS for NP is not sufficient from either a scientific or regulatory policy perspective for use in the context of a Product-Chemical Profile under the California SCP.

3.0 NP, NPE1EO and NP2EO are the most relevant degradants for assessment.

The Discussion Draft expresses concerned that "exposures to NPEs and NPEDs in California may be underestimated as most monitoring studies assessed only analyze for NP" and "yet research indicates that NP is not the dominant NPED in surface water, effluent and sediment". In understanding which degradation intermediates of NPE, or any other CEC, are "dominant" it is important to distinguish between concentrations in the environment and TEF adjusted NP-equivalent or effective toxicity.

In the case of NPEDs, it is reasonable to focus hazard and risk assessment on the most toxicologically relevant of the NPE metabolites - in this case NP, NP1EO and NP2EO - because substances with lower toxicity (e.g., higher mole NPE or NPEC), even when present in a mixture at higher concentrations, do not measurably contribute to the overall toxicity of the mixture. Due to their greater relative toxicity, NP, NP1EO and NP2EO contribute much more significantly to the aggregate ecotoxicity effects of NPE degradants than either the higher chain NPE or NPECs; therefore, these former compounds are the most appropriate for inclusion in any assessment of aggregate hazard or risk.

As discussed in Section 2.2 of these comments above, Canada has developed a scientifically valid TEQ approach to assess the aggregate toxicity of NPEDs in the environment. Using the

[19] Kopf, W. (1997). The action of endocrine substances in biological tests with aquatic organisms. Papers on Wastewater, Fisheries and River Biology. Volume 50. R. Oldenbourg Verlag, Munich

[20] European Chemicals Agency (ECHA). (2017.June). Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7b Endpoint Specific Guidance. Version 4.0

data set included in the environmental monitoring review paper by Klecka et al 2007, which included 19 investigations conducted nationwide in the U.S., TABLE I below summarizes the relative TEQ based contribution of NP, NP1EO, NP2EO and NPEC.[21]

TABLE I: Relative Contribution to Aggregate Toxicity of Environmentally Relevant Concentrations of NPEs and their Metabolites

Metabolite	Avg. Env. Concentration* (µg/L)	Unadjusted Contribution (%)	TEF***	NP-equivalent Concentration (µg/L)	NP-equivalent Contribution (%)
NP	1.7	12.8	1.0	1.7	48.7
NP1EO	1.2	9.0	0.5	0.6	17.2
NP2EO**	2.3	17.3	0.5	1.15	33.0
NPEC	8.1	60.9	0.005	0.04	1.1
Total	13.3	100.0	-	3.49	100.0

* Average concentrations from Klecka et al. (2007)

** Concentrations of NPE>1 reported in Klecka et al. (2007) are presented in this table as NP2EO based on confirmation from the author that it was NP2EO that was measured in at least 87% of the samples reported as NPE>1

*** Toxicity Equivalence Factors (TEFs) relative to NP developed by Environment Canada (2001)

As has been well established, higher mole NPEs are not generally detected in surface water or the environment due to their disposal through wastewater treatment plants, which break them down to the metabolites represented in TABLE I above. Therefore, monitoring of NP alone is expected to capture approximately half of the environmentally relevant NP-equivalent contribution of NPEDs. Monitoring of NP, NP1EO and NP2EO is expected to capture close to 99% of the environmentally relevant NP-equivalent NPEDs.

4.0 Analytical results reported for NP in water and the environment likely overstate the occurrence and concentration of this compound and other NPEDs due to analytical bias with high false positives identified for this compound.

The Discussion Draft expresses concern that "analytical challenges (e.g., high reporting limits) may obscure concentrations that may be of concern" and notes a lack of current monitoring, particularly in effluent dominated environments that complicates understanding of exposure to NP and NPEDs in the aquatic environment.

Klecka et al, 2007 presents a summary of Method Detection Limits (MDLs) for papers published on NPEs and NPEDs in the U.S. between 1990 and 2005 confirming that some older studies and

[21] Klecka, (2007).

studies designed to examine multiple contaminants simultaneously have higher MDLs. [22] However, the majority of papers (23 of 25) examined in this extensive review of U.S. monitoring studies on alkylphenols and ethoxylates had MDLs of less than 5µg/L, which is less than the U.S. EPA chronic WQC for NP. Of those, approximately half had MDLs of less than 1µg/L, which is less than the Canadian chronic EQS for NP/NPE. Therefore, many of the historic datasets available have sufficient MDLs to conducts a risk-based assessment relative to relevant GSCs. Generally speaking analytical methods in use today have MDLs significantly less than 1 µg/L in surface water, as evidenced in the results reported in Table E-4 of the Discussion Draft.

An equally important issue that should be recognized in the NPEs in Laundry profile relates to uncertainty with the analytical methodology for measuring NP in water samples related to a high occurrence of false positive detection of this compound. The high degree of analytical bias for false positive detections of NP in surface waters indicates that available monitoring data overstate the actual occurrence and concentrations of this compound in the environment.

A published paper by Vanderford *et al*, 2014 presented the results of a large-scale interlaboratory comparison study of 25 chemicals of concern (CECs), including NP to assess the accuracy and precision of available analytical methods with spiked samples of drinking water and source water. [23] The paper presents the results of two single-blind interlaboratory comparisons conducted at 25 research and commercial labs located in the EU, the United States, Canada and Australia. The study evaluated 10 different analytical methods for measuring NP in drinking water and 11 different methods for measuring NP in source water. The authors state that NP is difficult to analyze accurately at the low concentrations expected to be found in the environment and 69% of all unspiked samples were reported to have detectable NP, indicating an extremely high percentage of false positives. The rate of false negative results for NP was only 9%, suggesting only a low degree of concern for generating false negative results. The overall results for NP precluded the authors from recommending specific analytical methods for this compound. The authors concluded: "Perhaps most importantly, results from this work likely suggest that some studies in the literature have very high degrees of analytical bias and/or large numbers of false positives. Further, the use of occurrence data from unsuitable analytical procedures may have resulted in inappropriate risk assessments and prioritization for regulation. Thus, it is important that the consequences these data potentially have had on past decisions is recognized and critical that analytical quality and reliability be considered in future assessments." [24]

5.0 Trends in Monitoring

The Discussion Draft questions why NPEDs continue to be detected in wastewater effluent and the environment despite reported declines in the use of NPEs in consumer products and decreases in environmental concentrations. Specifically noting monitoring "data from Los Angeles County indicates that concentrations of NP, NP1EO, and NP2EO in effluent have

[22] Klecka, G. et al (2007)
[23] Vanderford, B.J., Drewes, J.E., Eaton, A., Guo, Y.C., Haghani, A., Hoppe-Jones, C., Schluesener, M.P., Snyder, S.A., Ternes, A. and Wood, C.J. **(2014).** Results of an Interlaboratory Comparison of Analytical Methods for Contaminants of Emerging Concern in Water. *Anal. Chem., 86* (1), pp 774–782
[24] Vanderford, B. J., et al. (2014).

remained relatively unchanged in the last decade (LACSD 2012; LACSD 2014a; LACSD 2015), although a recent collection event suggests a decline in NP1-2EOs (LACSD 2015)".

As mentioned above, the data sets from LACSD 2012-2015 are not sufficiently available to the public for review. However, consistent monitoring data from year to year may be related to the general bias in analytical methods for false positive results for NP discussed in Section 4.0 of these comments.

6.0 NPE exposure from use in pesticides and concern for synergistic effects

The Discussion Draft expresses concern about NPEs co-occurring in the environment due to their use in pesticide or herbicide products, these uses are already regulated at the national level under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and in California by the Department of Pesticide Regulation under California pesticide laws and regulations. Therefore, these uses are outside of the scope of the SCP Priority Products regulations.

The Discussion Draft also expresses concern that "Some studies have evaluated the potential for synergistic (greater than simply additive) effects of pesticides and other ingredients in the formulations, including alkylphenol and alkylphenol ethoxylates, which include NPEs, due in part to concern for estrogenic effects and the potential nexus to certain declining fish species in the San Francisco Bay-San Joaquin Delta as described in a study by Schlenk et al 2012.

In the Schlenk et al 2012 study, alkylphenols (APs) and alkylphenol ethoxylates (APEs), including NP and NPE were measured in the San Francisco Bay Delta, and the maximum concentrations that were detected across sampling locations were used to make a reconstituted mixture that was assessed both *in vitro* and *in vivo* using fish liver cell lines and medaka fish, respectively. [25] The reconstituted AP and APE mixtures did not result in significantly higher estrogenic activity either *in vitro* or *in vivo*. Only when maximal AP and APE concentrations were increased five-fold were some sensitive indications of estrogenic activity apparent. Thus, at environmentally relevant maximum concentrations, AP and APE mixtures in the San Francisco Bay Delta did not result in significant estrogenic activity either *in vitro* or *in vivo*. When mixtures of APs and APEs were combined with two pesticides (*i.e.* bifenthrin and diuron, both detected at only one sampling location in the San Francisco Bay Delta), higher estrogenic activity was noted *in vivo* (but not *in vitro)* than was expected based on the responses of these substance alone. The significance of these findings is unclear as no estrogenic responses were observed when fish were exposed to either bifenthrin or diuron alone. Without additional data, to include repeatability, it is impossible to draw conclusions regarding the biological plausibility of the discordance between these *in vivo* and *in vitro* results. These uncertainties notwithstanding, the data show that neither APs nor APEs cause significant estrogenic activity. It is important to keep in mind this study investigated biomarkers of estrogenic effects (*i.e.* vitellogenin concentrations), not effects likely to cause population-level adverse effects. This is especially important when evaluating data involving bifenthrin as it has recently been subjected

[25] Schlenk D, Sapozhnikova Y, Irwin MA, Xie L, Hwang W, Reddy S, Brownawell BJ, Armstrong J, Kelly M, Montagne DE, Kolodziej EP, Sedlak D, Snyder S. 2005. In vivo bioassay-guided fractionation of marine sediment extracts from the Southern California Bight, USA, for estrogenic activity. Environ Toxicol Chem 24:2820–2826.

to comprehensive screening for endocrine activity in amphibians, fish, and mammals as part of USEPA's Endocrine Disruptor Screening Program (EDSP). Based on this extensive study, the EPA concluded that: "Based on weight of evidence considerations, mammalian EDSP Tier 2 testing is not recommended for bifenthrin since there was no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways**."** [26]

Moreover, considering that bifenthrin and diruron were both detected at only one sampling site (#711) and at only 1 ng/L (just above the limit of detection) and 41 ng/L, respectively, the assertion by the authors that:

> "mixtures of pesticides with significantly different modes of action and AP/APEOs at environmentally relevant concentrations may be associated with estrogenic activity measured in water extracts and feral fish that have been shown to be in population decline in the San Francisco Bay Delta."

and the inference that there may be a causal link between the laboratory-measured activity and fish populations *is not* supported by the data.

7.0 Biosolids

The Discussion Draft expresses concern about biosolids from wastewater treatment plants applied to land as a soil amendment (fertilizer) as a secondary pathway that may also contribute NPEDs in runoff to surface water.

Since the use of biosolids as fertilizer is not a consumer use of NPE and it is regulated under US EPA regulations (40 CRR Part 503), CalRecyle regulations, as well as by local authorities, this use and route of exposure is sufficiently regulated by other authorities and it is not specifically relevant under the SCP regulations. [27] Monitoring of surface water and sediment detects NP, NP1EO and NP2EO from all pathways to the environment allowing comparison to existing GSC for NP in order to determine the risk for adverse effects in aquatic and benthic species from all of these pathways.

While not mentioned in the Discussion Draft, land application of biosolids is also a route of exposure to soil dwelling species. Staples et al (2016) developed an assessment, which was published as a paper by the Water Environment Federation that estimated potential risk from NP to soil-dwelling in biosolids-amended soil.[28] For NP there are chronic toxicity values for soil-dwelling arthropods, annelids, plants, and microbes, which were used to plot a range of protective chronic toxicity values for soil dwelling organisms. From the distribution of ecotoxicity values, median and lower-bound 5th centile no effect concentrations (NOECs) of 99

[26] US EPA Endocrine Disruptor Screening Program (EPA EDSP) (2015, June). Weight of Evidence Analysis of Potential Interaction with the Estrogen, Androgen or Thyroid Pathway: Bifenthrin.
[27] CalRecycle http://www.calrecycle.ca.gov/organics/biosolids/BioBkgd.htm#Resources
[28] Staples C.A. et al .(2016). Estimating exposure of nonylphenol to soil-dwelling macroinvertebrates and plants inhabiting the base of the terrestrial food web in biosolids-amended agricultural fields. Water Environment Federation. Proc. Residuals and Biosolids – Biosolids as a Resource. 2016. Milwaukee, WI.

and 26 mg/kg-dw were calculated. Concentrations of NP in biosolids from mainly US treatment plants were used to calculate concentrations in soil, incorporating a dissipation term that accounts for all biological and abiotic processes that reduce concentrations and bioavailability of constituents such as NP. Laboratory and field dissipation studies taken from the literature yielded a mean (±SD) dissipation half-life of 24±20 days. Distributions of soil concentrations calculated while varying dissipation rate and time after incorporation were all lower than all of chronic toxicity values for terrestrial organisms. [29] This indicates a low likelihood of adverse effects or risk to terrestrial organism based on practices for land application of biosolids containing NP at concentrations typically seen in biosolids in the US. In addition, these authors conclude migration of NP and low mole NPEO via rainwater runoff following application of the biosolids to agricultural soils would not be significant given the relatively high soil-water partition coefficients (10,000 to 50,000) for these compounds. [30]

8.0 Persistence, Bioaccumulation and Trophic Magnification

8.1 Persistence

The Discussion Draft expresses concern about the persistence of NP and NPEs in anoxic sediment noting reviews by authoritative organizations that "indicate that some NPEDs can exhibit environmental persistence", particularly in anoxic conditions and "various lab studies have found that some calculated half-lives of NP and NPEs in oxic and anoxic sediments exceed the definition of persistence (half-life greater than 2 months in sediments) for the purposes of the SCP regulations". Particular attention is drawn to a field study by Shang et al. 1999, which estimated a 60 year half life for NP and NPEs in coastal marine sediments.

APERC previously submitted comments to DTSC summarizing the status of NP and NPEs under governmental assessments specific to persistence. In summary, under aerobic conditions, commercial NPE undergo rapid degradation to short chain ethoxylates (i.e., NP1EO and NP2EO) and their ether carboxylates, which in turn degrade ultimately to carbon dioxide and water. Under anaerobic conditions, NPE degrade more slowly, and production of NP is more likely. [31] The available data for NPE show that "the commercial products and their degradation intermediates do not meet any national or international criteria for identifying these compounds as PBT substances". [32,33] Specific governmental assessments have been conducted by Environment Canada and Washington State Department of Ecology in 2006, which concluded that NP and/or NPEs do not meet their respective criteria for "persistent" and/or

[29] Staples, C.A. et al (2016)
[30] Staples, C.A., Klecka, G.M., Naylor, C.G., & Losey, B.S. (2008). C8- and C9-alkylphenols and ethoxylates: I. Identity, physical characterization, and biodegradation pathways analysis. Human and Ecological Risk Assessment, 14 (5), 1007–1024.
[31] Staples C.A. et al (2008).
[32] Alkylphenols & Ethoxylates Research Council (APERC). (2017, February 28). Comments on CA DTCS Potential Aquatic Impacts and Continued Uses of Nonylphenol Ethoxylates and Triclosan (November 15, 2016)
[33] . Klecka, G.M., Staples, C.A., Naylor, C.G., Woodburn, K.B., & Losey, B.S. (2008). C8- and C9-alkylphenols and ethoxylates: II. Assessment of environmental persistence and bioaccumulation potential. Human and Ecological Risk Assessment, 14 (5), 1025–1055.

"bioaccumulative" compounds. [34,35, 36] In addition, U.S. EPA does not categorize NP/NPE as having high persistence or bioaccumulation under its 2014 Work Plan.[37]

Biodegradation - the dominant removal process of NP and its ethoxylate from water, sediment, and soil - has been extensively studied and numerous studies have been conducted that focus on both the primary and ultimate degradation these compounds. Three main types of biodegradation studies have been performed. The first are stringent screening tests that measured the ready biodegradability of a test substance. The second are simulation tests in which biodegradation are measured in laboratory tests using procedures and bacterial inocula that simulate potential degradation in specific environmental compartments or within wastewater treatment plants. Simulation tests for the biodegradation of NP are available for all relevant environmental compartments including freshwater, freshwater sediment, seawater, marine sediment and soil. The third line of evidence that biodegradation is the key removal process for NP and their biodegradation intermediates is based on results of field studies.
The process of determining the quality of existing data is well established and takes into consideration three aspects - reliability, relevance and adequacy of the data. These terms as defined by Klimisch et al. (1997)[38] are generally accepted in the scientific community as well by governmental authorities as follows.

- Reliability: The inherent quality of a test report or publication relating preferably to standardized methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings. Reliability addresses the overall scientific integrity and validity of the information in a study;
- Relevance: The extent to which data and tests are appropriate for a particular hazard identification or risk characteristic; and,
- Adequacy: The usefulness of data for hazard/risk assessment purposes.

Governmental authorities such as the US Environmental Protection Agency (EPA) and the Organization for Economic Cooperation and Development (OECD) routinely require characterization of data quality in risk assessments and data submission. In order to be consistent with the hierarchy of data sources approach generally accepted in the scientific and regulatory communities, DTSC should consider the reliability, relevance and adequacy of the studies it relies on and assign the greatest weight to studies that are the most reliable, relevant and adequate in Product Chemical Profile assessments. Studies that do not meet these criteria should be considered only as supplementary information.

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[34] Environment Canada (EC),. (2006, September). Ecological categorization of substances on the Domestic Substance List; Categorization decisions
[35] Washington State Department of Ecology (WA DoE). (2006a, January) Rule Adoption Notice:Persistent Bioaccumulative Toxins Chapter 173-333 WAC. http://www.ecy.wa.gov/biblio/0607007.html
[36] Washington State Department of Ecology. (2006b, January) Concise Explanatory Statement and Responsiveness Summary for the Adoption of Chapter 173-333 WAC Persistent Bioaccumulative Toxins. Publication: 06-07-006.
[37] U.S. Environmental Protection Agency (US EPA). (2014, October). TSCA Work Plan for Chemical Assessments: 2014 Update
http://www.epa.gov/opptintr/existingchemicals/pubs/TSCA_Work_Plan_Chemicals_2014_Update-final.pdf
[38] Klimisch, H.J., Andreae, E., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental and Ecotoxicological Data. Reg. Tox. and Pharm., 25,1-5.

Of particular note is the reference for a 60 year half-life from a single sediment study by Shang (1999)[39] that was conducted on NP buried in deep, anoxic marine sediment, an environmental compartment that is not relevant to risk assessments or persistence definitions. Even the authors suggest that the NP in the sediment is entrained and therefore not biologically relevant noting, "If preservation is accomplished, as we suggest, by irreversibly sequestering into organic coatings on solids, NPnEOs may not be bioavailable." Furthermore, mass balance models,[40] which link emission rates to prevailing environmental concentrations include consideration of chemical degradation, partitioning and transport among all relevant media, consider burial to deep inaccessible and usually anaerobic sediments as a permanent loss from the biosphere. Since the surface layers of aquatic sediments are aerobic and contain higher levels of microorganisms, degradation of NP occurs in this more relevant sediment compartment. Therefore, should anaerobic sediments become re-suspended, any adsorbed NP would be expected to resume degradation under aerobic conditions.

Also, the 60 year marine sediment half-life range and the Shang (1999) citation was removed in the UNEP Regionally Based Assessment of Persistent Toxic Substances - 2nd Draft Global Report,[41] which is a compilation of all the UNEP regional reports that considered comments submitted from stakeholders. Since the Shang (1999) study does not represent persistence in a bioavailable compartment, it does not meet the data quality criteria for relevance and adequacy; therefore, while the half-life for NPEOs estimated in this paper most likely approximates that for this deep water anaerobic marine sediment location, it is not appropriate for other systems where the conditions are not like those observed at sampling sites in this study.

Finally, the finding in a single field study in a specific environment/location is not relevant to predicting the fate of that chemical in another environments/locations with differing conditions. As such, generalized conclusions regarding the degradation of NPEOs in sediments must be framed with the relevant uncertainties. Klecka et al, 2008 provides a comprehensive assessment of the biodegradation and persistence hazards of NP and NPEO.[42]

8.2 Bioaccumulation

The Discussion Draft states that "NP can bioaccumulate in aquatic organisms, although this can depend on environmental conditions and species. Reports by authoritative organizations do not discuss the potential for bioaccumulation among NPEs or other NPEDs and DTSC does not have enough information to determine if NPE and NPEDs are bioaccumulative.

Bioaccumulation is defined under Chapter 54 § 69405.2 as:

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[39] Shang, D.Y., Macdonald, R.W., and Ikonomou, M.G. (1999). Persistence of nonylphenol ethoxylate surfactants and their primary degradation products in sediments from a municipal outfall in the Strait of Georgia, British Columbia, Canada. Environ Sci Technol., 33, 1366-72.

[40] The ChemCAN model is widely being used in Canada. The BETR model applies to the entire continent of North America including Canada, US and Mexico. The Caltox model is widely used in California.

[41] UNEP. (2003). Regionally Based Assessment of Persistent Toxic Substances - 2nd Draft Global Report.

[42] Klecka, G. et al. (2008)

"(a) The bioaccumulation hazard trait is defined as the accumulation of a chemical substance in the tissue of organisms through any route, including respiration, ingestion, or dermal, including direct contact with contaminated water, sediment, and pore water in the sediment, or through transfer up the food chain.
(b) Evidence for the bioaccumulation hazard trait includes but is not limited to: the identification of a substance to be bioaccumulative by an authoritative organization; studies which show bioaccumulation in human, domesticated animal, wildlife or plant tissues; inhibition of an efflux transporter; transfer of the chemical up a food web; a trophic magnification factor or biomagnification factor greater than 1 in aquatic or terrestrial systems; for organic chemicals, a bioaccumulation or bioconcentration factor greater than 1000; a log octanol-water partition coefficient greater than or equal to 4, or a log octanol-air partition coefficient greater than or equal to 5; results from bioaccumulation models indicating potential for bioaccumulation; structural similarity to other bioaccumulative chemicals." (emphasis added)

Higher mole NPEs do not meet bioaccumulative criteria as they are highly soluble, hydrophilic surfactants and do not accumulate in lipids. While there are no bioconcentration studies with higher NPEO, estimation of their bioaccumulation potential can be made using octanol-water partitioning (log Kow). Using a correlation equation for prediction of hydrocarbon-water partitioning, that was converted to a correlation with octanol-water, Ahel & Giger, 1993 estimated the log Kow for NP9EO to be 1.0 (i.e. Kow = 10). This value is well below the criteria of log 4.0 (i.e. Kow =10,000).[43]

For NP there are several studies that have measured the bioconcentration of NP using methods that follow or were based on traditional USEPA guidelines and which measured parent material to yield bioconcentration factors. Results from these studies are shown in Table II below.

TABLE II Bioconcentration Studies		
NP	Uptake and depuration studies, guidelines used include USEPA and Japan MITI	75 to 741 L/kg Mean: 249 L/kg [44, 45, 46, 47, 48]

These studies show that the bioconcentration factor for NP does not meet the threshold of 1000 to be considered bioaccumulative under Chapter 54 § 69405.2

8.3 Trophic magnification

[43] Ahel M and Giger W. (1993). Partitioning of alkylphenols and alkylphenol polyethoxylates between water and organic solvents. Chemosphere 26: 1471-1478

[44] McLeese DW, Zitko V, Sergeant DB, *et al*. (1981). Lethality and accumulation of alkylphenols in aquatic fauna. Chemosphere 10:723–30

[45] Ward TJ and Boeri RL. (1991). Bioconcentration Test with Nonylphenol and the Fathead Minnow *Pimephales promelas.* Report for the Chemical Manufacturers Association, Washington, DC, USA

[46] Brooke, L.T. (1993b). Accumulation and Lethality forTwo Freshwater Fishes (Fathead Minnow and Bluegill) for Nonylphenol. EPA report 68 C1-0034. US Environmental Protection Agency, Duluth, MN, USA

[47] Giesy J.P., Pierens, S.L., Snyder, E.M., *et al.* (2000). Effects of 4-nonylphenol on fecundity and biomarkers of estrogenicity in fathead minnows (*Pimephales promelas*). Environ Toxicol Chem 19:1368–77

[48] Tsuda ,T., Takino, A., Muraki, K., *et al. (*2001). Evaluation of 4-nonylphenols and 4-*tert*-octylphenol contamination of fish in rivers by laboratory accumulation and excretion experiments. Wat Res 35:1786–92

With regard to trophic magnification and biomagnification potential, NP and NPEs are not considered to have the potential to biomagnify. Environment Canada's review of the data on NP and NPEs concluded that "there is no evidence in the current literature to suggest that NP or NPEs biomagnify". [49] Both Environment Canada and US EPA cited Ahel et al , 1993 in their reviews of data on NP and NPE on this point. [50, 51] Ahel et al, 1993 examined concentrations of NP, NP1E) and NP2EO in biota at several trophic levels in the Glatt River, Switzerland. They found for each of these substances, bioaccumulation factors (BAFs) in the algae *Cladophora glomerata* were significantly higher than the BAFs in three fish species (*Squalius cephalus*, *Barbus barbus* and *Oncorhynnchus mykiss*). Environment Canada noted "concentrations of nonylphenolic compounds detected in the tissues of a mallard duck (*Anas boscas*) were not significantly different from concentrations observed in fish tissues".[52] Both US EPA and Environment Canada concurred with the authors' conclusion that since the concentrations of NP and NPEs did not increase with increasing trophic level of organisms these compounds did not biomagnify. [53,54, 55]

In another study more specific to California, Diehl et al. (2012) examined the distribution of NP in various aquatic organisms, marine mammals, and terrestrial mammals in Morro Bay in California. [56]The authors collected samples of water and sediment from Morro Bay in California along with samples of several aquatic species, some of which came from locations in Oregon and Canada. The authors calculated biomagnification factors between several predator-prey couples and trophic magnification factors (TMF) for a Morro Bay food web. TMF that were calculated for the food web were about 1 and were not significantly different from 1. The authors concluded that the data did not indicate biomagnification. While this conclusion is probably correct, there were significant issues in the dataset that make this study unreliable for the calculation of TMFs in Morro Bay. First, the stable isotope ratios that are determined for each of the samples are used to determine trophic level or trophic position in the food web. The calculated trophic level data for Morro Bay indicated that the top predators included benthic organisms (TL 4.5) and the water sample containing plankton (Tl 4). This is completely backwards as compared to natural systems. Phytoplankton and zooplankton are the base of pelagic food webs and benthic invertebrates are the base of benthic food webs. In properly characterized food webs, plankton and benthos have TL typically in the range of 1 to 2, with top predator fish having TL of 4 to 5. Second, there is a mixed set of types of samples that are inappropriately compared. For instance for several species, only livers were collected. For sea lions and porpoises, and perhaps sea birds

[49] Environment Canada (EC) Environmental Quality Branch National Guidelines and Standards Office. (2001). Canadian Environmental Quality Guidelines for Nonylphenol and its Ethoxylates. Scientific Supporting Document (Water, Sediment, and Soil)
[50] EC and HC. (2001).
[51] US EPA. (2005)
[52] EC and HC. (2001).
[53] EC and HC. (2001).
[54] US EPA. (2005).
[55] Ahel & Giger. (1993).
[56] Diehl, J., Johnson, S.E., Xia, K., West, A., Tomenak, L. (2012). The distribution of 4-nonylphenol in marine organisms of North American Pacific Coast estuaries. Chemosphere. doi:10.1016/j.chemosphere.2011.12.040

and otters, this is understandable. However, to calculate TMF properly from concentrations for the various species in the food web, whole body lipid normalized concentrations are required. While the authors did provide both wet-weight and lipid-weight concentrations, they mixed whole body concentrations and liver-only concentrations into the food web. Lipophilic compounds such as NP are primarily accumulated in storage lipids. While some lipids are present in the liver and the liver serves to metabolize the NP, any accumulation in storage lipids present in any other body parts are lost. Thus the mix of types of samples (liver vs. whole body) give a distorted portrayal the distribution of NP in the food web.

In Diehl et al, 2012 the BMF for most predator-prey couplings were less than 1, with the exception of oysters and mussels consumed by otters (BMF=2.2, 10.9) and sculpins-gobies (BMF=2.7). However there are concerns with these calculations as well. For instance, the mussels were collected from both Morro Bay and a separate location in Canada that is nowhere near Morro Bay. Oysters were purchased from several sources in California, Oregon, and Canada. The locations of the collected sea otter carcasses were not identified. It is inappropriate to claim that the otters from unknown locations consumed either the mussels collected or oysters purchased in separate years from multiple distant locations.

With regards to the BMF of 2.7 for sculpins and gobies, concentrations of NP were only measured in livers and not whole bodies. As noted above, lipophilic compounds such as NP primarily accumulate in storage lipids. While some lipids are present in the liver and the liver serves to metabolize the NP, any accumulation in storage lipids present in any other body parts are lost. Thus the mix of types of samples (liver vs. whole body) give a distorted portrayal the distribution of NP in the food web.

In summary, Diehl et al. (2012) collected a variety of aquatic organisms, plus samples of marine mammals, seabirds, and sea otters from multiple locations on the west coast of North America and measured concentrations of 4-NP. While the study provides useful concentration data of 4-NP in such organisms, data from organisms collected in various locations outside Morro Bay cannot be used to examine trophic magnification or biomagnification. Similarly, data from livers-only cannot meaningfully be used to characterize lipid-based concentrations of a lipophilic compound such as 4-NP. All three BMFs calculated by Diehl et al. (2012) that exceeded 1 were based on either liver-only concentrations or included the oysters and mussels, which were collected in multiple geographies and not Morro Bay and were therefore not valid.

9.0 Human Adverse Impacts and Exposure

The Discussion Draft is clear that the proposal to make NPEs in laundry detergent a Priority Product is not based on human health impacts. APERC provides the following comments regarding adverse impacts and exposure to humans to provide clarification and in support for this approach.

9.1 Adverse Impacts to Humans

The Discussion Draft provides a brief review of reports by various authoritative organizations to identify the potential adverse impacts of NP and NPEs to humans. It identifies hazard traits for

NP and NPEs as including dermatotoxicity, ocular toxicity, nephrotoxicity, reproductive toxicity, developmental toxicity, and endocrine toxicity based on dermal and oral exposures. It is important to note that the toxicity of NP and NPEs, particularly those NPEs that might be used in laundry detergents (i.e., NP9EO) are distinctly different. Commercial NPEs are not endocrine active and have not been found to be nephrotoxicants or reproductive toxicants.

Both NP and NPEs are dermatologic and ocular toxicants with NP being more so than NPE. It is important to note that the nephrotoxic, reproductive and development hazards that have been identified for NP have been identified in animal toxicology studies through high dietary dosing studies that are not relevant to actual human exposures.

9.2 Exposure to Laundry Workers

In section 3.2.2 of the Discussion Draft "Use scenarios that may contribute to adverse impacts" DTSC notes that while human exposure to NPEs in laundry detergents is not the focus of the Discussion Draft, some sensitive subpopulations (e.g., workers in on-premise laundry operations) have a higher potential for exposure compared to the general population. DTSC notes that the greatest potential for occupational exposure to NPEs in laundries occurs when transferring chemicals into washers.

An EPA Engineering Report indicates EPA was able to develop worst-case estimates of laundry worker exposures to NPE using methods described in EPA's Generic Scenario document for industrial and institutional laundries. [57, 58] EPA's estimates were based on the scenario described above along with other worst-case exposure assumptions. For dermal exposure calculations EPA assumed exposure to a quantity of detergent (as defined by the EPA Generic Scenario document) completely covered both hands (840 cm^2) of the worker without being wiped off and that there was 100% relative dermal absorption.[59,60] Using the default methods presented in the Generic Scenario document EPA calculated estimated dermal exposures of up to 1,800 mg of NPE/day for laundry workers handling liquid detergents and up to 900 mg of NPE/day for workers handling granular detergents.[61] EPA also calculated an average daily dose of 42 mg NPE/day from inhalation exposure to granular laundry detergent based on the following assumptions:

The Agency concluded that inhalation from the use of liquid detergents was negligible since NPE is not volatile even at the temperature of the washers (130^{o}F).[62, 63]

While EPA's estimated exposures to NPE are low, APERC developed a margin of exposure (MOE) calculation to determine a sense of the risk related to this exposure. For dermal

[57] US Environmental Protection Agency (US EPA). (2007, July 18) Draft: Engineering report of nonylphenol (NP) and nonylphenol ethoxylates (NPEs) in response to section 21 petition.
[58] US Environmental Protection Agency (US EPA). (2006, October 24). Chemicals used in water-based washing operations at industrial and institutional laundries - generic scenario for estimating occupational exposures and environmental releases - draft. US Environmental Protection Agency, Washington, DC, USA.
[59] US EPA. (2006, October 24).
[60] US EPA. (2007, July 18).
[61] US EPA. (2007, July 18).
[62] US EPA. (2007, July 18).
[63] US EPA. (2006, October 24).

exposures, application of a 1% dermal absorption factor, based on a study by Monteiro-Riviere et al. (2000),[64] is applied to EPA's calculated dermal exposures to derive the daily absorbed dose. This value is then divided by 71.8 kg, the mean body weight (bw) for males and females aged 18 to less than 85 years as documented in EPA's Surrogate Exposure Guide - Estimates of Worker Exposure from the Pesticide Handler Exposure Database (PHED) Version 1.1[65] - as a model for chemical handling and exposure estimates - to provide a calculated absorbed dermal dose based on body weight (i.e., mg NPE absorbed/kg-bw/day). To calculate an MOE, the absorbed daily dose (for dermal exposure) or the inhaled daily dose (for respiratory exposure) is divided into the lowest no observed effect level (NOEL) for NPE9 (the NPE surfactant typically used in laundry detergents). A NOEL of 50 mg/kg-bw/day is provided as the lowest NOEL for NPE9 in EPA's decision memo related to the Agency's human health assessment of NPE for their use as inert ingredients in pesticides.[66] Note that the 50 mg/kg-bw/day NOEL for NPE9 was taken from a study by Meyer et al. (1988) that found effects in rats at the highest two doses in the study (250 mg/kg-bw/day and 500 mg/kg-bw/day) but found no effects at the lowest dose of 50 mg/kg-bw/day.[67]

In the case of dermal exposure to NPE from liquid detergents, a 1% dermal absorption factor is applied to EPA's calculated dermal exposure of 1,800 mg NPE/day and the product (18 mg NPE/day) is divided by 71.8 kg-bw to derive an absorbed daily dose of 0.25 mg NPE/kg-bw/day. Dividing the lowest NOEL for NPE9 (50 mg/kg-bw/day) by 0.25 mg NPE/kg-bw/day gives an MOE of approximately 200 for this worst-case scenario related to the dermal exposure of laundry workers to NPE in liquid detergents.

In the case of dermal exposure to NPE from granular detergents, a 1% dermal absorption factor is applied to EPA's calculated dermal exposure of 900 mg NPE/day and the product (9 mg NPE/day) is divided by 71.8 kg-bw to derive a dermal absorbed dose of 0.125 mg NPE/kg-bw/day. Dividing the lowest NOEL for NPE9 (50 mg/kg-bw/day) by the absorbed dose of 0.125 mg NPE/kg-bw/day an MOE of approximately 400 is calculated.

In the case of respiratory exposure to NPE from granular detergents, the EPA estimated daily inhalation exposure of 42 mg/day is divided by 71.8 kg-bw to derive a daily inhaled dose of 0.58 mg/kg-bw/day. Dividing the lowest NOEL for NPE9 (50 mg/kg-bw/day) by the estimated daily inhalation exposure of 0.58 mg NPE/kg-bw/day provides a calculated MOE of approximately 86 for this worst-case exposure scenario to NPE from granular or powdered laundry detergent. While the MOEs for NPE exposure to laundry workers, as calculated in the EPA Engineering Report, are generally not of concern - especially considering the extremely conservative

[64] Monteiro-Riviere, N.A., Van Miller, J.P., Simon, G., Joiner, R.L., Brooks, J.D., & Riviere, J.E. (2000). Comparative in vitro percutaneous absorption of nonylphenol and nonylphenol ethoxylates (NPE-4 and NPE-9) through human, porcine and rat skin. Toxicology and Industrial Health, 16, 49-57.
[65] US Environmental Protection Agency (US EPA). (1998). Surrogate Exposure Guide - Estimates of Worker Exposure from the Pesticide Handler Exposure Database (PHED) Version 1.1. Washington, DC, USA.
[66] US Environmental Protection Agency (US EPA). (2006, July 31) Action memo by Wagner, P., Chief, Inert Ingredient Assessment Branch, US EPA. Inert reassessments: Four exemptions from the requirement of a tolerance for nonylphenol ethoxylates. US Environmental Protection Agency, Washington, DC, USA.
[67] Meyer, O., Andersen, P.H., Hansen, E.V., & Larsen, J.C. (1988). Tertogencity and in vitro mutagenicity studies on nonoxynol-9 and -30. Pharmacology & Toxicology, 62, 236-238.

assumptions built into EPA's exposure calculation - the exposure assumptions, calculations and related MOEs can be further refined as discussed below.

9.2.1. Refinements to respiratory exposure to NPE and MOE for powdered laundry detergent

EPA relies on the OSHA Particulate Not Otherwise Regulated (PNOR) Permissible Exposure Limit (PEL) for nuisance dust (15 mg/m^3) to calculate inhalation exposure to NPE. Another approach is to consider data regarding the actual characteristics of dust in granular laundry detergent.

Assumptions regarding the inhalation exposure of NPE from granular detergents can be refined based on data presented in a paper by Hendricks, 1970, which examined dust levels and characteristics in powdered laundry detergents.[68] While the focus of this paper was on enzyme exposure, it provides the following useful data regarding the characteristics of dust in laundry detergent. First, on average 0.27 µg detergent dust exposure per cup of product was found for double-pour machine loading with powdered detergent. "Double-pour" indicates pouring from a large container to a measuring container and then pouring from that measuring container into the washing machine; this is similar to the worst-case work practice assumptions in EPA's Engineering Report. Also, Hendrix reported a maximum of only 0.2% of the dust from granular detergent was found to be less than 5 µ for consumer powdered laundry detergents. The author notes that particles larger than 5 µ are generally considered to be too large to be respirable.

Based on these data provided in the Hendricks, 1970 paper and other assumptions provided in the EPA Engineering Report (i.e., an average laundry site handles 154 kg detergent per day), APERC calculated an inhalation dose of 0.00012 mg NPE /day from granular detergent as shown in Table IIIA. APERC assumed one worker handles all 154 kg of laundry detergent during the course of a single 8 hour work shift; the worker double pours the powdered laundry detergent, and no personal protection equipment is worn. Dividing the estimated daily inhalation dose of 0.00012 mg/day by a mean body weight of 71.8 kg results in an average daily dose of 0.0000016 mg/kg-bw/day. When the lowest NOEL for NPE9 (50 mg/kg-bw/day) is divided by this calculated exposure an MOE of ≥30,800,000 is calculated.

9.2.2. Refinements to dermal exposures to NPE and MOE for powdered and liquid laundry detergent

For dermal exposure calculations EPA assumed that both hands of the worker (840 cm^2) were completely exposed to a quantity of detergent (as defined by the EPA Generic Scenario document) without being wiped off and that there was 100% relative dermal absorption.[69,70] APERC used an alternate approach to refine the dermal exposure calculations that relied on

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[68] Hendricks, M.H. (1970). Measurement of enzyme laundry product dust levels and characteristics in consumer use. Journal of the American Oil Chemists' Society, 47, 207-211.

[69] US Environmental Protection Agency (US EPA). (2006, October 24). Chemicals used in water-based washing operations at industrial and institutional laundries - generic scenario for estimating occupational exposures and environmental releases - draft. US Environmental Protection Agency, Washington, DC, USA.

[69] US EPA. (2006, October 24).

[70] . US Environmental Protection Agency (US EPA). (2007, July 18) Draft: Engineering report of nonylphenol (NP) and nonylphenol ethoxylates (NPEs) in response to section 21 petition.

surrogate dermal unit exposure values from the 1998 EPA Pesticide Handler Exposure Database (PHED)[71] to estimate exposures for manual loading of solid and liquid detergents. EPA commonly uses PHED data, which is based on actual monitoring in occupational settings, for screening level exposure analyses in the absence of monitoring data for other occupational settings as described below.

> *PHED provides generic pesticide worker (i.e., mixer/loader and applicator) exposure estimates. The dermal and inhalation exposure estimates generated by PHED are based on actual field monitoring data, which are reported generically (i.e., chemical specific names not reported) in PHED. It has been the Agency's policy to use a surrogate or generic exposure data for pesticide applicators in certain circumstances because it is believed that the physical parameters or application technique, not the chemical properties of the pesticide, attribute to exposure levels. [Note: Vapor pressures for the chemicals in PHED are in the range of E-5 to E-7 mm Hg.] Chemical specific properties are accounted for by correcting the exposure data for study specific field and laboratory recovery values as specified by the PHED grading criteria. PHED handler exposure data are generally provided on a normalized basis for use in exposure assessments. The most common method for normalizing exposure is by pounds of active ingredient (ai) handled per replicate (i.e., exposure in mg per replicate is divided by the amount of ai handled in that particular replicate). These unit exposures are expressed as mg/lb ai handled. This normalization method presumes that dermal and inhalation exposures are linear based on the amount of active ingredient handled.*[72]

Commonalities between the process used for loading pesticide into a mixing tank and that used for loading laundry detergent into a washing machine further supports the usefulness of this approach to estimating laundry worker exposure to NPE in detergents. The potential dermal exposure of a laundry worker to NPE from laundry detergent was calculated using data from PHED and the following assumptions during various scenarios of loading detergent:

- Unit exposure factor for **open** mixing and loading of **granular** products, with a single layer of clothing without gloves is 0.0084 mg /lb handled.[73]
- Unit exposure value of 2.9 mg /lb handled for all **liquids**, **open** mixing and loading based on a single layer of clothing without gloves and 0.023 mg/lb handled using gloves.[74]
- Unit exposure value of 0.0086 mg /lb handled for all **liquids**, **closed** mixing and loading based on a single layer of clothing using gloves (Note the EPA PHED did not have a value for a closed system loading not wearing gloves).[75]
- An average of 154 kg (340 lb) of solid powder detergent was used per site per day.[76]
- An average of 154 kg (340 lb) of liquid detergent is used per site per day.

[71] US Environmental Protection Agency (US EPA). (1998). Surrogate Exposure Guide - Estimates of Worker Exposure from the Pesticide Handler Exposure Database (PHED) Version 1.1. Washington, DC, USA.
[72] US Environmental Protection Agency (US EPA). (2008, January 9). Occupational and residential exposure chapter for diiodomethyl p-tolyl sulfone.
[73] US EPA. (1998).
[74] US EPA. (1998).
[75] US EPA. (1998).
[76] US EPA. (2007, July 18).

- The NPE represents 28% of the granular detergent and 100% of the liquid detergent formulations.[77]
- One worker manually does all the detergent loading for the site (154 kg) during an 8-hour shift and cleans his/her skin at the end of the shift.
- The relative dermal absorption of NPE was less than 1% of the applied dose in solution after 8 hours of exposure based on Monteiro-Riviere et al. (2000).[78]
- The mean body weight was 71.8 kg for an adult male or female from age 18 to 75.[79]

Table IIIB, attached to these comments, provides estimated dermal exposures to NPE for various scenarios (*i.e.,* with and without gloves; open or closed loading; open or closed mixing /washing) based on ingredient exposures measured in the EPA PHED. Assumptions and calculations to derive daily exposures (mg/kg-bw/day) and MOEs are also provided in Table IIIB. For workers using granular laundry detergent with no gloves and open loading and mixing/washing, a daily absorbed dose of 0.000111mg/kg-bw/day was estimated. The MOE for this exposure based on the same lowest NOEL for NPE9 (50 mg/kg-bw.day) is calculated as approximately 450,000. For workers using liquid laundry detergent with no gloves, open loading /mixing/washing, a daily absorbed dose of 0.137 mg/kg-bw/day was estimated and a corresponding MOE was calculated as approximately 365. For workers using liquid laundry detergent with gloves and open loading /washing/mixing a daily absorbed dose of 0.0011mg/kg-bw/day was estimated and a corresponding MOE of approximately 46,000 was calculated. Finally, for workers using liquid laundry detergent with gloves and closed loading/washing/mixing, a daily absorbed dose of 0.00041mg/kg-bw/day was estimated and a corresponding MOE of approximately 123,000 was calculated.

Clearly methods exist to calculate exposure of laundry workers to NPE from their use in detergents. EPA has already calculated such exposure based on extremely conservative assumptions as described in these comments. APERC has also calculated exposures based on recognized methods and refined, though still conservative, assumptions. All of the estimated exposures are low and their corresponding MOE values indicate very low risk to laundry workers - even under worst-case scenarios and assumptions.

9.3 Human Exposure from Potable Reuse of Water

The Discussion Draft raises the potential for human exposure from the potable reuse of water, which APERC agrees is a valid exposure route for consideration. Recently a Science Advisory Panel (SAP) convened by the California State Water Resources Control Board issued a Draft Final Report "Monitoring Strategies for Constituents of Emerging Concern (CECs) in Recycled Water: Recommendations of a Science Advisory Panel (January 31, 2018)". [80] The SAP report specifically addressed NP as a potential CEC in potable reuse water based on conservatively

[77] US EPA. (2007, July 18).
[78] Monteiro-Riviere et al. (2000).
[79] US EPA. (1998).
[80] Drewes, J.E., Anderson, P., Denslow, N., Jakubowski, W., Olivieri, A. Schlenk, D., and Snyder,S.(2018, January 31) Monitoring Strategies for Constituents of Emerging Concern (CECs) in Recycled Water: Recommendations of a Science Advisory Panel Convened by the California State Water Resources Control Board

derived exposure/hazard ratios for NP concluded a low concern for human risk from this route for exposure.

The SAP report and recommendation provide well-founded framework for CEC monitoring in recycled water in California that is protective of human health. The methodology developed by the SAP provides a highly conservative, risk-based framework to prioritize and monitor CECs in potable and non-potable recycled water. The SAP relies on 90th percentile 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. The SAP also provided 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.

In the SAP report Monitoring Trigger Levels (MTLs), which are 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, are provided. A conservative MTL of 110 µg/L was derived for NP, which is well supported by four high-quality multi-generation rat studies that address all life stages and include reproductive and developmental endpoints. The SAP based the MTL for NP 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. [81] 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. [82,83] 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. [84,85]

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. [86] The earliest was the three-generation study conducted by the National Toxicology Program (NTP) and reported

[81] US EPA Office of Water (2016, November). Contaminant Information Sheets for the Final Fourth Contaminant Candidate List (CCL4). EPA 815-R-16-003.
[82] World Health Organization, International Programme on Chemical Safety (WHO IPCS). (2004). Integrated Risk Assessment: Nonylphenol Case Study.
[83] 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.
[84] 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/. Accessed on May 12, 2014.
[85] 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
[86] Osimitz, T., Droege, W., Driver, J. (2015). Human Risk Assessment for Nonylphenol. Human and Ecological Risk Assessment. Accepted author version posted online: 09 Jan 2015 (DOI:10.1080/10807039.2014.99952)

by Chapin et al. 1999 mentioned above. Then Nagao et al., 2001 published a two-generation reproductive study. [87] 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. [88] 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/day for reproductive toxicity. It also provided a NOAEL for male rat kidney toxicity of 15 mg/kg/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 in males) for kidney effects. [89]

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.

The SAP compared MECs for individual CECs from the 2010 report to utility data for the period 2008 to 2017. 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 the low priority for monitoring in recycled water assigned to NP by the SAP and indicates a low likelihood of human health risk from the potable reuse of water.

9.4 Human exposure from consumption of shellfish and human biomonitoring

The detection of NP in mussels and oysters in Southern California, as in the Diehl et al. 2012 paper, raises the question of risk to humans from consumption of these shellfish. [90] Therefore, APERC calculated Margins of Exposure (MOE) to adult human males and females based on consumption rates for freshwater and estuarine fish (edible portion) estimated for the U.S. population and selected subpopulations by the US National Health and Nutrition Examination Survey with results presented in Table IV.[91] While fish and oyster are not expected to be consumed at the same rate as fish, the fish consumption rates provide a conservative basis for calculation of Margins of Exposure for oysters and mussels containing levels of NP as reported in Diehl et al. 2012. A conservative No Observed Adverse Effects Level (NOAEL) of 13,000

[87] 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.
[88] 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.
[89] National Center for Toxicological Research (NCTR). (2009). Para-Nonylphenol: Evaluation of Reproductive Effects over Multiple Generations. Study Report # E2135
[90] Diehl J, Johnson SE, Xia K, West A, Tomanek L (2012) The distribution of 4-nonylphenol in marine organisms of North American Pacific Coast estuaries. Chemosphere 87(5):490-7
[91] US National Health and Nutrition Examination Survey (NHANES). 2003-2014. Estimated Fish Consumption Rates for the U.S. Population and Selected Subpopulations.

µg/kg body weight / day, which was used as the basis for the MOE calculation, was based on reproductive and systemic effects as reported in multigenerational rat studies. [92, 93, 94, 95, 96] This is also consistent with the NOAEL selected by the Science Advisory Panel (SAP) on CECs that was convened by the California State Water Resources Control Board.

TABLE IV Margins of Exposure Calculated for Human Consumption of Oysters and Mussels Containing NP at Concentrations Reported in Diehl et al, 2012

	Consumption estimates freshwater + estuarine fish edible portion*	Oyster 99th Percentile Consumption		Mussel 99th Percentile Consumption	
Population	99th Percentile (g/day raw weight)	Internal Dose (ug/kg)**	MOE	Internal Dose (ug/kg)**	MOE
Adults (≥21 yrs)	61.1	0.479635	27,104	0.09699625	134,026
Female	48.2	0.37837	34,358	0.0765175	169,896
Male	71.9	0.564415	23,033	0.11414125	113,894

** EPA (2014): Estimated Fish Consumption Rates for the U.S. Population and Selected Subpopulations (NHANES 2003-2010).*

***Calculated using concentrations in oyster and mussels reported in Diehl et al. 2012*

MOEs for the 99th percentile consumption of oysters and mussels, containing NP as reported in Diehl et al. 2012 indicated very low to no likelihood of adverse effects from consumption of these shellfish.

9.5 Aggregate Humans Exposure and Biomonitoring

Osimitz *et al*, 2015 conducted a risk assessment for human exposure to NP based on environmental monitoring data as well as on human biomonitoring data. [97] Human biomonitoring studies can provide a basis to estimate aggregate exposure to a chemical. Using

[92] Specifically, acceleration of vaginal opening in females (Chapin et al. 1999) and toxicologically significant changes in the kidney from males (Chapin et al. 1999; Nagao et al. 2001; NCTR 2009; Tyl et al. 2006)

[93] Tyl, R.W., et al., (2006).Three-generation evaluation of dietary para-nonylphenol in CD (Sprague-Dawley) rats. *Toxicol Sci*, **92**(1): p. 295-310.

[94]Chapin, R.E., et al., (1999). The effects of 4-nonylphenol in rats: a multigeneration reproduction study. *Toxicol Sci*, 1999. **52**(1): p. 80-91.

[95] Nagao, T., et al., *Reproductive effects of nonylphenol in rats after gavage administration: a two-generation study.* Reprod Toxicol, 2001. **15**(3): p. 293-315.

[96] NCTR (National Center for Toxicology Research), *para-Nonylphenol: Evaluation of Reproductive Effects over Multiple Generations (E0213501). Available at URL:* http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/. 2009.

[97] Osimitz, T. et al. (2015).

the daily absorbed dose estimates for NP, MOEs were calculated based on the same NOAEL of 15 mg/kg.day as described above, for sensitive toxicological endpoints of interest, *i.e.*, systemic and reproductive toxicity from continuous-feeding more than 3.5 generations in rats. The MOEs were all greater than 1,000 clearly indicating reasonable certainty of no harm for source-specific and aggregate (based on biomonitoring) exposures to NP.[98]

[98] Osimitz. T et al., (2015).