

**Comments of the
the Alkylphenols & Ethoxylates Research Council
on the
Notice: US EPA Draft Drinking Water Contaminant Candidate List 4
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The Alkylphenols & Ethoxylates Research Council (APERC) appreciates this opportunity to comment on US EPA's Draft Fourth Drinking Water Contaminant Candidate List (CCL4). The Draft CCL 4 includes 100 chemicals or chemical groups and 12 microbial contaminants including nonylphenol (NP). (U.S. EPA, 2015, February 4). These comments will respond to EPA's specific request for information and comment on nonylphenol (NP) as a candidate for the CCL4 and will also provide information regarding nonylphenol ethoxylate (NPE), octylphenol (OP) and octylphenol ethoxylate (OPE), which were nominated for consideration to be added to the CCL4.

APERC is a North American organization whose mission is to promote the safe use of alkylphenols (APs), alkylphenol ethoxylates (APEs), including NP, NPE, OP and OPE through science-based research, product stewardship and outreach efforts, 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 AP and APEs. Therefore, APERC can contribute substantively as a resource to EPA on these compounds.

These comments will also respond to EPA's request for comment on improvements to the selection process for future CCLs. The alkylphenol compounds discussed in these comments provide good examples of issues with transparency related to the specific data used in the CCL4 selection process as well as limitations related to reliance on the RTECS[®] database as a source for chemical information for chemicals nominated for the CCL process, particularly when primary source material is not reviewed to confirm or clarify values in the database.

Background and EPA Prioritization Approach for PCCL4

The Safe Drinking Water Act (SDWA) directs EPA to consider the health effects and occurrence information for unregulated contaminants to identify those contaminants that present the greatest public health concern related to exposure from drinking water. The statute further directs the agency to take into consideration the effect of contaminants upon subgroups that

comprise a meaningful portion of the general population (such as infants, children, pregnant women, the elderly and individuals with a history of serious illness or other subpopulations) that are identifiable as being at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population.

The 1996 SDWA Amendments specify three criteria to determine whether a contaminant may require regulation:

- The contaminant may have an adverse effect on the health of persons;
- The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and
- In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

In accordance with these mandates of the SDWA, the method used by EPA to prioritize compounds and microbes nominated for the PCCL4 categorizes nominated chemicals by Toxicity Categories and then screens them as candidates for CCL4 based on certain exposure or occurrence thresholds. The following table, which is Exhibit 2 in the Screening Document for the Draft PCCL 4 Nominated Contaminants (US EPA, 2015d), provides the criteria for Toxicity Categories 1 through 5, where Toxicity Category 1 and Toxicity Category 5 represent the highest and lowest toxicity or hazard respectively.

Potency Measures for Universe Data Element Partitioned Based on Toxicity (mg/kg/day or mg/kg) (EPA, 2015a)					
	RfD	NOAEL	LOAEL	MRDD	LD ₅₀
Toxicity Category 1	<0.0001	<0.01	<0.01	<0.01	<1
Toxicity Category 2	0.0001 - <0.001	0.01 - <1	0.01 - <1	0.01 - <1	1 - <50
Toxicity Category 3	0.001 - <0.05	1 - <10	1 - <10	1 - <10	50 - <500
Toxicity Category 4	0.05 - <0.1	10 - <1000	10 - <1000	10 - <1000	500 - <5000
Toxicity Category 5	≥0.1	≥1000	≥1000	≥1000	≥5000

Exhibit 4 in the Screening Document for the Draft PCCL4 Nominated Contaminants, which is presented below, provides the exposure criteria needed for each Toxicity Category to proceed to the PCCL (U.S. EPA, 2015a, 2015e)

Health Effects	Occurrence (by data type)		
	Finished/Ambient Water Concentrations	Release Amount (per year)	Production Volume (per year)
Toxicity Category 1	All Concentrations	All Amounts	
Toxicity Category 2	$\geq 1 \mu\text{g/l}$	$\geq 10,000 \text{ lbs/yr}$	0.01 - <1
Toxicity Category 3	$\geq 10 \mu\text{g/l}$	$\geq 100,000 \text{ lbs/yr}$	1 - <10
Toxicity Category 4	$\geq 100 \mu\text{g/l}$	$\geq 1 \text{ M lbs/yr}$	10 - < 1000
Toxicity Category 5	$\geq 1,000 \mu\text{g/l}$	$\geq 10 \text{ M lbs/yr}$	≥ 1000

Executive Summary of APERC Comments

This general approach of assigning a Toxicity Category ranking to a compound and prioritizing based on that ranking relative to specified volume thresholds is a reasonable method to identify higher priority drinking water contaminants. However, it is important that the selected toxicity values for a candidate chemical are transparent with regard to their source and at a minimum accurately reflect the findings in the primary source study and that the toxicity endpoints most appropriate to exposure via drinking water are selected to assign the Toxicity Category. This was not the case in the PCCL4 screening of NP. Also, recognizing that certain compounds will have more exposure data relevant to drinking water than others, use of those exposure data that are most relevant to drinking water should be used in prioritization (i.e., finished drinking water data should have greater relevance than source water, which should have greater relevance than wastewater effluent data). In the case of NP a single historical worst-case surface water value was selected to represent occurrence and potential drinking water exposure when monitoring in drinking water is available. (Snyder, 2008)

The data used by EPA to screen NP, NPE, OP and OPE for the PCCL4 is summarized in the table in Appendix 1 of the Screening Document for the Draft PCCL4 Nominated Chemicals and

will be reviewed as each compound is addressed in these comments below. (U.S. EPA, 2015a, 2015b)

According to EPA's Screening Document, to assess the universe of CCL4 candidates they are prioritized based on both "potency measures" and "occurrence data". (US EPA, 2015d) When accurate and relevant toxicity data and appropriate exposure data in drinking water are considered, NP, OP and their ethoxylates NPE and OPE do not pass the screen for prioritization to CCL4.

Furthermore, the estrogenic activity of NP noted by EPA in the Federal Register Notice (US EPA 2015a) does not preclude the risk-based assessment of this compound for CCL4 screening purposes. While NP and OP have weak estrogenic-like activity based on various *in vitro* and *in vivo* studies with potencies that generally range from 1,000 to 1,000,000-fold weaker than the endogenous estrogen, estradiol. (Coady et al., 2010; Van Miller and Staples, 2005; Wenzel et al., 2001), the baseline toxicity (i.e., non-endocrine, non-specific toxicity) of NP and OP occurs at doses that are either similar or lower than the doses required to adversely affect development and reproduction, which are endpoints that may be linked to estrogenic activity. (Coady, 2013) Thus, in higher-tier multigenerational mammalian studies, the relatively weak estrogenic activity of NP and OP is not the critical effect. (Coady, 2013)

EPA's screening assessment of NP for CCL4 was based on an erroneous Lowest Observed Adverse Effect Level (LOAEL) value of 2 mg/kg-bw/day and therefore an incorrect potency or Toxicity Category was derived. This, along with single out-of-date and worst-case surface water monitoring data point of 40 µg/L, which is not relevant to current drinking water levels of this compound, led EPA to propose moving NP forward to the CCL4. When accurate and relevant toxicity data are considered, including chronic and multi-generational studies with rats that cover all sensitive life stages as well as reproductive or developmental effects - as required under the SDWA - NP, NPE, OP and OPE all fall into Toxicity Category 4 for CCL4 screening purposes. Also, studies that monitored for the occurrence and concentration of NP and OP in U.S. drinking water are available that indicate that OP is not detected in drinking water and concentrations of NP in drinking water are below the CCL4 screening criteria for occurrence for

Toxicity Category 4 (100µg/L); in fact they are even below those for Toxicity Category 3 (10 µg/L) and Toxicity Category 2 (1µg/L). Therefore, neither of these compounds pass the screening criteria for CCL4. In addition, NPE and OPE have not been reported as occurring in U.S. finished drinking water and their concentrations in ambient surface water in the US are have been found to be generally below the occurrence criteria for Toxicity Category 4 (100 µg/L) and on that basis should not pass to CCL4. (Klecka, 2007)

Perhaps more relevant than the CCL4 screening criteria, assessments of the risk to humans from NP and OP in drinking water have been conducted and indicate high Margins of Exposure (MOEs) and therefore a high margin of safety for this exposure source. (Snyder, 2008; Osimitz, 2015).

Also, there are human biomonitoring data available for NP and OP, which can be used to characterize human risk for each of these compounds from all sources, not just drinking water. It is pertinent to note that the US Centers for Disease Control (CDC) indicates that OP has been largely undetectable in human biomonitoring (urine) and is therefore no longer reporting for this compound under the National Report on Human Exposure to Environmental Chemicals. (US CDC, 2015, February) While NP was not subject to monitoring by the CDC, there are human biomonitoring data available in the published literature as well as Margin of Exposure (MOE) calculations based on the use of a No-Observed-Adverse-Effect-Level (NOAEL) for the most sensitive toxicological endpoints of interest (i.e., systemic and reproductive toxicity). Based on levels of NP in human urine Osimitz et al, 2015 derive biomonitoring-based MOEs for NP ranging from 1,251 to 8.4×10^7 for populations in Taiwan, Korea, Japan, and China (Osimitz, 2015). The MOE for a study on the urine of US adults was approximately 6.5×10^5 , which is greater than 1,000, clearly indicating reasonable certainty of no harm and aggregate (based on biomonitoring) exposures to NP. (Calafat, 2005; Osimitz, 2015)

Taken together, the low concentrations of NP in drinking water, the high MOEs for NP in drinking water and the human biomonitoring data and MOEs that indicate that this compound does not occur in public water systems, or other sources of exposure, at levels of public health concern. Furthermore, assigning NP to the CCL4 or for further regulation under the SDWA

would not provide a meaningful opportunity for health risk reduction for persons served by public water systems. In addition, NP is already subject to regulation in surface water under the Clean Water Act by Water Quality Criteria (WQC) at the federal level and Water Quality Standards (WQS) at the state level; the NP chronic freshwater WQC (6.6 µg/L) that were developed to protect aquatic species will also ensure that surface water concentrations of this compound remain below the surface water threshold for Toxicity Category 4 compounds (100 µg/L) and even for Toxicity Category 3 compounds (10 µg/L). (US EPA, 2005, US EPA 2006, February 23)

Also, OP, OPE and NPE, all of which are Toxicity Category 4, do not occur in either drinking water or surface water at levels of public health concern and do not warrant addition to the CCL4 or further regulation under the SDWA as this would not provide a meaningful opportunity for health risk reduction for persons served by public water systems.

The following comments provide more detail on each of the above points.

COMMENTS

1.0 EPA’s assessment of NP under the CCL4 screening process was based on an erroneous toxicity value and therefore an incorrect potency classification, along with an out-of-date, worst-case surface water monitoring data point that is not relevant to current drinking water levels of this compound.

The Federal Register Notice requesting comment on the CCL4 notes that NP was previously considered for CCL 3 but was not included in the PCCL3 or CCL3. (USEPA, 2015a) The Notice goes on to say that updated health and occurrence data are now available and were considered by the agency in evaluating NP for the Draft CCL 4. Specifically, the agency found that “nonylphenol and some of its degradation products have been found to have estrogenic activity in rats and mice” based on a report by the World Health Organization. (WHO, 2004). Also, the agency found occurrence data from a USGS National Reconnaissance monitoring study of ambient water (Kolpin et al., 2002). Based on this information and “additional data that NP

is anticipated to occur in Public Water Systems”, EPA determined that NP merits listing on the Draft CCL4. (US EPA, 2015a)

The following comments will explain that EPA’s assessment of NP under the CCL4 screening process was based on an erroneous toxicity value of 2 mg/kg-bw/day and therefore the compound was incorrectly classified as Toxicity Category 3. This along with an out-of-date, worst-case surface water monitoring data point of 40 µg/L, which is not relevant to current drinking water levels of this compound, led EPA to propose moving NP to the CCL4.

1.1 The Toxicity value selected by EPA for the Potency Classification of NP in the CCL4 screening process is erroneously based on an incorrect LOAEL for NP in the RTECS® database; NP should be a Toxicity Category 4 not Category 3.

1.1.1 While the estrogenic activity of NP merits consideration, it does not preclude a risk-based assessment or prioritization of the compound.

While NP and OP have weak estrogenic-like activity based on various *in vitro* and *in vivo* studies the potencies generally range from 1,000 to 1,000,000-fold weaker than the endogenous estrogen, estradiol. (Coady et al., 2010; Van Miller and Staples, 2005; Wenzel et al., 2001), the baseline toxicity (*i.e.* non-endocrine/non-specific toxicity) of NP and OP occurs at doses that are either similar or lower than the doses required to adversely affect development and reproduction, which are endpoints that may be linked to estrogenic activity. (Coady, 2013) Thus, in higher-tier multigenerational mammalian studies, the relatively weak estrogenic activity of NP and OP is not the critical effect. (Coady, 2013) Therefore, while the estrogenic activity of NP merits consideration, it does not preclude a risk-based assessment or prioritization of the compound. As discussed in more detail later in these comments, there are four multi-generation rat studies available for NP from which an appropriate and sensitive NOAEL and LOAEL can be identified. (NTP, 1997; Chapin, 1999; Nagao, 2001; Tyl, 2006; NCTR, 2009, Osimitz, 2015)

1.1.2 The Potency Value of 2 mg/kg-bw/d selected for NP and listed on both the CCL4 Contaminant Information Sheet for NP and the Screening Document (USEPA, 2015b, 2015d) is erroneously based on an incorrect LOAEL for NP in the RTECS® database and does not reflect the findings of either of the possible

cited sources or the weight-of-evidence for NP, which includes four multi-generation rat studies.

In reviewing the CCL4 Contaminant Information Sheet NP three health effects data are listed:

- A No Observed Effect Level (NOEL) for NP of 60 mg/kg/day citing CTD JPN.
- A NOAEL for NP of 15 mg/kg/day sourced from a secondary source published by the World Health Organization. (WHO, 2004). The primary source for the 15 mg/kg-d NOAEL was the European Union Risk Assessment Report on Nonylphenol. (ECB, 2002).
- The lowest value is a LOAEL of 2 mg/kg-bw/day that cites a 2001 study from the RTECS[®] data base with " Endocrine - Androgenic, Reproductive - Paternal Effects - testes, epididymis, sperm duct." effects¹ (US EPA, 2015b)

While APERC agrees with the reliance on the first two references above, use of the RTECS[®] cited value of 2 mg/kg-bw/d value is problematic. As noted in Section 8.0 of these comments, the process of study review and interpretation employed by the RTECS[®] database or EPA is not disclosed to the user, so it impossible to comment on EPA's rationale for selection of this value. Nonetheless, the identification of 2 mg/kg-w/day as a LOAEL for NP is incorrect and its application in the CCL4 process is not warranted.

EPA provides a citation for the 2 mg/kg-bw/day, which corresponds to a two generation rat study published by Nagao et al, 2001; however, RTECS[®] does not list 2 mg/kg-bw/day as either a LOAEL or a TDLo (lowest published toxicity dose) for this study. RTECS[®] does list 2 mg/kg-bw/day as a TDLo for another study by Laurenzana et al, 2002. RTECS[®] defines TDLo--Toxic Dose Low—as “the lowest dose of a substance introduced by any route, other than inhalation, over any given period of time and reported to produce any toxic effect in humans or animals, or to produce tumorigenic, reproductive, or multiple dose effects in animals.” (Accelrys, 2012, April 10) A TDLo is not equivalent to a LOAEL. Since it is not clear which

¹ RTECS cites “REPTED Reproductive Toxicology. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.1- 1987- Volume(issue)/page/year 15,293,2001” as the source for this value. This corresponds to two generation rat study published by Nagao et al (2001).

study EPA was referencing, both the Nagao et al, 2001 and the Laurenzana et al, 2002 studies are discussed below; however 2 mg/kg-bw/day is an erroneous LOAEL for both studies.

1.1.2.1 The LOAEL and NOAEL for NP reported in Nagao et al, 2001 are 50 mg/kg-bw/ d and 10 mg/kg-bw/d respectively; therefore 2 mg/kg-bw/d is an erroneous LOAEL assigned to this study, which should be removed from the Contaminant Information Sheet for NP.

While it is not clear whether EPA meant to reference the study by Nagao et al, 2001 as the source of a LOAEL of 2 mg/kg-bw/day it should be noted that in this paper “ppm” is used as the unit for dose levels throughout the publication; the unit of mg/kg/day or mg/kg-bw/day is not used but the authors state "daily dose varied approx. from 2 to 240 mg/kg/day". However, referring to the original paper and based on the authors' conclusions the LOAEL and NOAEL for NP reported in Nagao et al, 2001 are 50 mg/kg-d and 10 mg/kg respectively. So, the LOAEL for the Nagao et al, 2001 paper is 50 mg/kg-bw/d not 2 mg/kg-d/day as reported in the EPA Contaminant Information Sheet and Summary Document.

In searching for some rationale that EPA may have used to derive a LOAEL of 2 mg/kg-bw/day for Nagao et al. (2001) the study was reviewed. It reports on a two-generation study in which rats were given daily gavage doses of 0, 2, 10, 50 mg/kg NP. In F0 and F1 animals of the 50 mg/kg/day treated group, effects on liver weights (absolute and/or relative to body weight) in males and females as well as kidneys of males were reported. A decrease in the number of implants and live pups born was noted in the 50 mg/kg group. Ovary weight was significantly decreased in F0 and F1 females, possibly related to the decrease in implantations. A decrease in the time of vaginal opening was noted in the F1 females at 50 mg/kg. Relative thyroid gland and pituitary gland weights were elevated in males at 50 mg/kg. No histologic changes were noted in these glands. For the study as a whole, the authors reported a LOAEL of 50 mg/kg and a NOAEL of 10 mg/kg.

It is possible that a reviewer erroneously assigned a LOAEL value of 2 mg/kg-bw/d based on an observation in the study that in postpubertal rats, a significant decrease in T₃ concentration was observed male rats in the 2 and 50 mg/kg groups. However, additional review of the study shows

that the authors conclude the “changes in weanling hormone concentrations are not toxicologically and biologically significant effects from NP treatment, and that a clear conclusion cannot be drawn from the hormone data in the present study”. (Nagao, 2001)

1.1.2.2 Laurenzana et al, 2002 is a study of endocrine biomarkers and measures estrogenic activity rather than adverse effects; therefore the study did not define a NOAEL or LOAEL and 2 mg/kg-bw/day is an erroneous LOAEL assigned to this study, which should be removed from the Contaminant Information Sheet for NP.

While it is also not clear if EPA intended to reference Laurenzana et al, 2002 in support of a 2 mg/kg-bw/day LOAEL on the Contaminant Information Sheet for NP, this was a study on the effect of dietary administration of genistein, nonylphenol or ethinyl estradiol on hepatic testosterone metabolism, cytochrome P-450 enzymes, and estrogen receptor alpha expression to determine their suitability as estrogenic biomarkers. Since no adverse effects were being measured, the authors did not define a NOAEL or LOAEL. In this study “ppm” was used as unit for dose levels throughout the publication and the unit of mg/kg/day is not used but the authors state "daily dose varied approx. from 2 to 240 mg/kg/day". RTECS lists a TDLo of 2 mg/kg/day for this study for the endpoint “Reproductive - Specific Developmental Abnormalities - hepatobiliary system Reproductive - Effects on Newborn - biochemical and metabolic”. This TDLo does not correspond to a LOAEL.

Laurenzana et al, 2002 concluded:

"Both nonylphenol and genistein caused an increase in hepatic ERa in female rats, whereas EE2 did not. It is doubtful that the small changes in hepatic ERa induced by genistein and nonylphenol in female rats are sufficient to alter normal physiological processes." Furthermore, "The results from the studies reported here suggest that dietary exposure to the endocrine active test compounds, all of which have demonstrated estrogenic activity, during development can result in alterations in testosterone hydroxylase and 5a-reductase activities, CYP450 and ERa expression in the liver, particularly in male rats, but that these changes cannot be directly linked to their estrogenic activities. Thus, these assays are not appropriate as biomarkers for exposure to

estrogenic agents. The implications of the observed changes for the biological activity of the compounds is (sic) unclear." (Laurenzana et al, 2002)

Given that the effects noted in this study have not been deemed to be adverse, it is certainly incorrect to use the 2 mg/kg-bw/day value as a LOAEL and this should be removed from EPA's Contaminant Information Sheet for NP.

Furthermore, correspondence from Barry DelClos, FDA National Center for Toxicological Research (NCTR) to APERC regarding several studies by Lauranzano, including the study of interest here, indicate that it was conducted as an ancillary study to a five-generation rat study on NP performed by NCTR and conducted at dietary doses of 25, 200 and 750 ppm. (DelClos, 2000, April 13) That extensive NCTR study covered all sensitive life stages and five generations and was sufficient to address any implications of the observed changes for the biological activity of the compounds that may have been unclear when the study by Lorenzano et al (2002) was conducted. The NCTR five-generation rat study found a NOAEL for reproductive effects at 750 ppm (51 and 80 mg/kg for males and females, respectively), which was the highest dose tested. It also found a NOAEL for kidney effects in males at 200 ppm (14 mg/kg/day). (NCTR, 2009)

1.2 EPA's assessment of NP under the CCL4 screening process was based on single, out-of-date surface water monitoring data point that is not relevant to current drinking water levels of this compound.

1.2.1 The occurrence value of 40 µg/L selected in the Screening Document for NP reflects the maximum and worst-case value for NP reported in the Kolpin et al (2002) reconnaissance study of contaminants in U.S. surface water and exaggerates the potential exposure to NP in both surface and drinking water; furthermore this study was published 13 years ago and does not reflect lower current use patterns for NP and its derivative NPE.

The Kolpin et al, 2002 national reconnaissance study is cited by EPA as the source of the 40 µg/L NP in the Screening Document for the Draft CCL4. (US EPA, 2015d) In a review of monitoring data on AP and APE, Klecka et al, 2007 conducted a statistical analysis of the data for these compounds collected by Kolpin et al, 2002. Klecka reports the highest value of 40

µg/L “is the concentration of NP measured in a sample collected from the Santa Cruz River, AZ” and citing personal communication with Kolpin noted “further communication with the author indicated that samples from this river were essentially 100% effluent from the local wastewater treatment plant”. (Klecka, 2007) Klecka reports that “other than this single high value, the remaining AP/APE concentrations in Kolpin et al, 2002 are clustered in the range from 2 to 20 µg/L, with most values (90th centile) less than 1 µg/L” and “NP levels in the samples also show a few values clustered in the 3 to 10 µg/L range, with most values less than 3 µg/L (90th centile).

Section 1.2.4 below in these comments addresses market shifts away from the use of NPE surfactants in down-the-drain products, which have now made the data in Klecka et al, 2007 and Kolpin et al, 2002 out-of-date and an overestimate of current levels of NP in surface water.

Reliance on a single worst-case and out-of-date surface water monitoring value of 40 µg/L as representing occurrence of NP in drinking water is inappropriate and unnecessary given that drinking water monitoring data are available for this compound.

1.2.2 The STORET data cited on the EPA Contaminant Information Sheet for NP do not meet the threshold for ambient water to pass either a Toxicity Category 4 (100 µg/L) or a Toxicity Category 3 (10 µg/L) compound onto the CCL4.

Other data for NP are listed under Supplemental Water Data on the EPA Contaminant Information Sheet and cites the STORET database as the source. These appear to be surface water concentration for 5 of 15 samples with concentrations ranging from 3.26 to 5.17 µg/L. (US EPA, 2015b) However, it is not clear what the original source of these data are or when the samples were taken. Regardless, they are still below the occurrence thresholds for ambient water concentrations for Toxicity Category 4 (100µg/L) and Toxicity Category 3 (10 µg/L) and would not warrant passing NP to CCL4.

Existing drinking water monitoring data, which are discussed below, provide a better basis for assessing the risk of NP in drinking water and for the purposes of CCL4 prioritization.

1.2.3 Concentrations of NP in U.S. ambient surface water were generally below the CCL4 Occurrence Thresholds for Toxicity Category 4 (100 µg/L) and

Toxicity Category 3 (10 µg/L) even before market shifts away from NPE in high emission cleaning and laundry products began.

The most comprehensive assessment of U.S. surface water monitoring studies was conducted by Klecka et al, 2007. This paper reviewed the published or publicly available literature to develop a statistical understanding of exposures to AP and APE, including NP, NPE, OP and OPE in US surface waters. A literature search was conducted to identify environmental monitoring studies published during the 15 year period between 1990 and 2005, which contained information on surface water and/or sediment concentrations of APE and its metabolites in US waters. Nineteen reliable monitoring studies, most of which were conducted by the US Geological Survey (USGS), were reviewed and the highest concentrations of all NPE metabolites were generally observed for rivers in heavily urbanized or industrialized locations with average NP concentrations of 1.7 µg/L. (Klecka, 2007) As discussed below, the data presented by Klecka et al, 2007 present surface water occurrence for NP, as well as NPE, that pre-date major downward shifts high emission uses of NPE. Therefore, this monitoring, which conducted in the 15 years prior to 2005 is no longer representative and overstates the use and exposure patterns for these compounds. Current use patterns would predict significantly lower concentrations in both surface and drinking water.

1.2.4 Market shifts away from the use of NPE surfactants in down-the-drain cleaning and laundry products have significantly reduced the volume of emissions of NPE and NP to the aquatic environment, and potentially to drinking water source waters; current use patterns would predict significantly lower concentrations in surface water than those reported in either Kolpin et al (2002) or Klecka et al (2007).

The use of NPE surfactants in cleaning products and detergents for institutional and consumer use was at one time their predominant use; however these uses declined significantly in recent years due to US EPA Design for Environment(DfE) initiatives and market pressures in North America generally that have been underway since 2005. (Wal-Mart, 2006; US EPA DfE, 2005) Market trends indicate decreasing use of NP and NPEs in applications that result in high aquatic emissions. Consumption of APE (i.e. NPE and OPE), which is considered to be primarily (>85%) NPE, in North America (including the U.S., Canada and Mexico) dropped by 44.8%

between 2004 (232,000 tons) and 2013 (128,000 tons). (Colin A. Houston & Associates, Inc., 2006, 2013) The drop in the US was influenced by environmental concerns with NPE and NP not human health concerns. Voluntary initiatives under the U.S. EPA Design for Environment Program and market pressures due a policy announcement by Wal-Mart in 2006 to restrict the use of NPEs in cleaning and laundry products that it sells influenced the decline in use in these applications. Therefore, the likelihood of significant ongoing or new exposure or risk from NP or NPE these uses of NPE is low.

Therefore, the surface monitoring data from Klecka et al (2007) and Kolpin et al (2002) discussed above is out dated and overstates the occurrence, concentrations and exposure of NP and NPE in surface water and drinking water in the U.S.

1.2.5 More recent papers reporting monitoring for NP in US surface waters and even wastewater effluent report results consistent with reductions in high emission uses and further support that NP occurrences do not warrant placing it on the CCL4.

Surface water samples collected from the Back River, MD contained 0.49 µg/L NP. (Loyo-Rosales, 2007) In a study that monitored twenty-one wastewater samples collected from a range of sites, including 16 residential, commercial, or industrial samples, and five samples from influent and effluent streams at the WWTP, NP was not detected in any samples (Jackson and Sutton, 2008) In a study conducted in an, an urban estuary in San Francisco Bay, CA that receives direct discharge from over forty municipal and industrial wastewater outfalls. NP was detected at concentrations ranging from <2 to 73 ng/L). (Klosterhaus, 2013) While these wastewater effluent studies have low relevance to drinking water they demonstrate that more recent monitoring of NP are lower than those reported by Klecka et al, 2007 and are consistent with reductions in high emission uses further supporting that NP occurrences do not warrant placing it on the CCL4.

2.0 Measured concentrations of NP in finished drinking water in the US are the most appropriate data for assessment of the occurrence of this compound for CCL4; available data show that NP concentrations in U.S. drinking water generally fall in the range of 92-110 ng/L (0.92-0.11 µg/L), which is one thousand-fold lower than the CCL4 occurrence threshold (100 µg/L) for Toxicity Category 4 compounds.

Several papers examining the concentration of NP in finished drinking water in the U.S. are available, which provide more relevant data than the 40 µg/L effluent dominated surface water concentration that provided the basis for EPA's CCL4 assessment. Snyder et al. (2008), detected a maximum NP concentration of 0.11 µg/L (110 ng/L) when analyzing raw and finished waters of 20 U.S. drinking water facilities. Benotti et al.(2009) measured a median NP concentration of 93 ng/L in finished water from 19 U.S. water treatment plants. Stackelberg et al. (2007) found an average NP concentration of 92 ng/L in twelve drinking water samples from a U.S. water treatment plant. These concentrations are one thousand-fold lower than the CCL4 occurrence threshold (100 µg/L) for Toxicity Category 4 compounds

Another paper by Magi et al (2010) measured NP in a sample taken in a drinking water treatment plant using polar organic chemical integrative samplers, which do not give results in µg/ L of water. The study found “rather low concentrations of NP” were measured in the inlet to the drinking water treatment; however no NP was detected in the outlet for finished drinking water using this method. (Magi, 2010)

3.0 NP is a Toxicity Category 4, its occurrence in drinking water is generally much less than 1 µg/L and Margins of Exposure (MOEs) for NP in U.S. drinking water are very high indicating that this compound does not occur in public water systems at levels of public health concern and its regulation under the SDWA would not present a meaningful opportunity for health risk reduction for persons served by public water systems.

3.1 Four multi-generation rat studies that address all life stages and include reproductive and developmental endpoints, as required under the SDWA, indicate that the NOAEL for

NP for both systemic and endocrine toxicities fall in the range of 10 to 15 mg/kg/day, which falls within the Toxicity Category 4 for CCL4.

Four multi-generation reproductive toxicology studies have been reported for NP, the latter studies building on or clarifying the findings of the earlier studies. Each of these was reviewed and considered with respect to the critical effect and the selection of the point of departure for risk assessment. (Osimitz, 2015)

The earliest was a three-generation study conducted by the National Toxicology Program (NTP) and reported by Chapin et al. 1999. Rats were given a diet with 0, 200, 650 and 2000 ppm of *p*-nonylphenol. Various decreases in weight gains were observed across generations at doses of 650 and 2000 ppm and the NOAEL for this study was 200ppm based on this effect. Increased kidney to body weights ratios were observed at 650 ppm and/or 2000 ppm in adult males from the F0, F1, and F2 generations and in the F1 2000 ppm adult females. An increase in the treatment-related incidence of renal tubular degeneration and/or dilatation was seen in males from all generations in the 200, 650, and 2000 ppm treatments and also in F1, F2, and F3 females in the 2000 ppm treatment and additionally in F3 females in the 200 and 650 ppm treatments. However, convincing dose-response relationships were not always evident for this effect. Moreover, in an independent expert pathologist review, the effects at the lowest dose were found to be non-adverse due to being minimal in severity without accompanying inflammation or significant changes in kidney weights or body weights (Hard, 1998). Reproductive changes were seen in both male and female adults at or above 650 ppm and included decreased epididymal sperm density and testicular sperm head counts in males, and increased estrous cycle length and decreased ovarian weights observed in females. The most notable observation was the acceleration of vaginal opening in all three generations tested at 2.9-6.0 days at 2000 ppm and at 1.5-7.3 days at 650 ppm (the LOAEL). There were no effects on fertility and mating performance in any dose group. Thus, NOAEL for reproduction and systemic toxicity was 200 ppm (approximately 13-19 mg/kg/day). (Chapin, 1999; Osimitz, 2015)

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. No treatment-related effects were seen on any reproductive parameters including sperm parameters in any generation. Dose related histologic changes (mineralization at the corticomedullary junction) occurred in the kidney at

650 and 2000 ppm in the F0 and F2 males and at 200, 650, and 2000 in the F1 males. Tyl et al, 2006 concluded that this study demonstrated a lack of transgenerational effects on epididymal sperm counts or on any other reproductive endpoint and that 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.

As discussed earlier in these comments, Nagao et al, 2001 reported on a two-generation study in which rats were given daily gavage doses of 0, 2, 10, 50 mg/kg NP. In F0 and F1 animals of the 50 mg/kg/day treated group, effects on liver weights (absolute and/or relative to body weight) in males and females as well as kidneys of males were reported. A decrease in the number of implants and live pups born was noted in the 50 mg/kg group. Ovary weight was significantly decreased in F0 and F1 females, possibly related to the decrease in implantations. As with Chapin et al. (1999), a decrease in the time of vaginal opening was noted in the F1 females at 50 mg/kg. Relative thyroid gland and pituitary gland weights were elevated in males at 50 mg/kg. No histologic changes were noted in these glands. For the study as a whole, the LOAEL was 50 mg/kg, whereas the NOAEL was 10 mg/kg. This is comparable to the 13-19 mg/kg equating to the 200 ppm dietary dose in Chapin et al. (1999) and the 15 mg/kg/day in Tyl et al (2006).

The most extensive study of reproductive toxicology of NP was a five-generation study was performed by the National Center for Toxicological Research (NCTR, 2009) at dietary doses of 25, 200, and 750 ppm. No clear adverse effects were observed on any of the multiple reproductive endpoints assessed and no general toxicity was observed in male or female rats at doses up to and including 750 ppm (51 mg/kg and 80 mg/kg for males and females, respectively). Microscopic evaluation revealed treatment effects only in the male kidney (mineralization) at the 750 ppm dose in the F0 through F2 generations. The NCTR five-generation rat 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 (14 mg/kg in males) for kidney effects.

Together, the multi-generational studies revealed only marginal effects on reproduction and there were no functional disturbances of the reproduction. All effects *in vivo* were found at doses in the range or above the LOAEL for systemic toxicity. These studies demonstrate that NP is not a

selective reproductive toxicant, and because of non-reproductive effects being manifest at comparable and lower doses than the reproductive effects, suggest that endpoints of NP potentially mediated by an estrogenic mode of action are not as sensitive as other non-estrogenically mediated effects such as kidney effects. (Chapin, 1999, Nagao 2001, Tyl, 2006)

The most sensitive effects in the multigeneration reproduction studies were the acceleration of vaginal opening in females (Chapin et al. 1999), and toxicologically-significant changes in the kidney from males (Chapin et al., 1999, Tyl et al. 2006; Nagao et al., 2001; NCTR, 2009, Osimitz, 2015), both of which occurred at doses of >200 ppm (13-19 mg/kg-d). It is noteworthy that no vaginal effects were observed in a five-generation study at doses up to and including 750 ppm (the highest dose tested), whereas kidney effects were seen *only* at 750 ppm. (NCTR, 2009)

- 3.2 Assessments of the human health risk of NP in U.S. drinking water have been conducted and indicate high MOEs or margins of safety ranging from 1.6×10^4 to 5.9×10^9 and low likelihood of risk to humans from this route of exposure.

Based on monitoring reported for NP in the peer-reviewed literature over a 15 year period from 1998 to 2013, Osimitz et al (2015) presented a source-specific human health risk assessment for drinking water using a NOAEL of 13 mg/kg/day. This Point of Departure was selected for the risk assessment was based on the most sensitive repeat dose study, which was a three generation reproductive toxicity study in which rats were given a diet with 0, 200, 650 and 2000 ppm (approximately 0, 13-19, 43-64, and 274-322 mg/kg/day) of NP. (NTP, 1997) Based on decreased body weight the LOAEL (adult systemic toxicity) was 650 ppm (~ 43-64 mg/kg-bw/day) and the NOAEL (adult systemic toxicity) was 200 ppm (~13-19 mg/kg body weight/day). Based on decreased epididymal sperm density and testicular sperm head counts in males, and increased estrous cycle length and decreased ovarian weights in females, the LOAEL (adult reproductive toxicity) was 650 ppm (~ 43-64 mg/kg body weight/day) and the NOAEL (adult reproductive toxicity) was 200 ppm (~ 13-19 mg/kg body weight/day). Based on accelerated vaginal opening in pups, the LOAEL (offspring toxicity) was 650 ppm (~ 43-64 mg/kg body weight/ day) and the NOAEL (offspring toxicity) was 200 ppm (~ 13-19 mg/kg body weight/day). Therefore the authors selected 13 mg/kg-bw/day (the lowest and most conservative value as the Point of Departure for the calculation of MOE. (Osimitz, 2015)

Three studies based on U.S. drinking water were included. Snyder et al., 2008, which detected a maximum finished water NP concentration of 0.11 µg/L when analyzing raw and finished waters of 20 U.S. drinking water facilities resulting in an MOE of 5.0×10^9 . Benotti et al., 2009 measured a median NP concentration of 93 ng/L in finished water from 19 United States water treatment plants resulting in an MOE of 5.9×10^9 . Stackelberg et al., 2007 found an average NP concentration of 92 ng/L in twelve drinking water samples from a United States water treatment plant resulting in an MOE of 5.9×10^9 . (Osimitz, 2015)

The Snyder et al, 2008 paper mentioned above also calculated a Drinking Water Exposure Level (DWEL) for NP based on NOAEL of 1.5 mg/kg-bw/day from a 3-generation rat study by Tyl et al , 2006. (Snyder, 2008). The NOAEL from the Tyl et al, 2006 study was actually 15 mg/kg-bw/day based on male rat kidney toxicity. Still, even with that conservative basis the minimum margin of safety calculated by Snyder et al, 2008 for NP was 1.6×10^4 .

While the Osimitz et al (2015) paper was in press a paper by Padhye et al (2014) was published describing a yearlong monitoring study of an urban drinking water system in Georgia. The median concentration for NP was 83 ng/L, which is slightly less than the concentrations described above by Osimitz et al (2015); therefore similar MOEs would be expected. (Padhye, 2014)

- 3.3 Analytical results reported for NP in surface and drinking water may overstate the occurrence and concentration of this compound due to analytical difficulties with high false positives identified for this compound.

A published paper by Vanderford *et al*, 2014 presented the results of a large-scale interlaboratory comparison study of 25 chemicals of concern, including NP to assess the accuracy and precision of available analytical methods with spiked samples of drinking water and source water. 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.” (Vanderford *et al*, 2014)

This information about analytical quality and high false positives for NP in drinking water monitoring indicates that all occurrence and MOE values previously discussed are likely overly conservative.

4.0 High MOEs for NP in human biomonitoring studies provide another level of assurance that human exposures from all sources, including drinking water, is very low indicating addition of NP to the CCL4 or its regulation under the SDWA would not present a meaningful opportunity for health risk reduction for persons served by public water systems.

Based on levels of NP in human urine Osimitz *et al*, 2015 derive biomonitoring-based MOEs for NP ranging from 1,251 to 8.4×10^7 for populations in Taiwan, Korea, Japan and China (Osimitz, 2014). One study on biomonitoring conducted on urine take from adults in the U.S. found that 49% of the samples had no detectable NP concentration. The median concentration for NP was < 0.1 µg/L and the highest median concentration was in the subpopulation of men (0.17 µg/L) (Calafat, 2005). These results yield an MOE in excess of 6.5×10^6 .

5.0 NP is otherwise regulated under the Clean Water Act (CWA) and Water Quality Criteria (WQC) at the federal level and Water Quality Standards (WQS) at the state level for NP can be used to ensure that surface water concentrations of this

compound remain below the ambient water threshold for Toxicity Category 4 compounds (100 µg/L) and even those for Toxicity Category 3 compounds (10 µg/L) under the CCL4 screen.

US EPA announced final WQC for Nonylphenol (NP) on February 23, 2006 (71 FR 9337). The final WQC were developed pursuant to Section 304 (a)(1) of the CWA. According to EPA, an “ambient WQC is a level of a pollutant or other measurable substance in water that, when met, will protect aquatic life.” EPA’s WQC for NP provides guidelines to states and users about ambient levels of NP that are protective of aquatic life; WQC are incorporated into state level WQS. The final chronic freshwater WQC for NP is 6.6 µg/L, which is well below the 100 µg/L threshold for Toxicity Category 4 compounds under the CCL4 screen. It is also less than the 10 µg/L threshold for Toxicity Category 3 compounds.

Klecka et al, 2007 conducted a statistical analysis of U.S. surface water concentrations of NP, including NPE, OP and OPE, which examined samples taken from 40 states during 1989 through 2004. The analysis showed that levels of NP in US surface waters even at that time were almost always below EPA’s final chronic WQC value of 6.6 µg/L. The analysis, which included samples taken by the US Geological survey and other researchers found that only five locations in the country (less than 0.5% of the 1255 samples tested), had NP concentrations above 6.6 µg/L. In fact, NP was not even detected in 53% of samples tested. (Klecka, 2007) As discussed earlier in these comments, the concentrations in surface water today are expected to be even lower than those reported in the Klecka et al, 2007 paper due to declining use of NPEs in cleaning and detergent products.

6.0 OP is a Toxicity Category 4, APERC is not aware of studies finding OP in U.S. drinking water and it does not pose a human health risk from any source based on human biomonitoring results; therefore it does not pass the screen to move onto the CCL4.

Currently the EPA Screening Document for CCCL4 states that no health effect data are available for OP, which is not accurate.

The UK Environmental Risk Assessment for OP conducted an environmental risk assessment, which includes a useful review of the mammalian toxicity studies for this compound. (UK, 2005) and identifies a NOAEL for mammalian risk assessment, based on a two-generation study on rats with exposure through food (Tyl, 1999). The NOAEL in the Tyl et al, 1999 study is 15 mg/kg-bw/day, The UK Risk Environmental Risk Assessment indicates that this NOAEL is supported by the results of two shorter (28 and 29day) oral gavage studies. The UK Authority notes that “both of the gavage studies have NOAEL values of 15 mg/kg/day, which were for relatively minor effects and the next tested levels were 70 and 150 mg/kg/day”. The UK Authority also notes that a study by Sharpe et al (1995) is “not considered valid in view of the later comments from the authors.” The UK Authority also views “the significance of effects seen at lower doses on sperm (tail abnormalities) in a drinking water study by Blake et al, 2004 to be unclear based on that study itself”. (UK, 2005) It goes on to note that no effects on sperm numbers or morphology were seen in the two generation rat study by Tyl et al (1999) , where the dose levels overlap those at the higher end in the drinking water study by Blake et al (2004) and there were no effects on reproduction overall. The UK Risk Assessment relies on the NOAEL of 15 mg/kg/day from the 2-generation Tyl study for their mammalian risk assessment from environmental sources. (UK, 2005)

Based on this most sensitive NOAEL of 15 mg/kg-bw/day , OP is a Toxicity Category 4, which specifies a NOAEL/LOAEL range of 10 - <1000 mg/kg-bw/day.

OP has been detected in surface water a frequency and concentrations less than that of NP, well below 1 µg/L; however is not detected in drinking water. (Klecka, 2007; Snyder, 2008)

Snyder et al (2008) calculated a Drinking Water Equivalent Level (DWEL) of 5,300 for OP based on a LOAEL, of 15 mg/kg-bw/day, which was actually a NOAEL, from the same 3-generation rat study by Tyl et al, 1999. Since OP was not detected in drinking water in this study a margin of safety of $> 1.2 \times 10^5$ was calculated based on the analytical Limit of Detection (0.025 µg/L).

It is pertinent to note that the US Centers for Disease Control (CDC) indicates that OP has been largely undetectable in human biomonitoring (urine) and is therefore no longer reporting for this compound under the National Report on Human Exposure to Environmental Chemicals

Considering that OP is a Toxicity Category 4 compound that is not detected in drinking water or in human biomonitoring studies in the U.S., it does not warrant passing to the CCL4.

7.0 Both NPE and OPE are Toxicity Category 4 and are not detected in surface water at concentrations greater than the corresponding occurrence threshold (100 µg/L); therefore neither compound passes the screen to move onto the CCL4.

NPE and OPE are significantly less toxic than their synthesis reactants and degradation intermediates NP and OP. Both NPE and OPE have been assessed and cleared for certain inert ingredient tolerance exemptions for use on growing on crops. (U.S. EPA OPPTS, 2006, July 31; U.S. EPA OPPTS, 2012, May 11). Inert reassessments are conducted in order to determine the risks from aggregate exposure to pesticide inert ingredients. The Agency considers the toxicity of the inert in conjunction with possible exposure to residues of the inert ingredient through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings. If EPA is able to determine that a finite tolerance is not necessary to ensure that there is a reasonable certainty that no harm will result from aggregate exposure to the inert ingredient, an exemption from the requirement of a tolerance may be established.

After its reassessment of NPE under the Federal Food, Drug and Cosmetic Act (FFDCA), EPA recommended that four exemptions from the requirement of a tolerance established for residues of NPE can be considered as safe under section 408(q) of the FFDCA. (2006, July 31) Also, an exemption from the requirement of a tolerance was established for residues of OPE (called α -[p-(1,1,3,3-tetramethylbutyl)phenyl]- ω -hydroxypoly (oxyethylene) in the assessment) when used as an inert ingredient at levels not to exceed 7% in pesticide formulations applied to growing crops and raw agricultural commodities after harvest under 40 CFR 180.910. (2010, April 5)

The EPA OPPTS inert reassessments for NPE and OPE provide a summary of the available toxicity data for these compounds. NPE are classified as slightly toxic or non-toxic for acute

exposure and LD50 values for varying NPE ethoxylates range from 1680 to over 5000 mg/kg-bw/day. (U.S. EPA OPPTS, 2006, July 31). Developmental/teratology studies were conducted on nonylphenol ethoxylates. None of the studies showed any sensitivity in developing animals. There were no maternal or fetal effects at any dose level for NP30EO up to the limit does of 1000 mg/kg-bw/day. For NP9EO, the lowest dose level of 50 mg/kg-bw/day was determined to be the NOEL for both maternal and developmental effects. The LOAELs for both NPE4EO and NP9EO were 250 mg/kg-bw/day for both maternal and developmental effects. (US EPA OPPT, 2006, July 31)

The available toxicity data indicate that OPE inerts have low to moderate acute oral toxicity. (US EPA OPPTS, 2010, April 5) The inert reassessment concludes regarding the parent compound, OPE that there was no increased susceptibility to the offspring of rats following pre- and post-natal exposure in an OECD 422 combined repeated dose toxicity study with the reproduction developmental toxicity screening test. The offspring effects (decreased body weight in male and female offspring) occurred at 300 mg/kg/day in the presence of maternal toxicity, which was manifested as clinical signs, decreased body-weight gain, increased liver weight and liver hypertrophy in males, and decreased thymus weight in females at 300 mg/kg/day. (US EPA OPPTS, 2012, May 11) EPA OPPTS selected the point of departure from the OECD 422 study based on a NOAEL of 150 mg/kg/day and decreased body-weight gain in both sexes during the premating period, decreased thymus weight in females, and increased liver weight and liver hypertrophy in males at the LOAEL of 300 mg/kg/day. The OPE reassessment also relies on the reproduction study on the degradant OP by Tyl *et al.* (1999), which was discussed earlier in these comments.

Both NPE and OPE are Toxicity Category 4 (LD50 500 - < 5000 mg/kg, NOAEL/LOAEL 10- <1000 mg/kg-bw/day) for the purposes of the CCL4 screening prioritization.

Klecka et al (2007) also looked at concentrations of NPE and OPE in aggregate with NP and OP in U.S. surface waters. The authors founds, based on a conservative evaluation that 97% of the samples contained aggregate NP-equivalent of NP, OP, OPE and NPE concentrations below 6.6 µg/L, suggesting that on a nationwide basis there were generally a low concentrations of these

compounds in U.S. surface water, even at that time, before reductions in the use of NPE in high emission uses such as cleaning products and laundry detergent. (Klecka, 2007)

8.0 EPA's assessment of NP under the CCL4 process raises issues with the CCL4 screening process related to the transparency of the data sources and the basis of determinations for the screening assessments; issues with relying on the RTECS® database without careful review of primary sources; and issues with relying on less relevant occurrence/exposure data when drinking water monitoring data are available.

As discussed above in Section 1.0 of these comments the reference provided by EPA for the erroneous 2 mg/kg-bw/day LOAEL listed on the CCL4 Contaminant Information Sheet for NP was a citation to RTECS® (lacking the authors' name) that, once tracked down, was related to a paper by Nagao et al, 2001. However, RTECS® did not list either a LOAEL or a TDLo of 2 mg/kg-bw/day for this study. Further review of RTECS® found a TDLo of 2 mg/kg related to a different study by Laurenzana et al, 2002. So, there was a lack of transparency in the documentation EPA provided to support the use of a LOAEL of 2 mg/kg-bw/day for NP. In fact, neither study provides a basis for a LOAEL of 2 mg/kg-bw/day, which resulted in the CCL4 screening assessment being based on an erroneous toxicity value and an incorrect Toxicity Category.

RTECS® is a compendium of data extracted from the open scientific literature. The data are recorded in the format developed by the RTECS staff and arranged in alphabetical order by prime chemical name. Six types of toxicity data are included in the file: (1) primary irritation; (2) mutagenic effects; (3) reproductive effects; (4) tumorigenic effects; (5) acute toxicity; and (6) other multiple dose toxicity. Specific numeric toxicity values such as LD50, LC50, TDLo, and TCLo are noted as well as species studied and route of administration used. For each citation, the bibliographic source is listed thereby enabling the user to access the actual studies cited. However, no attempt is made to evaluate the studies cited in RTECS®. The User Guide for the database clearly states that the user has the responsibility of making such assessments. (Accelrys, 2012, April 10)

APEREC cautions that the values in RTECS[®] should be confirmed by careful review of primary sources by an EPA toxicologist to confirm they are valid and appropriate for use in assigning CCL Toxicity Categories to chemicals. In addition, the primary source of the data should be cited in a clear and transparent manner in the Contaminant Information Sheets and the CCL Screening Documents rather than the RTECS[®] database.

Finally, EPA's reliance on a single worst-case and out-of-date surface water monitoring value of 40 µg/L as representing occurrence of NP in drinking water is inappropriate and unnecessary given that drinking water monitoring data are available for this compound.

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