Comments of the

European Council for Alkylphenols and Derivatives

and

the Alkylphenols & Ethoxylates Research Council

On the Draft Background Document for 4-Nonylphenol, Branched and Linear, Ethoxylated, Developed in the Context of ECHA's Sixth Recommendation for the Inclusion of Substances in Annex XIV (September 2, 2014)

Submitted November 29, 2014

Executive Summary

The European Council for Alkylphenols and Derivatives (CEPAD) and the Alkylphenols & Ethoxylates Research Council (APERC) jointly submit these comments in objection to the European Chemicals Agency (ECHA) proposal to prioritize 4-Nonylphenol (NP), branched and linear, ethoxylated, more commonly known as nonylphenol ethoxylates (NPEs), for Authorisation under Annex XIV of REACH.

The Draft Background Document proposing the prioritization of NPEs for Authorisation provides rankings assigned by ECHA for the intrinsic properties, volumes in commerce in the EU, and dispersiveness of use of these compounds. As discussed below in these comments the background document overstates the priority assigned to the intrinsic properties and dispersiveness in the use of NPEs in the EU; therefore these assigned prioritization scores, as well as the total score overstate the need for prioritization of NPEs.

NPEs do not themselves meet any of the inherent toxicity criteria for prioritization. NPEs are not persistent (P) or bioaccumulative (B), nor are they carcinogenic (C), mutagenic (M) or reproductive (R) toxicants. NPEs were designated as "of equivalent concern" under Article 57(f) on the basis that nonylphenol (NP), one of their degradation intermediates, was previously designated as a Substance of Very High Concern (SVHC) due to concerns for endocrine activity in the environment. A closer look at the data now available for NP provides evidence that it operates by several modes of toxicity, not just an estrogenic mode of action, within the same environmental concentration ranges, and that thresholds are evident for both its estrogenic activity and apical endpoints. Therefore, NP does not impart a special or more sensitive toxicity in aquatic species than its other co-occurring mechanisms of toxicity. For these reasons, the score applied to NPEs for inherent properties (IP) in the Background Document overstates their need for prioritization.

In addition, the Draft Background Document applies a score for Wide Dispersiveness of Uses (WDU) for NPEs that overstates the dispersiveness of the uses of NPE that remain in the EU. It does not consider that other existing regulatory instruments are already in place in the EU that

restrict dispersive uses of NPEs (EP&C, 2003, June 18) and control site specific emissions of NPEs and its degradation intermediate NP (EP&C, 2000, 23 October; EP&C1996, September 24). It also does not consider ongoing consideration of restrictions on textile articles containing NPE, which may be forthcoming. (SCA, 2013, July 29; RAC, 2014, June 3)

Also, the uses of NPE that remain in the EU are not as widely dispersive as indicated by the WDU score in the Background document and should be refined and reduced.

The Draft Background Document for NPEs also does not adequately consider available environmental monitoring data that indicate that NP, a degradation intermediate of NPEs and the actual compound of interest, do not support a need to prioritize NPEs under Annex XIV.

The following comments provide further explanation about why the Background Document overstates the hazard and dispersiveness of NPE and why these compounds do not warrant prioritization for Authorisation, especially given the already extensive restrictions in place on the use and emissions of NP and NPE in the EU and the potential for their forthcoming restriction in textile articles.

1.0 THE PRIORITIZATION SCORE IN THE BACKGROUND DOCUMENT FOR NPES OVERSTATES THE HAZARD OF THEIR INTRINSIC PROPERTIES.

For the purpose of prioritization for Authorisation, the hazard information that is available for a substance is scored (ranging from 0 to 15) and then the volume and dispersive use scores are added to obtain a total score. The total score can be seen as a proxy for potential risk to human health or the environment. Following are the scoring criteria for inherent properties as listed in the ECHA General Approach for Prioritisation of SVHCs for Inclusion in the List of Substances Subject to Authorisation (ECHA, 2014, February 10).

Inherent Properties under Article 57	Category	Score
57(a) Carcinogen Cat. 1 or 2; 57(b) Mutagen Cat. 1 or 2; 57(c) Reproductive Toxicant, Cat 1 or 2; 57(f) "of equivalent concern but <u>not</u> endocrine disruptors"	Low	1
57(f) "of equivalent concern" for endocrine disruptor	Medium	7

57(d) PBT or 57 e) vPvB	High	13
57(d) PBT and at least one other SVHC property	High	15
57(e) vPvB and at least one other SVHC property	High	15

The ECHA Background Document on NPEs gives a total inherent property score of 7 for these compounds on the basis that "NPE meet the criteria of Article 57(f) because through their degradation they are substances with endocrine disrupting properties and cause probable serious effects to the environment, which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH". (ECHA, 2014, September 1) The General Approach to Prioritisation of SVHCs for inclusion in the Annex XIV Authorisation List states that a score of 7 (medium) for compounds with "endocrine disrupting (ED) properties" is assigned to reflect the "current focus on concerns related to substances having with ED properties". (EHCA, 2014, 10 February) While this explanation does not provide a scientific basis for why endocrine active compounds categorized under Article 57(f) as giving "rise to an equivalent level of concern" (emphasis added) as CMRs are assigned a greater prioritization score of 7 (medium) rather than an equivalent score of 1 (low) the presumption is that there is concern that endocrine activity affords a special type of ecotoxicity or that endocrine mediated effects are more sensitive than traditional apical effects.

As discussed below, neither NPE nor NP meet the criteria for designation as a SVHC under Article 57(a) – (e) of REACH. In addition, the weak estrogenic activity of NP does not impart special or more sensitive toxicity in aquatic species. A closer look at multiple lines of evidence now available for NP indicates that it operates by several modes of toxicity, not just an estrogenic mode of action. In addition, adverse apical effects and biomarkers due to estrogenic mode of action occur within the same exposure concentration ranges and thresholds are evident for both its estrogenic activity and apical endpoints.

1.1 Neither NPEs nor their degradation intermediate NP meet the criteria for designation as a SVHC listed under Article 57 (a) – (e) of REACH.

NP and NPE do not meet the criteria under the carcinogenic category under Article 57(a), which means GHS carcinogen categories 1A or 1B. Nor do they meet the mutagenic criteria under Article 57(b), which means GHS mutagen categories 1A or 1B. NP and NPE also do not meet the criteria for reproductive toxicant under Article 57(c), which means GHS reproductive toxicant categories 1A or 1B. In addition, as described in companion papers by Staples *et al* 2008 and Klecka *et al* ,2008 that review the persistence and bioaccumulation potentials for NP and NPEs, neither of the parent compound NPE, nor any of its biodegradation metabolites, meet various regulatory criteria for PBT or vPvB compounds, including those criteria listed in Annex XIII of REACH and under Article 57(d) and (e).

1.2 While NP has weak estrogenic activity, the adverse apical effects observed in fish exposed to NP are not clearly endocrine mediated, and the weak estrogenic activity of NP does not impart special or more sensitive toxicity in aquatic species.

NPEs were not identified as a SVHC under Article 57(f) of Regulation (EC) 1907/2006 (REACH) due to any concern for their own intrinsic properties or hazards. NPEs were identified as a SVHC "because (through their degradation) they are substances with endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which give rise to an equivalent level of concern to those of other substances listed under Article 57(a) through (e) of REACH" (ECHA, 2013, June 13). Therefore the concern is actually with NP, the degradation intermediate, not with NPEs themselves. Since NPEs do not themselves meet any of the inherent toxicity criteria for prioritization, this should be basis enough not to prioritize these compounds for Authorisation.

Given the focus of concern for NPEs is the estrogenic activity of their degradant NP, it is useful to consider the estrogenic potency of NP when developing a prioritization score for Inherent Properties (IP). The estrogenic activity of NP varies depending on the assay used and is generally in the range of 1,000 - 1,000,000 fold less potent than the endogenous estrogen, 17β-estradiol (E2) (Coady *et al*., 2010; Wenzel *et al*., 2001). Therefore NP is only weakly estrogenic.

In addition, it is reasonable to consider the role of estrogenic modes of activity in the toxicity of a compound as well as whether thresholds for the estrogenic effects of a compound exist. Some argue that a threshold cannot be determined experimentally due to limitations of available test systems and in understanding the underlying biology; indeed consideration is still under way in the EU regarding whether a threshold can be determined for endocrine active compounds. The data for NP indicate that there are thresholds for its estrogenic activity and mode of action, especially in light of the availability of results using new molecular level assays designed to understand toxicity mechanisms.

In the case of NP, recent reviews of the extensive data set for this compound utilizing studies on adverse apical endpoints that can be associated with an estrogenic mode of action as well as data from new tests systems developed under the US EPA ToxCast™ program that provide further insight into the mechanisms of ecotoxicity have been conducted. (USEPA ToxCast™ , Coady *et al*, 2013; Coady *et al*, 2014a, Coady *et al* 2014b) A closer look at multiple lines of evidence now available for NP indicates that it operates by multiple modes of toxicity, not just an estrogenic mode of action. The findings indicate that the estrogenic activity of NP does not impart a special or more sensitive toxicity in aquatic species than other co-occurring mechanisms of toxicity. In addition, adverse apical effects (i.e., reproduction) and biomarkers (i.e., vitellogenin and histopathological effects) potentially due to the estrogenic activity of NP occur within the same exposure concentration ranges as effects not estrogenically mediated (i.e., survival and growth). Therefore, while NP has weak estrogenic activity, the adverse apical effects observed in fish exposed to NP are not clearly estrogenically mediated and thresholds exist for its adverse effects and biomarkers of its estrogenic activity.

1.2.1 Several lines of evidence support that NP has multiple modes of action and that the adverse effects noted in toxicity studies with NP are not clearly endocrine mediated.

The difference between the ecotoxicity modes of action for NP versus E2 is clear based on their vastly different acute to chronic ratios (ACR). The ACRs for NP are 22 to 116, depending on the species tested, and the ACR for E2 is 5,730,000. (Coady *et al*, 2014b) This is explained by the

weak estrogenic activity of NP and the non-endocrine modes of toxicity, which have been identified for NP including narcosis, or baseline toxicity (Soares *et al*, 2008; Talmage, 1994).

Recently Coady *et al*, 2014a undertook a weight of evidence approach in order to determine the relevance of the weak estrogenic activity of NP in the context of assessing risk for both humans and environmental organisms. An evaluation of the genomic and high through-put molecular responses, as well as the *in vivo* toxicological data sets for NP demonstrated that other modes of action, apart from endocrine activity, are influential in both human health and environmental hazard assessment of this compound. Molecular evidence in both mammalian and fish models have demonstrated that NP influences a greater suite of genes than estrogens. For example, 425 genes were differentially expressed in liver tissue from zebrafish exposed to 10^{-7}M NP, while 153 genes were differentially expressed in liver tissue from zebrafish exposed to 10^{-7}M E2. Of the 30 most differentiated genes affected by NP compared to controls, only 1/3 of these genes were also altered among E2-exposed fish, and then not all in the same direction of change. (Ruggeri *et al*., 2008).

The relevance of multiple modes of toxicity in NP is particularly apparent when examining the effects in higher-tiered, definitive toxicity tests (chronic, multigenerational *in vivo* studies with apical endpoints), which show that chronic apical effects in fish not associated with an endocrine mode of action (i.e., survival and growth) and those potentially associated with an endocrine mode of action (i.e., reproduction) occur within similar concentration ranges. Table 1 below in these comments shows that No Observed Effect Concentrations (NOECs) from valid chronic toxicity studies in fish range from 1-100µg/L for survival, 6-126 µg/L for growth and 1-183 µg/L for reproduction. (Coady *et al*, 2013; Coady *et al*, 2014a, Coady *et al*, 2014b) Exposure biomarker endpoints in fish, which are not indicators of population level adverse effects, also occur within the same concentrations with vitellogenin induction in fish occurring in the range 1-100 µg/L and alterations in fish gonadal histopathology occurring in the range 1.6 – 100 µg/L. (Coady *et al*, 2014b) Other modes of toxic action, such as interference with membrane permeability and active transport are notable and other biological targets besides the estrogen receptor (*i.e.* mitochondrial toxicity) also appear to be important for determining NP toxicity *in vivo.* (Coady *et al*, 2013; Coady *et al* 2014a)

Coady *et al*, 2014a also found that the weak estrogenic activity of these compounds is not definitively linked to the critical effect (point of departure) in both mammalian and non-mammalian hazard assessments. This analysis suggests that apical effects observed, for example, in Tier 2 or Tier-2 type tests may not be reflective of an endocrine mode of action, particularly in the case of industrial compounds that are not designed to have a specific biological activity.

The weight of evidence case study with NP presented by Coady *et al*, 2014a illustrates the need to incorporate the concepts of potency, critical effect, exposure, and risk to support decision-making regarding determinations of endocrine disruption and assessments of human health and environmental impacts. These same concepts are useful in assessing compound for prioritization for Authorisation.

1.2.2 Various studies show dose-response and clear thresholds for endocrine activity and adverse effects for NP in aquatic species.

The data set available for NP allows for a comparison of adverse effects and the dose or exposure levels necessary to induce them in different organisms. These adverse effect levels with NP can also be compared with potencies and apparent thresholds for various potential modes of toxic action, including the potential for an estrogenic mode of action. An examination of the toxicity data set for environmental organisms reveals that adverse effects, which are not necessarily specific to estrogenic activity, occur at doses below the thresholds necessary for adverse effects that are clearly mediated by estrogenic activity. In other words, non-estrogenically mediated effects of NP are more sensitive than those that are likely due to an estrogenic mode of action.

Based on the results of targeted *in vitro* studies, NP has shown a weak binding affinity for the nuclear estrogen receptor, and can at sufficient concentrations also cause subsequent estrogen-receptor dependent transactivation (Recchia *et al* , 2004; Olsen *et al* , 2005; Preuss *et al*, 2006; Van den Belt *et al* , 2004; USEPA, 2009). The estrogenic activity of NP varies, depending on

the assay used to measure it and is generally in the range of one thousand to one million-fold less potent than the endogenous estrogen, E2. (Coady *et al*., 2010; Wenzel *et al*., 2001).

Based on *in vivo* tests and consistent with NP's known potential to bind and activate the estrogen receptor, NP exposure can increase circulating levels of vitellogenin (VTG) in fish. VTG is a yolk-precursor protein normally expressed in female oviparous species that has been demonstrated to be a highly responsive biomarker for estrogen receptor agonists, especially in male fish that carry the VTG gene but do not ordinarily express it (Jobling and Sumpter, 1993; Harries *et al*., 2000; Dussault *et al*., 2005; Olsen *et al*., 2005). VTG is induced among various fish species at concentrations of NP ranging from 1 to 100 μg/L (Coady *et al*., 2010; USEPA, 2007; Karels *et al*., 2003; Jobling *et al*., 1996; Rasmussen *et al*., 2002; Seki *et al*., 2003). In addition, reports of histopathological changes among gonadal tissues in fish exposed to NP have been reported in the range of 1.6 to 200 μg/L (Miles-Richardson *et al*., 1999; Gray and Metcalfe, 1997; Jobling *et al*., 1996; Staples *et al*., 2004; USEPA, 2007; Rasmussen *et al*., 2005; Karels *et al*., 2003; Rasmussen *et al*., 2002). While the observation of increased VTG in male fish and the occurrence of altered gonadal histopathology can inform upon one of the potential estrogenic modes of action of NP, these biochemical and histopathological endpoints have not traditionally been used as indicators of adverse effects in ecological risk assessments. For NP the threshold for estrogenic activity (measured as induction of the yolk-precursor protein, VTG, and alterations in gonadal histomorphology) in fish is in the range of 1 to 200 μg/L.

1.2.3 While the dose-response relationship for effects of NP indicates thresholds for endocrine activity, the critical effects for NP and OP are not necessarily endocrine-mediated.

While NP has weak estrogenic activity, adverse effects in aquatic organisms that are caused by these compounds are not necessarily mediated through this mode of action. The data for NP demonstrate clear exposure thresholds, which are necessary to induce biomarkers of estrogenic activity such as VTG and altered gonadal histopathology. Higher exposure thresholds are generally necessary to induce estrogenically mediated adverse effects on survival, growth and

reproduction. The existence of thresholds for endocrine related activity and effects is consistent with the endocrine mechanisms described by Borgert *et al*, 2013.

In chronic fish studies, NP affects reproductive endpoints, such as sex ratio and spawning activity, at concentrations similar to those that affect growth and survival (See Table 1). Effects on growth and survival, as pointed out by the OECD Guidance Document on the assessment of chemicals for endocrine disruption, do not lead to a conclusion of endocrine disruption in fish (OECD, 2011). Thus, the endocrine activities of NP via binding to the estrogen receptor are not clearly the critical effect responsible for observed adverse effects in fish. In fact, the European Chemicals Bureau (ECB) Assessment on NP stated: "Concentrations of nonylphenol at which oestrogenic effects are observed appear to be higher than those producing other effects" (ECB, 2002).

Data in Table 1 show a range of NOECs from 1 to 183 µg/L across all apical endpoints, regardless of mode of toxicity (Coady *et al*., 2013). This supports the understanding that multiple modes of toxicity are relevant for NP and those apical effects known to be impacted by an estrogenic mode of action are not more sensitive than those not impacted by an estrogen mode of action.

Table 1. NOECs for Apical Endpoints and Estrogenic Biomarkers for NP in Fish

Fish NOEC Values for Apical Endpoints	NP (µg/L)	References
NOEC (Growth)	6 – 126	Brooke, 1993a; Harries *et al*., 2000; Ward and Boeri, 1991b; Brooke *et al*, 1993b; Balch and Metcalfe, 2006; Nimrod and Benson, 1998; Yokota *et al*, 2001; Seki *et al*., 2003; Lin and Janz., 2006; Zha *et al*., 2007 *Coady et al*, 2013
NOEC (Survival)	1 – 100	Harris *et al*., 2001; Brooke, 1993a; Schwaiger *et al*., 2002; Harries *et al.*, 2000; Ward and Boeri, 1991b; Brooke, 1993b; Giesy et al., 2000; Balch and Metcalfe, 2006; Nimrod and Benson, 1998; Yokota *et al*, 2001; Seki *et al*., 2003; Lin and Janz., 2006; Zha *et al.*, 2007; Moore *et al*., 2003; Afonso *et*

		al., 2002); Coady *et al*, 2013
NOEC (Reproduction)	1 – 183	Brooke *et al*, 1993a; Schwaiger *et al*., 2002; Harries *et al*., 2000; Giesy *et al.*, 2000; Balch and Metcalfe, 2006; Nimrod and Benson, 1998; Yokota, 2001; Seki *et al*., 2003; Lin and Janz., 2006; Afonso *et al.*, 2002; Shioda and Wakabayashi, 2000; Coady *et al*, 2013
Fish NOEC Values for Estrogenic Biomarkers	NP (µg/L)	References
NOEC (VTG induction)	1 - 100	Coady *et al*., 2010; Jobling *et al*., 1996; Seki *et al*., 2003
NOEC (Gonadal histopathology)	1.6 -100 µg/L	Miles-Richardson *et al*., 1999; Gray and Metcalfe, 1997; Jobling *et al*., 1996; Staples *et al*., 2004.

1.2.4 Thresholds exist for the estrogenic activity and the adverse apical effects of NP in aquatic species

Based on the wealth of biochemical, histological, developmental, and toxicity data available for NP, clear exposure and dose thresholds can be determined for endocrine-related effects and other toxicities observed with these compounds. From an examination of these data, threshold values for estrogen-specific endpoints in fish (i.e. alterations in VTG, gonadal histopathology) were apparent and occur against a background of non-endocrine mediated effects. (See Table 1)The existence of endocrine thresholds in this compound are explained by the fundamental principles of endocrine pharmacology. (Borgert *et al*, 2013) The adverse effects of this weakly endocrine active compound collectively integrate various molecular interactions (endocrine and non-endocrine) and by examining the wealth of aquatic toxicity data available for NP, threshold values can be derived for both estrogenic activity (although these are not necessarily relevant for risk assessment) and for the protection from adverse effects for both human health and the environment.

1.3 Environmental Quality Standards (EQS) have been established for NP under the Water Framework Directive (WFD), which are protective of adverse effects due to the estrogenic activity of this compound and can be used for hazard and risk assessment.

Under the WFD an Annual Average Environmental Quality Standards (AA-EQS) of 0.3 µg/L and a Maximum Allowable Environmental Quality Standard (MA-EQS of 2.0 µg/L) have been established for NP (EP&C, 2008, December 16) The WFD AA-EQS is more conservative (i.e., lower than) the proposed Predicted No Effect Concentration (PNEC) of 0.4 µg/L developed by the European Chemicals Agency Committee for Risk Assessment (RAC) in its Opinion on the Annex VX dossier proposing restrictions on NP and NPE in textile articles. (RAC, 2014, June 3). The AA-EQS value for NP is set at a value that is also protective of the weak estrogenic activity of this compound.

2.0 THE PRIORITIZATION SCORE FOR WIDESPREAD DISPERSIVE USES (WDU) IN THE BACKGROUND DOCUMENT OVERSTATES THE DISPERSIVENESS OF THE USES OF NPE THAT REMAIN IN THE EU; FURTHERMORE IT DOES NOT CONSIDER EXISTING REGULATORY RESTRICTIONS OR THE MINIMALLY DISPERSIVE CONSUMER USES THAT REMAIN IN THE EU.

The Draft Background Document for NPEs does not consider that other existing regulatory instruments are already in place in the EU that restrict dispersive uses of NPEs (EP&C, 2003, June 18) and control site specific emissions of NPEs and its degradation intermediate NP (EP&C, 2000, 23 October and EP&C, 1996, September 24) It also does not consider potentially forthcoming restrictions on textile articles containing NPE (SCA, 2013, July 29; RAC, 2014, June 3). The WDU Prioritization Score for NPE in the Background Document also does not consider that the emissions from the use of NPE in paint, both Professional (PROF) and Consumer (CONS) are minimally dispersive. Article 58(3) provides for discretion regarding the development and design of a prioritisation approach that in the end provides the Candidate Substances for which the recommendation to include them in Annex XIV is most relevant and appropriate. Therefore, the WDU prioritization scores for NPEs should be refined and lowered to reflect a lesser degree of dispersiveness and therefore lesser potential risk.

2.1 The tonnage of NPEs used in the EU has been steadily declining, primarily due to their restriction in dispersive uses under the Marketing and Use (EU Dir. 2003/53/EC, 2003, June 18).

The Annex XIV Background Document for NPE acknowledges that since there are no registrants for NPE under REACH, information on volumes, uses and the supply chain are lacking. Therefore, based on the estimated fraction of NP used to manufacture its ethoxylates, the volume of NPEs produced is assumed in the Background Document to be in the range of 10,000 – 50,000 t/y. Based on this tonnage estimate the Background Document scores NPE as "very high" with a score of "15".

Due to antitrust regulations, APERC and CEPAD cannot share market and volume information directly; however based on market reports, NPE use declined in use in Central and Western Europe by 57% between 2005 and 2013 (Colin A. Houston & Associates, Inc., 2013, December). The same report indicates that the NPE volume in 2013 was estimated at less than 20,000 tons and was projected to continue declining. This drastic decline in the volume of NPE used in the EU since 2005 is due primarily to restrictions of their marketing and use under EU Directive 2003/53/EC (EP&C, 2003, June 18), which focused on restricting the dispersive uses of these compounds that result in entry into the environment, which were identified in the EU Risk Assessment for NP and NPE. (ECB, 2002)

The Market and Use Directive stated that NP and NPE "may not be placed on the market or used as a substance or constituent of preparations in concentrations equal or higher than 0,1 % by mass for the following purposes:

(1) industrial and institutional cleaning except:

— controlled closed dry cleaning systems where the washing liquid is recycled or incinerated,

— cleaning systems with special treatment where the washing liquid is recycled or incinerated;

(2) domestic cleaning;

(3) textiles and leather processing except:

— processing with no release into waste water,

— systems with special treatment where the process water is pretreated to remove the organic fraction completely prior to biological waste water treatment (degreasing of sheepskin);

(4) emulsifier in agricultural teat dips;

(5) metal working, except uses in controlled closed systems where the washing liquid is recycled or incinerated;

(6) manufacturing of pulp and paper;

(7) cosmetic products;

(8) other personal care products, except spermicides;

(9) co-formulants in pesticides and biocides.

The Market and Use Directive for NP and NPE focused the major dispersive uses with potential to enter the environment and any remaining uses of NPE are not highly dispersive. Therefore the WDU prioritization score in the Background Document overstates the dispersiveness of the remaining uses of NPE in the EU, even those that fall into the CONS category.

2.2 ECHA restrictions on NPE in textile articles are currently under consideration and should be reflected in the WDU prioritization scoring for NPE.

The Background Document mentions that NPEs are also "used in articles" as justification for a WDU score of 15. While no detail is provided in the Background Document as to what types of articles might contain NPE, the most notable use of NPE in articles that can result in dispersive environmental emissions is residual levels of NPE that remain on textile articles after their use as textile processing aids. Recent opinions were recently issued by the Committee for Risk Assessment (RAC) and the Committee for Socio-economic Analysis (SEAC) supporting an Annex XV proposal to restrict textile articles that contain NPE at equal to or greater than 0.01% by weight. (RAC, 2014, June; SEAC, 2014, September 9; SCA, 2013, July 29). While this restriction is still under consideration, the opinions signal the possibility of forthcoming EU-wide restrictions that will address the presence of NPEs in textile articles.

Justification for the restriction of NPE in textile articles relies on assumptions about the overall amounts of NP thought to arise in the environment from NPE released by textile washing in comparison to other sources. The RAC concluded that textile laundering appears to contribute up to approximately 30% of the amount of NP in EU surface waters. (RAC, 2014, June). So, it appears that the proposed restriction of the use of NPE in textile articles, if adopted, will address what the RAC considers to be a substantial source of these compounds to the aquatic environment.

2.3 The prioritization score for WDU in the Background Document for NPEs overstates the dispersiveness of the Consumer (CONS) uses of NPEs that remain in the EU; therefore it should be refined and reduced to more accurately reflect a minimal degree of dispersiveness and risk from the remaining use of NPE in consumer products.

The General Approach for Recommending Substances for Authorisation determines the dispersiveness of uses based on the "types of actors", or categories of use. There are three main use types: industrial (IND)[1], professional (PROF)[2] and consumer (CONS)[3] uses. CONS uses are defined as including "the use of substances as such or in mixtures carried out by consumers leading to dispersive uses." (ECHA, 2014, February 10)

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[1] ***Industrial use (IND)****: Application of the substance as such or in a mixture in an industrial process with the purpose of incorporating the substance into an article, or technically supporting the production process but not intentionally becoming part of theproduct (processing aid). As a result of the use the substance has reacted, or become part of an article, or it has been released, and/or is contained in waste from this use.Uses are carried out at industrial sites (small or large).*

[2] ***Professional use (PROF)****: Application [...] in skilled trade premises. Professional usemay include the use of substances as such or in mixtures, in order to deliver services tobusiness or private customers. This may include sophisticated equipment andspecialised, trained personnel. Uses by professional workers are considered to take place in a wide-dispersive manner. Compared to the use at single industrial sites, wide dispersive uses take place everywhere (corresponding to a municipal structure) by multiple actors each at low scale. The risk management capacity of the single actor is low, e.g. there is no site-based technical infrastructure to control releases.*

[3] ***Consumer use (CONS)****: includes the use of substances as such or in mixtures carried out by consumers leading to dispersive uses. It is assumed that the user is not trained. Use can take place in closed systems (lubricants for vehicles or hydraulic systems) or open systems (lubricants for bicycles). It may also include processing of material.*

The Draft Background Document draws information about the uses of NPEs from the registration information for NP and from information from the Annex XV report for NPE. (BAuA, 2013, March 1). It briefly justifies a score of 15 for WDU stating NPE "are used at industrial sites and by professional workers and by consumers… and the substances are used in articles". The score of 15 is presumably driven by the use of NPEs in consumer paint products, which is identified as the only example of a consumer use in the Background document. However, the EU Risk Assessment on NP assessed the environmental risk of the use of NPE in consumer and industrial paints and concluded there "is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already". (ECB, 2002) Also, regarding the human health risk from the use of NPEs in consumer products, the EU Risk Assessment also concluded that "there is at present no need for further information and/or testing for risk reduction measures beyond those which are being applied already" based on the fact that "there are sufficiently large margins between actual or modeled exposures and LD50 values and N(L)OAELs, so that it can be concluded that there is no cause for concern for human health." (ECB, 2002)

Environmental exposure to NPEs from their use in paint arises primarily from cleanup activities and the majority of NPE is expected to be retained in the cured paint. This use is a minimally dispersive use in comparison to other consumer uses generally and to other previously restricted uses of NPE (i.e., cleaning and laundry products, textile and paper processing).

2.4 The WDU prioritization score in the Background Document for NPEs also overstates the dispersiveness of uses of these compounds because in addition to not considering existing and forthcoming EU regulations that already -or will - restrict and control the dispersive uses and emissions of NPE specifically, it does not consider other regulations that control NPEs more generally; the WDU score should be refined and reduced to reflect existing restrictions and regulations.

The General Approach to Prioritization of SVHC substances for Annex XIV states that the purpose of prioritization is to recommend substances on the Candidate list "in such an order that the more relevant substances are included in Annex XIV before less relevant substances". This

should certainly consider whether existing regulatory instruments restrict and control the volumes, uses and dispersiveness of the candidate chemicals and prioritize those with little or no regulation over those that are already highly regulated. As discussed above in Sections 2.1 and 2.2, the use of NPEs and NP are already highly restricted and controlled by the Market and Use Directive for these compounds and are anticipated to be subject to further restrictions in textile articles.

The remaining uses of NPE in the EU are primarily industrial (IND) with releases limited to particular industrial sites, which are also subject to additional regulations that affect the release of NPEs. Directive 96/61/EC concerning integrated pollution prevention and control (IPPC Directive) is intended to achieve integrated prevention and control of pollution arising and lays down measures designed to prevent or, where that is not practicable, to reduce emissions in the air, water and land in order to achieve a high level of protection of the environment taken as a whole. (EP&C, 1996) Annex I of the IPPC Directive lists categories of industrial activities subject to regulation by the Directive. Surfactants and surface active chemicals are specifically covered under Annex I. Since NPEs are surfactants they are specifically covered by the IPPC Directive. Other categories of industrial activities that are subject to the IPPC Directive that are relevant to the use of NPEs in paint and coatings include the chemical industry, including basic polymers and dyes and pigments. Industrial activities subject to the IPPC Directive where NPE use is <u>not expected</u> due to the Market and Use Directive mentioned earlier in these comments include industrial plants that process pulp and paper, plants for the pre-treatment or dyeing of fibers and textiles and tanning facilities. In addition, Annex III to the IPPC Directive is a list including the main polluting substances in water to be taken into account, which includes "Substances and preparations which have been proved to possess carcinogenic or mutagenic properties or properties which may affect reproduction in or via the aquatic environment". As noted in Section 1.0 of these comments, NPEs are not a C, M or R toxicant; however, if there is concern about potential reproductive effects in aquatic species, the IPPC Directive provides an existing regulatory mechanism for addressing these compounds.

Also, the WFD applies to NP, the environmental degradant of concern from NPE. (EP&C, 2000, October 23). As noted in section 1.2.4 in these comments, the WFD established an AA-EQS

value of 0.3 µg/L and a MA-EQS of 2.0 µg/L for NP in inland surface water. It requires the Members States to measure aquatic concentrations of compounds relative to these established EQS and take action in case these values are exceeded. The WFD ultimately requires that all NP emissions and discharges to water be eliminated.

Finally, NP is already going through the REACH Community Rolling Action Plan (CoRAP) Process. The CoRAP justification document for NP indicates that the evaluation will be used to "check whether all potential uses are adequately addressed and quantified, especially in comparison with available monitoring data". **(**ECHA/UKCA, 2014, March 26 updated) Considering that the CoRAP process will assess all uses of NP, not just those related to NPE it seems that the findings of this process could inform the decision about prioritizing NPE for Authorisation.

2.5 The extensive existing and possibly forthcoming EU regulations related to NP and NPE contribute to the low dispersiveness and risk from the remaining uses of NPEs (i.e., in consumer paints); this should be considered and the WDU prioritization score should be refined and reduced.

Section 5.3.1 of the ECHA General Approach for Recommendations for Inclusion of Substances on Annex XIV provides the possibility of further refinement of the WDU prioritization score if additional information is available. Therefore, considering that the highly dispersive uses of NPE have already been address through the Market and Use Directive (EP&C, 2003, June 18) and it is expected that residual NPEs in textile articles will be restricted in forthcoming regulations (RAC, 2014, June 3; SCA, 2013, July 29; SEAC, 2014, September 9), the current WDU score for NPEs overstates the dispersiveness of their uses. The WFD and the IPPC Directive also directly regulate and impose emission reductions on NP, which is the primary degradant of concern from NPE. The extensive existing and forthcoming regulations related to NP and NPE contribute to the low dispersiveness and risk from the remaining uses of NPEs (i.e., in consumer paints); this should be considered and the WDU prioritization score should be refined and reduced.

3.0 CONCENTRATIONS OF NP AND NPES IN EUROPEAN SURFACE WATERS DO NOT SUPPORT A NEED TO PRIORITIZE NPES FOR AUTHORISATION UNDER REACH, ESPECIALLY CONSIDERING EXTENSIVE EXISTING RESTRICTIONS AND THE LIKELIHOOD OF ADDITIONAL FORTHCOMING RESTRICTIONS ON NPES IN TEXTILE ARTICLES.

The proposal to prioritize NPEs for Authorisation is a significant regulatory action with considerable expected compliance and administrative costs. For this reason, it seems appropriate that adequate evidence of an EU-wide risk to the environment be provided to justify prioritization. In the case of NPE, which are already subject to significant restrictions and regulation in the EU, the recent RAC opinion indicates that the majority of EU waters contain concentrations of NP that are less than the AA-EQS for this compound and projects that expected restrictions on NPE in textile article will significantly reduce emissions to the aquatic environment in the EU further. (RAC, 2014, June) It should also be noted that all environmental monitoring results for NP represent emissions from all of its uses, not just from the use of NPEs.

3.1 NPEs were determined to be SVHC under REACH based on the argument that due to their degradation they are "an environmental source" of NP, which was previously designated as SVHC: therefore the focus of environmental monitoring is most appropriately focused on NP.

Biodegradation has been shown to be the dominant mechanism responsible for removal of NPEs, NP and other alkylphenol (AP) and alkylphenol ethoxylates (APEs) during wastewater treatment and in the environment (Staples *et al*, 1999; Staples *et al*, 2001, Staples *et al*, 2008, Melcer, *et al*, 2007). While NPEs are highly treatable in wastewater treatment plants (WWTPs), with removal rates commonly greater than 90% in those with secondary treatment, low levels of their degradation metabolites have been reported in effluent and surface waters (Melcer, 2007). These intermediates continue to degrade in the environment, including mineralization of the phenolic ring, to carbon dioxide (Ahel *et al*,, 1994, Staples, 1999, Staples, 2001, Staples, 2008, Naylor *et al*, 2006).

Considering that NP is the most toxic of the NPE degradation intermediates, and that degradation to NP is the primary reason that NPEs were proposed to be SVHC and are now proposed for prioritization for Authorisation, focus of environmental monitoring is most appropriately on NP.

3.2 An AA-EQS Value of 0.3 µg/L established under the WFD and a Risk Assessment Committee (RAC) recommended Predicted No Effect Concentration (PNEC) of 0.4 µg/L are available for NP, which can be used to assess the risk of NP in EU surface waters.

As discussed above, NP is already regulated under the WFD, which was established as a framework for European Community (EC) water policy and strategies against water pollution and requires Member States to take action for the progressive reduction of emissions of priority hazardous substances via the aquatic environment, through setting Environmental Quality Standard (EQS) values and establishing emission control measures. (EP&C, 2000, 23 October)

Under the WFD an AA-EQS of 0.3 µg/L and a MA-EQS of 2.0 µg/L have been established for NP (EP&C, 2008, December 16) The WFD AA-EQS is more conservative (i.e., lower than) the proposed PNEC of 0.4 µg/L developed by the RAC in its Opinion on the Annex VX dossier proposing restrictions on NP and NPE in textile articles. (RAC, 2014, June 3).

3.3 Results from monitoring in the EU indicate that the majority of surface water samples contain concentrations of NP that are less than the AA-EQS despite issues with bias in analytical methods that result in higher than actual values.

Results of monitoring conducted in the EU are available through monitoring conducted under the WFD. While consideration of environmental levels of SVHC compounds is not necessarily required in the prioritization process, it seems a logical factor to consider, especially for compounds such as NP that are already regulated by the WFD and have monitoring data are

available. The purpose of prioritization is to identify the Candidate Substances for which the recommendation to include them in Annex XIV is most relevant and appropriate; therefore it would seem that those substances that have monitoring data that indicate they present a widespread risk to the environment or human health in the EU, or those that are not currently monitored would warrant a greater priority. In the case of NP, the NPE degradant of interest, monitoring conducted under the WFD indicates that the majority of surface water samples in the EU do not exceed the AA-EQS for this compound, despite data bias due to a high number of nondetectable samples, which are recorded at half the analytical Limit of Detection (LOD). (RAC, 2014, June) Monitoring results are also generally in compliance with the AA-EQS and despite issues with high biases in analytical methods used to monitor for NP.

3.4 Monitoring data for NP in the EU is biased by the great number of samples that were found to be "non-detects" and reported as half the analytical MDL and the high false positive bias in analytical methods used to monitoring NP; this may be evident in the inconsistencies in reported aquatic concentrations for NP.

In the monitoring data available for NP, an overwhelming number of samples are reported as below the analytical LOD and are reported at half the LOD. In addition, evidence of a high false-positive bias in analytical methods used to measure NP in surface water raises concerns about a bias in the monitoring data reported for NP.

In addition, there is concern that inconsistencies in sampling and analytical methods may create uncertainties about the validity of the measured data. For example in the Annex XV proposal to restrict NPE in textile articles, a freshwater Predicted Environmental Concentration (PEC) reported for Finland of 1.54 µg/L is thirty times higher than the PEC of 0.05 µg/L for neighboring Sweden. (SCA, 2013, Jul 29) As a reality check of the data, this does not make sense. The marine PEC for Finland (based on 2 samples) is also almost twice that of Denmark, the only other country with detectable NP in marine samples. This type of discrepancy should prompt measures to confirm what appears to be a potential analytical method discrepancy in the samples from Finland, or exploration of other factors that are resulting unlikely or outlier values.

The issue of analytical reliability is an important consideration relative to water monitoring for NP. A recently 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 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)

4.0 SUMMARY

The purpose of prioritization is to ensure that more relevant candidate chemicals are included in Annex XIV before those that are less relevant. Therefore, it is reasonable that there should be consideration of whether existing regulatory instruments restrict and control the volumes, uses and dispersiveness of the candidate chemicals in order to prioritize those with little or no regulation over those that are already highly regulated. It is also reasonable to prioritize candidate chemicals with evidence that environmental concentrations exceed regulatory limits and/or pose a risk in the EU.

Both NPE and NP are already highly restricted and controlled by the Market and Use Directive for these compounds and are anticipated to be subject to further restrictions in textile articles. They are also regulated under the WFD and IPPC Directive. Further regulation of NPEs is being considered for their use in textile articles and NP is in the CoRAP process.

NPEs do not meet the criteria under Article 57 on their own and were designated as SVHC only on the basis that NP, a degradation intermediate, was already a SVHC. The concern with NP relates to "probably serious effects" in the environment due to its estrogenic activity.
The concepts of potency, critical effect, exposure, and risk are useful in assessing endocrine active compounds for prioritization for Authorisation. The adverse effects of NP, a weak estrogenically active compound, collectively integrate various molecular interactions (endocrine and non-endocrine) and by examining the wealth of aquatic toxicity data available for NP along with more recent molecular assays, threshold values can be derived for both the estrogenic activity (although these are not necessarily relevant for risk assessment) and the adverse effects of this compound. While NP has weak estrogenic activity, the adverse apical effects observed in fish exposed to NP are not clearly endocrine mediated, and the weak estrogenic activity of NP does not appear to impart special or more sensitive toxicity in aquatic species. AA-EQS and MA-EQS have been established for NP under the WFD, which are protective of adverse effects due to the estrogenic activity of this compound and can be used for hazard and risk assessment.

The recent RAC opinion related to the proposal to restrict NPEs in textile articles indicates that the majority of EU waters contain concentrations of NP that are less than the AA-EQS for this compound and projects that expected restrictions on NPE in textile article will significantly reduce emissions to the aquatic environment in the EU further. (RAC, 2014, June) It should also be noted that all environmental monitoring results for NP represent emissions from all of its uses, not just from the use of NPEs.

Finally, the CONS uses of NPEs that remain in the EU are not as dispersive as the highly dispersive uses of these compounds that are already restricted under the Market and Use Directive.

All of these factors indicate that NPEs are already highly restricted in the EU and that the IP and WDU prioritization scores assigned to NPE overstate their inherent hazard and the dispersiveness of their remaining uses in the EU. Therefore, CEPAD and APERC recommend that these scores should be reduced and NPE should not be prioritized for Authorisation under Annex XIV.

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