NONYLPHENOL AND ITS ETHOXYLATES (NP/NPEs)

Comments on the **environmental sections** of the CEPA PSL Draft Assessment Report on Nonylphenol and its Ethoxylates were provided by:

1. Wildlife Toxicology World Wildlife Fund
2. Alkylphenols and Ethoxylates Research Council
3. Canadian Pulp and Paper Association.

Comments and responses are summarized below by Environment Canada. (All were based on the English version of the report).

Comment[(source)]	**Response**
NP/NPEs in pesticides should be addressed [(1)].	There is no regulatory responsibility in this area under CEPA 1999. The Pesticide Management Regulatory Agency (PMRA) administers the Pest Control Products Act, which regulates the use of pesticides in Canada. For this reason, our assessment of this "substance" did not include pesticidal uses.
The benefits of biodegradation of NPEs in municipal treatment systems are overstated[(1)].	NP/NPE degradation pathways reported in the literature have been included in the Assessment Report. The degradation pathway, leading to production of NP was indicated in Figure 2 on page 24 of the Assessment Report. Additionally, it was stated in the first paragraph that although primary degradation of NPEs in MWWTPs is readily achievable (which includes the degradation of the higher ethoxylates to lower ethoxylates, carboxylates and NP), but that ultimate biodegradation in these systems does not occur. (Page 25)
Application of contaminated sludge to agricultural land needs further assessment[(1)].	Rapid degradation of NP to CO_2 occurs following sludge application to agricultural land as a result of soil microbial activity. Continued degradation of NPEs results in NP production, therefore, a non-linear disappearance of NP is observed, although degradation under these field situations are rapid. In the conclusions of the assessment report, it is noted that application of municipal sludges containing NP/NPEs to agricultural fields may also represent a minor risk to these environments. Due

Comment[(source)]	Response
	to the relatively small risk to terrestrial environments the assessment was focussed on aquatic environments.
Not all MWWTPs are equipped with secondary and tertiary treatment systems. Direct discharge of NP/NPEs would further contribute to the overall contamination of ambient waters and sediments[(1)].	The issue of differing treatment processes between MWWTP sites has been addressed with respect to effluent composition in the exposure section. The dominant form of NPEs in the effluent occur as higher ethoxylated compounds (e.g., NP9EO). In the characterization of risk, it is stated that the MWWTPs functioning with primary treatment exclusively result in the greatest exceedences of risk quotients.
The NP assessment report ignores important releases/sources[(1)].	Effluents from all types of industrial sources were sampled and analyzed for NP/NPE loadings, although the types of effluents causing the greatest concern were focussed on in the assessment.
Based on the analysis presented in the assessment report, the higher ethoxylated (NP3-100E) should not be included in the conclusion of "CEPA toxic"[(2)].	The higher ethoxylated products degrade to the lower ethoxylates and to NP itself, therefore, the higher ethoxylated products also must be considered toxic under section 64(a).
The Assessment Report should not include data on octylphenol or octylphenol ethoxylates[(2)].	Although data on octylphenol are present in the Supporting Document, they are not included in the Assessment Report for nonylphenol and its ethoxylates because the actual assessment was performed exclusively for nonylphenol and its ethoxylates. The data in the Supporting Document help to show the toxicity of nonylphenol and its ethoxylates relative to other alkylphenols and their ethoxylates. Octylphenol and its ethoxylates are a good choice for this comparison because many data are available for these compounds.
The assessment of environmental effects based on conventional endpoints is adequate to evaluate potential endocrine effects[(2)].	The assessment of nonylphenol and its ethoxylates was based on the "conventional" endpoints. Endocrine disrupting qualities do impact biological organisms, therefore, the inclusion of such data was necessary to provide a complete review of the literature.
NPE undergoes rapid biodegradation in wastewater treatment and continues to degrade in the environment[(2)].	In the section describing degradation of NP/NPEs in municipal wastewater treatment plants (MWWTPs), numerous studies are quoted indicating that the pathway of degradation results

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	in formation of the lower ethoxylated NPEs and NP indicated in Figure 2 on page 24 of the Assessment Report. Primary degradation of NPEs in MWWTPs is readily achievable (which includes the degradation of the higher ethoxylates to lower ethoxylates, carboxylates and NP), but that ultimate biodegradation in these systems does not occur, based on research reported in the literature.
The Assessment Report does not adequately characterize the degradation pathway. The degradation pathway suggests that the degradation of NPE stops at NP[(2)].	The figure used to indicate the degradation of NPEs is representative of the accepted degradation pathway. Literature reports of biodegradation of NPEs and NP has been studied through to mineralization, resulting in CO_2 production. Specific studies of the further degradation of NP/NPEs were reviewed in the Supporting Document upon which the Assessment Report for NP/NPEs is based. The report acknowledges that further degradation of NP occurs in aqueous and terrestrial environments.
NPEs are readily degradable[(2)].	A key factor pointed out in the public comment itself, is that in the OECD 28-day test, NP degradation did not meet the standards to be classified as readily degradable.
APE metabolites are degradable in rivers and soils and should not be considered stable[(2)].	The key factor in this argument is that APEs are ultimately degraded, although the rate of degradation is slower than the necessary criteria to be classified as "readily degradable". Degradation studies that have been performed both in Switzerland and Canada have reflected these results.
Include the study of NP/NPE persistence in sludge amended soils reported by Hughes, Fisher and Brumbaugh, 1996[(2)].	The data reported by Hughes et al. (1996) has been included in the discussion on biodegradation in soil.
The Assessment Report should emphasize that the BAFs reported in section 2.3.3.6 are expressed on a dry weight basis[(2)].	In section 2.3.3.6, concentrations data are reported and clarification as to whether the data are reported as wet weight, fresh weight or dry weight are included in the discussion.
Poor quality data should not be included in the Assessment Report. Additionally, OP/OPEs should not be considered in the assessment of NP/NPEs[(2)].	The data included in the assessment of NP/NPEs was comprehensive and indicated all of the current literature on these compounds, therefore, the poorer quality data was included. By ranking the

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	data, there is a clear acknowledgment of the quality of data under consideration and the weight of evidence was placed on good quality data. OP/OPEs were only mentioned in the Assessment Report as a comparison to the NP/NPEs and were not assessed.
The study by Ashfield *et al*. (1998) is inadequately presented[(2)].	The Ashfield *et al*., 1998 paper is reviewed in the Supporting Document, not the Assessment Report and indicates the specific points brought forward in the public comment. The review acknowledges that the results of the study were inconsistent. The study's inclusion is important to insure a comprehensive review of the literature.
The route of exposure used in the Christiansen *et al*., 1998 paper is irrelevant and should be noted[(2)].	The route of exposure has been identified in the summary of this work. Many studies on a wide variety of compounds in the literature have used this route of exposure, therefore, mentioning this route should be all that is necessary.
Gimeno *et al*., 1997 studied tert-pentyl phenol (TPP), not NP and should be removed from the Supporting Document[(2)].	TPP, similar to OP and NP, is an alkylphenol and its inclusion in the Supporting Documentation is useful for comparative purposes.
EBA (2000) performed an avian dietary study using bobwhite quail chicks and feeding NP9E at concentrations ranging from 0-5000 ppm and no behavioural or mortalities were observed[(2)].	This paper is currently not available and the alkylphenol research council has offered to provide a copy upon availability. At this time, we cannot include information that we have not seen.
The purity of materials tested in the Jobling and Sumpter (1993) study were not well determined, extrapolations were used without validation and it is the only study indicating estrogenic activity of NP9E and should be considered questionable [(2)].	Jobling and Sumpter (1993) reported the source for each of the compounds under investigation and they are companies known to provide analytical standards. Methods used in the preparation of samples followed routine preparation techniques and, therefore, the results should not be discounted.
Routledge and Sumpter (1996) did not study the estrogenicity of NP9E, therefore, the reference to this article when a comparison of the estrogenicity of NP9E is considered should be removed from the Assessment Report and Supporting Document[(2)].	The public comment is correct in that NP9E was not studied by Routledge and Sumpter (1996), therefore, the reference was removed from the statement suggesting otherwise.
Jobling *et al*., (1996) did not evaluate vitellogenin induction in *in vitro* trout hepatocytes[(2)].	Correction has been made.
Recent work by C. Metcalfe suggests that NP1EC has no estrogenic activity in the yeast	These results were not provided to the assessment team during the assessment process and remain

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estrogen screen assay. If OP and OPE are included in the Assessment Report, it should include that C. Metcalfe (personal communication) found similar negative results for these compounds [(2)].	unpublished at this time, therefore, we have no mechanism for assessing these results. Until we are provided with the data, we can not include it in our assessment. OP and OPEs are not included in the assessment of NP/NPEs in terms of assessing these compounds under CEPA.
The PSL guidance document permits use of a lower application factor than what was used (10). We recommended a factor of 5[(2)].	The application factor of 10 is usually used in these instances. These values are based on professional judgment and were confirmed when outside specialists were consulted on this matter.
K_d is probably intended to mean "distribution coefficient" not "dissociation constant"[(2)].	Correction has been made.
The footnote in Table 7 should read 95% water content for algae and 85% in fish, not 95% in both[(2)].	The footnote has been corrected.
Clarification as to why a TEQ of 1 is found in Table 11 and a TEQ of 2 is found in Table 12, needs to be made[(2)].	There is a typo in Table 12 and the TEQ should be 1. This correction has been made.
Endocrine modulation should be considered a mechanism or mode of action, rather than an endpoint used to assess aquatic risks[(2)].	Endocrine modulation was discussed in both the Assessment Report and the Supporting Document, however, the assessment of risk was based on traditional endpoints (e.g., mortality). A discussion was included in these documents indicating that there was debate as to what the endocrine results meant. In future, if endocrine modulation is shown to result in a specific result, this may lead to a change in perspective and that the endocrine issue may be used in the assessment of risk.
The data quoted in the Assessment Report do not indicate that the field results seem to contradict the laboratory results for toxicity in terrestrial environments[(2)].	The data indicating contradictions were presented as part of a workshop/conference and not in the literature, available for review. The public comment on this issue agrees with the determination that examination beyond a conservative scenario is not necessary.
Comments on research needs in the area of treatability and degradation: 1) these data gaps will increase the knowledge on NP/NPE fate, but are not needed to determine whether these compounds are "CEPA toxic"; 2) Results of New York State studies have indicated that halogenated by products are not a significant issue; 3) Photo-	1)These research needs were not developed with respect to making a determination of "CEPA toxic", but rather to identify areas where additional information would aid in the knowledge base surrounding nonylphenolic compounds with respect to fate and effects. 2) These results seem to indicate that the there may be reduced risk

Comment[(source)]	Response
oxidation can easily be calculated and Hughes (1996) has shown that mineralization is extensive[(2)].	associated with halogenated derivatives of NPE degradation products, however, they should be confirmed in the Canadian environment. 3) Although estimates of degradation rates are possible, for confirmation, it is always advantageous to measure the results. Other studies have indicated rapid degradation of NPEs in soils, however, these studies need to be performed on a variety of soil types, field conditions and weather cycles.
Comments on research needs in the area of biological effects: 1) the data indicate a linear relationship between ethoxylate chain length and toxicity, therefore, further data is not necessary; 2) the conclusion that the ability of NP and NPEs to bioaccumulate is low to moderate is correct, therefore, further study is unnecessary and OP/OPE should not be included in the assessment; 3) partitioning properties (e.g. Koc) can be reliably predicted from structure; 4) It is unclear why additional endpoints for endocrine modulation are needed to assess "CEPA toxicity"; 5) It is unclear as to how validation of predicted responses in aquatic studies would be done; 6) APERC supports collection of monitoring data to verify predicted concentrations; 7) A feeding study with NP9E indicated no effects at the highest dose (5000 ppm in the diet); 8) Determination of the relative contribution to the toxicity of complex mixtures (many types of substances) is too complicated and beyond the assessment of "CEPA toxicity". [(2)]	1) The key point made here is that the data should be made in a standardized manner, so that direct comparisons between studies can be made. 2) Past studies have lead to the conclusion regarding bioaccumulation, but new information is always advantageous especially given the vast number of organisms exposed to these compounds. 3) It is better to have measured values than predicted. 4) There is considerable debate regarding the endocrine issue within the scientific community and, therefore, further investigation of these mechanisms are important. They were not included in the assessment of "CEPA toxic". 5) Validation of predicted responses would involve research measuring endpoints at determined exposure levels to identified organisms. 6) No response required. 7) We have not seen the results of this study, therefore, can not include them in the assessment. 8) The CEPA assessment, was based on NP/NPE results exclusively, however, additional data regarding the impacts of complex mixtures to organisms would be beneficial.
Recommendation that the assessment be further reviewed before the decision is made. CPPA membership have altered rates of use and emissions of NPEs in processing[(3)].	We applaud the forward thinking of the CPPA in their reduction of NP/NPE emissions. Although the CPPA is able to provide additional information on the rates of release to the assessment group, the assessment is complete. These data, however, will be useful in the risk management phase. The reduction in NP/NPE emission was indicated in the results of samples collected in 1998 and this observation was indicated in the assessment

Comment[(source)]	Response
	report.

NONYLPHENOL AND ITS ETHOXYLATES (NP/NPEs)

Comments on the **health-related sections** of the CEPA PSL Assessment Report on Nonylphenol and its ethoxylates were provided by the World Wildlife Fund Canada, Toronto, Ontario, and by the Alkylphenols and Ethoxylates Research Council, Washington, D.C.

To ensure transparency and defensibility of the assessments, a cut-off date for consideration of new data is specified. In addition, the process for assessing the risks to human health includes several stages of internal and external review to ensure both quality and transparency. Addition of new data beyond the cut-off date, even if it was certain that these were the only new relevant data, would require an additional round of both internal and external reviews. This is impractical given the legally mandated time limits for completing these assessments. Such data are flagged for consideration in the Strategic Options Process (the subsequent and separate risk management phase) or a subsequent re-assessment.

Comment	Response
Human exposure to NP and NPEs, from multiple sources, needs further attention. If more attention was given to human health effects, dermal absorption and other human exposure pathways to NP/NPEs in the Assessment Report, more aggressive action could be justified to reduce human exposure.	The Assessment Report includes reference to all relevant effects-related data (including those in humans) identified in extensive literature searches and by several expert peer reviewers. With respect to exposure from multiple sources, the report includes reasonable worst-case or worst-case estimates of intake of NP/NPE from a wide variety of environmental media and consumer products. No other exposure scenarios were identified during peer review or public comment. As noted in the Conclusions, the relatively low margin of exposure estimated for some products indicates that additional information is necessary to refine assessments of potential risks to human health from exposure to NP/NPEs in specific products, to determine the need for measures to reduce public exposure through the Acts (other than CEPA) under which they are regulated.
The Assessment Report should clearly reflect the lack of estrogenic effects that has been observed for commercial NPEs. The commentor also noted that the estrogenic activity of short-chain NPEs mentioned in the Assessment Report was limited to in vitro systems	The lack of in vivo estrogenic activity of commercial NPEs was noted at several points in the Assessment Report; that estrogenic activity of short-chain NPEs was limited to in vitro systems has been clarified in the report.
The Assessment Report should distinguish data on NP from those on NPEs. While it is agreed that	This was not implied in the Assessment Report; however, to avoid any such misunderstanding, the

Comment	Response
NP can be considered to be the "worst case" for evaluation of the potential effects of these products, the Assessment Report should clearly state that NPEs have not been shown to have effects similar to NP (i.e., kidney mineralization in rats).	text of the Assessment Report has been modified accordingly.
Skin absorption data are available to refine estimates of exposure. Based on recent in vitro studies, the worst-case estimate of skin absorption for NP and NPE should be 1% of the dose and the margins of exposure should be recalculated.	These recent data on absorption were provided after the cut-off date for consideration of new information. The need for such additional information to refine the worst case estimates of exposure and potential risks to human health from exposure to NP/NPEs in specific products was noted in the Assessment Report. It is anticipated that this information would be taken into consideration (along with additional data identified based on an updated systematic search) as a basis for determination of the need for measures to reduce public exposure through the Acts (other than CEPA) under which they are regulated, as recommended in the Assessment Report. Based on preliminary review of the recent *in vitro* data, 1% absorption is probably a considerable underestimate. It is considered likely that the NPE penetrating the skin is biologically available (rather than that in the receptor fluid alone), in which case the estimated absorption for a leave-on product is many times greater than 1% for some products. In addition, while the protocols of these new studies are considerably improved over those of earlier investigations, uncertainties still to be addressed in development of estimates of absorption include the viability of the skin, purity of radiolabel, conditions of skin washing, and extrapolation from *in vitro* to *in vivo* conditions. There are also uncertainties with respect to the extent of absorption via the oral route, and the systemic bioavailability of NP/NPEs absorbed via the dermal versus the oral route.
The fugacity modelling of NP presented in the Assessment Report utilized overly long degradation half lives which are not supported by the data presented in the report.	The half-lives used in the fugacity modelling have been changed to reflect the data which were presented elsewhere in the Assessment Report, or from articles cited therein. Given the considerable uncertainties regarding persistence of NP in various

Comment	Response
	environmental media, the approach of 'bracketing' the available half-lives in the fugacity modelling has been retained. Based on the revised fugacity modelling, the overall impression of environmental fate remains similar, but the percentage distributions have changed somewhat.
In the discussion in the Assessment Report of the multigeneration study of NP in rats, the increase in gestational length in treated rats is a statistical aberration, and should not be cited.	The text has been modified to indicate that the increases in gestation length and in percent abnormal epididymal sperm morphology observed in the F_2 generation were probably not treatment-related. In both cases, the increase was small, not clearly dose-related, and within the range of control values from other generations and from historical controls. As well, these effects were not observed in other generations, and the F_2 control values were unusually low.
The inclusion of reference to the studies by de Jager et al. (1999a, 1999b) should be reconsidered. The mortality observed in rats exposed to NP in these studies was not observed at similar doses in several other studies.	The text of the Assessment Report has been modified to indicate that, while there were histological effects noted in the seminiferous vesicles, this was accompanied by compound-related mortality at doses that did not cause deaths in several other studies.
Reference to the results of the studies by Lee (1998) should be removed from the Assessment Report, as these were not reproducible, even when NP was administered intraperitoneally, in soon-to-be-published studies.	These unpublished studies were provided after the cutoff date specified in the introduction to the Assessment Report, but based on preliminary consideration, would not impact significantly on the content of the assessment. The study by Lee (1998), which involved intraperitoneal administration of NP, did not contribute meaningfully to the health assessment. Instead, the risk characterization was focussed on studies in which NP/NPEs were administered by more relevant routes.