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Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

Nonylphenol and its Ethoxylates

Canada

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Environment Canada
Health Canada

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List of Acronyms and Abbreviations

ACR	acute to chronic ratio
AF	application factor
AP	alkylphenol
APE	alkylphenol ethoxylate (as a general class)
APEC	alkylphenol carboxylate on ethoxylate chain (as a general class)
APnEC	alkylphenol carboxylate (on ethoxylate chain); where n = specific number of ethoxylate groups
APnEO	alkylphenol ethoxylate; where n = specific number of ethoxylate groups
BAF	bioaccumulation factor
BCF	bioconcentration factor
CAPE	alkylphenol with alkyl chain carboxylated
CAPEC	alkylphenol with carboxylate groups on both the alkyl and ethoxylate chains
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CTV	Critical Toxicity Value
dw	dry weight
E_2	estradiol
EC_{50}	median effective concentration
EEQ	Estrogenic Equivalency Quotient
EEV	Estimated Exposure Value
EEV_{EEQ}	Estimated Estrogenic Exposure Value relative to NP
EEV_{TEQ}	Estimated Toxic Exposure Value relative to NP
ENEV	Estimated No-Effects Value
EO	ethoxylate
K_{oc}	organic carbon/water partition coefficient
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOEC	Lowest-Observed-Effect Concentration
LOEL	Lowest-Observed-Effect Level
MWWTP	municipal wastewater treatment plant
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
NP	nonylphenol
NPE	nonylphenol ethoxylate or polyethoxylate (as a general class)

NPEC	nonylphenol carboxylate on ethoxylate chain (as a general class)
NPnEC	nonylphenol carboxylate on ethoxylate chain; where n = specific number of ethoxylate groups
NPnEO	nonylphenol ethoxylate; where n = specific number of ethoxylate groups
OP	octylphenol
OPE	octylphenol ethoxylate (as a general class)
pK_a	negative logarithm of the acid dissociation constant
PSL	Priority Substances List
PVC	polyvinyl chloride
SRT	sludge retention time
TEQ	Toxic Equivalency Quotient
TNPP	tris(nonylphenyl)phosphite
YES	yeast estrogen screen

SYNOPSIS

Nonylphenol ethoxylates (NPEs) are a class of the broader group of compounds known as alkylphenol ethoxylates (APEs). NPEs are high-volume chemicals that have been used for more than 40 years as detergents, emulsifiers, wetting agents and dispersing agents. Nonylphenol polyethoxylate-containing products are used in many sectors, including textile processing, pulp and paper processing, paints, resins and protective coatings, oil and gas recovery, steel manufacturing, pest control products and power generation. A variety of cleaning products, degreasers and detergents are also available for institutional and domestic use. These products have numerous applications, including controlling deposits on machinery, cleaning equipment, scouring fibres, as wetting and de-wetting agents, in dyeing, in machine felt cleaning and conditioning and in product finishing. NPEs are also used in a wide range of consumer products, including cosmetics, cleaners and paints, and in a variety of applications.

NPEs and their degradation products (e.g., nonylphenol [NP]) are not produced naturally. Their presence in the environment is solely a consequence of anthropogenic activity. NP and NPEs enter the environment primarily via industrial effluents and municipal wastewater treatment plant (MWWTP) effluents (liquid and sludge), but also by direct discharge, although it is not known how significant the latter pathway is in Canada. Once NPEs are released to sewage treatment systems, several transformations can occur. The mechanism of degradation is complex, but, in general, there is an initial loss of ethoxylate (EO) groups from the original moiety. Under aerobic and anaerobic treatment conditions, biodegradation to more toxic (and estrogenic) metabolites occurs. These products are NP, nonylphenol ethoxylate (NP1EO), nonylphenol diethoxylate (NP2EO), nonylphenoxyacetic acid (NP1EC) and nonylphenoxyethoxyacetic acid (NP2EC).

NPEs can be biodegraded through a mechanism of stepwise loss of ethoxy groups to form lower ethoxylated congeners, carboxylated products and NP. The intermediate and final products of metabolism are more persistent than the parent NPEs, but these intermediates are expected to be ultimately biodegraded. In aquatic environments, primary biodegradation of NPEs is fast, but the resultant products, such as NP1EO, NP2EO, NP1EC, NP2EC and NP, are moderately persistent, especially under anaerobic conditions. Microbial acclimation to such chemicals is required for optimal degradation efficiencies. Photodegradation of such products is also expected to be important. Based on the limited data available, NP and the lower ethoxylates and carboxylates are persistent in groundwater. NP can be moderately persistent in sediments. It appears to be persistent in landfills under anaerobic conditions, but it does not appear to be persistent in soil under aerobic conditions.

NP and NPEs are present at low concentrations in ambient air, water, soil, sediments and biota. There are limited data on the occurrence of NP and NPEs, and their degradation products, in the Canadian environment. Additionally, there are very few data available for NP/NPEs in Canadian soils, including those that have had sludge additions. Nevertheless, in Canada, these chemicals have been found in fresh water, sediment, fish and beluga whale tissue, textile mill effluents, pulp and paper mill effluents, MWWTP influents, effluents and sludges, and soil to which municipal sludges had been applied.

There are a large number of studies reporting acute and chronic effects of NP in aquatic biota. There are, however, fewer studies reporting the toxicity of NPEs, and only a few studies that included the NPECs. Although studies described in the literature have used many species, different test methods and different chemicals, there is a consistent pattern in the

toxicity reported. The range of acute toxicity for NP is similar for different organisms: for example, fish (17–1400 μg/L), invertebrates (20–3000 μg/L) and algae (27–2500 μg/L). Chronic toxicity values (No-Observed-Effect Concentrations, or NOECs) for NP are as low as 6 μg/L in fish and 3.9 μg/L in invertebrates. An acute to chronic toxicity ratio of 4:1 was determined based on the available literature.

NP and NPEs have been reported to cause a number of estrogenic responses in a variety of aquatic organisms. Experiments in several different *in vitro* systems have indicated similar relative potencies among such compounds. NPEs bind to the estrogen receptor, resulting in the expression of several responses both *in vitro* and *in vivo*, including the induction of vitellogenin in trout. NP is, however, 100 000 times less potent than estradiol. In one study, NP2EO and NP1EC were only slightly less potent than NP in inducing vitellogenin in trout hepatocytes. NP, NPEs and NPECs are found as complex mixtures in effluents, and their combined estrogenic effects on aquatic organisms should be considered together. A critical consideration is the relative estrogenic potency of the APs and APEs and validation of the assumption of additivity. Estrogenic responses occur at concentrations similar to those at which chronic toxicity occurs, although biochemical and histological changes have been reported at concentrations a factor of 10 lower. The relative importance and significance of estrogenic responses in aquatic organisms to the individual or population are not currently well understood.

The literature suggests that the bioaccumulation of NP and NPEs in aquatic biota in the environment is low to moderate. Bioconcentration factors (BCFs) and bioaccumulation factors (BAFs) in biota, including algae, plants, invertebrates and fish, range from 0.9 to 3400. There are relatively few data available for NPEs, but, based on their structure, the BCF is expected to decrease with increasing chain length, and NPECs are not expected to bioaccumulate.

The major route for the release of NP and NPEs to the Canadian environment is through discharge of effluents. The composition of the mixture can differ considerably among the various effluents, depending on the source and the degree and type of treatment. Textile mill effluents represent a major source of NPEs to the environment. Untreated or partially treated textile mill effluents can have high concentrations of nonylphenol-9-polyethoxylate (NP9EO), NP1EO and NP2EO. There appears to be a recent decrease in discharge of NPEs from pulp and paper mills, but there are very few data available to validate this conclusion. Municipal effluents are a significant source of NPEs and are widespread across Canada. Untreated effluents can have high levels of NP, NP1EO and NP2EO, which may exceed thresholds for chronic effects in the aquatic environment. Treated effluents have relatively low levels of NPEs with longer EO chain lengths. NP1EO and NP2EO can remain at levels that may result in potential chronic toxicity in final effluents. There is potential for chronic toxicity to occur in aquatic biota due to exposure to NPEs and their metabolites in a variety of effluents. This can be associated with different metabolites of NPEs, depending on the source and degree and type of treatment. It is important that all of the NPE metabolites, not only NP, be considered together to assess the potential for impacts in the environment.

The concentration of NP is generally low in treated effluents, as it degrades and sorbs to sludge particles; however, NP sorbed to sediments may represent an alternative route of exposure that may result in chronic toxicity to sediment-dwelling organisms. Despite NP's relatively low potential to bioaccumulate, sediment-dwelling organisms may be exposed to NP directly, either through contact with water or sediment or through ingestion of sediment or food.

Humans are exposed to environmental media and consumer products that can contain large numbers of different NP/NPEs. The database on both exposure and effects for the individual NP/NPEs that make up these complex

mixtures is extremely limited. Consequently, a screening approach has been adopted for the assessment of potential risks to humans from exposure of the general population to this group of substances, primarily to ensure that conclusions drawn on the basis of a more robust data set on effects on environmental organisms are protective with respect to human health, at least for sources controllable under the *Canadian Environmental Protection Act*, *1999* (CEPA 1999), and to identify priorities for acquisition of additional data. This approach entailed comparison of identified effect levels for NP/NPEs with reasonable worst-case or bounding estimates of exposure for the entire class of substances. The estimated worst-case intake of NP/NPEs in food, the likely principal medium of exposure, is considerably less than the lowest effect level identified, for histopathological effects on the kidneys of male rats exposed to NP in the diet over three generations. (While NP has estrogenic activity in mammalian systems, the results of available studies indicate that this occurs at relatively high dose levels.) The margin between this effect level and estimated dermal intakes from some consumer products is relatively small; however, this comparison is based on the assumption that the NP/NPEs are absorbed through the skin to the same extent as via the gastrointestinal tract, whereas available data, although inadequate, indicate that dermal absorption is likely lower. Therefore, refinement of the assessment presented herein to incorporate, for example, results of additional research into the dermal absorption of these substances is a clear priority for further work to permit more meaningful assessment of exposure to NP/NPEs from these products. NP and NPEs are also likely early candidates for additional investigation when more sensitive frameworks for testing and assessment of endocrine-disrupting substances are developed.

Based on the information available, it is concluded that nonylphenol and its ethoxylates are entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. It is concluded, however, that nonylphenol and its ethoxylates are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends. Therefore, nonylphenol and its ethoxylates are considered to be "toxic" as defined in Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999). On the basis of consideration of the margin of exposure between effect levels and reasonable worst-case or bounding estimates of intake by the general population from environmental media, NP and NPEs are not considered a priority for investigation of options to reduce human exposure through control of sources that are addressed under CEPA 1999. However, the relatively low margin of exposure estimated for some products indicates that there is an important need for refinement of this assessment, in order to determine the need for measures to reduce public exposure to NP and NPEs in products through the Acts under which they are regulated. Of priority in this respect is research into dermal absorption of these substances from such products and evaluation of the potential endocrine-mediated adverse health effects of NP and NPEs upon completion of more sensitive testing.

Under current use patterns, NP and NPEs in Canada can result in environmental concentrations that exceed the levels of concern in textile mill, pulp and paper mill and MWWTP effluents. At present, routine monitoring of these sites for NP/NPEs is not performed. Risk management of NP/NPEs should lead to a reduction in the use and release of these compounds in the processing of textiles and pulp and paper, thereby reducing environmental exposure.

The scope of this Assessment Report as specified by the Ministers' Expert Advisory Panel on the Second Priority Substances List is limited

to nonylphenol and its ethoxylates. However, because of the similar toxicological properties of octylphenol and its ethoxylates (OP/OPEs) and because they are present in similar environmental compartments, relevant data on these compounds have been reviewed in the supporting documentation for environmental effects (Servos *et al*., 2000). Based on preliminary review of these data, estrogenicity of these compounds in environmental organisms may be greater than that of NP/NPEs. Hence, additional assessment of these compounds under CEPA 1999 will be prioritized. Based on the results of this preliminary review, it should also be recognized that replacement of NPEs with OPEs may amplify rather than reduce the risk to the environment.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined in Section 64 of the Act, which states:

> …a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on an initial screening of readily accessible information, the rationale for assessing nonylphenol (NP) and its ethoxylates (NPEs) provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> NPEs are discharged into the environment primarily from textile and pulp and paper production facilities. They are also used in coal processing, latex paints, grease and lubricating oils, pesticides and industrial detergents. Acute adverse effects have been reported in invertebrates, fish, mammals and algae. There are also concerns that these substances may interfere with endocrine function. An assessment is required to determine exposure levels and the risk they may pose to the environment and human health in Canada.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

> Environmental Protection Publications
> Environmental Technology Advancement Directorate
> Environment Canada
> Ottawa, Ontario
> K1A 0H3

It is also available on the Internet at www.ec.gc.ca/cceb1/ese/eng/esehome.htm under the heading "Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al*., 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to the assessment of potential effects on the environment (prior to December 1998) and on human health (prior to November 1999) are presented in Appendix A. The environmental assessment included data from research commissioned specifically for use in this assessment. These data were obtained following December 1998. Additional literature was considered for the assessment as the authors became aware of its existence. A separate PSL assessment of textile mill effluents was initiated concurrently and the assessment report on textile mill effluents is currently available.

The environmental risk assessment of NP and its ethoxylates was developed by members of the Environmental Resource Group, established by Environment Canada. Members were selected on the basis of their expertise, notably in the areas of analytical chemistry, environmental monitoring, environmental chemistry and environmental toxicology. Members of the Environmental Resource Group were:

D.T. Bennie, National Water Research Institute, Environment Canada
P. Cureton, Commercial Chemicals Evaluation Branch, Environment Canada
H.-B. Lee, National Water Research Institute, Environment Canada
K. Lloyd, Commercial Chemicals Evaluation Branch, Environment Canada
R.J. Maguire, National Water Research Institute, Environment Canada
M.R. Servos, National Water Research Institute, Environment Canada.

The environmental risk assessment was led by P. Cureton. In developing the environmental assessment, review articles were consulted where appropriate. However, all original studies that form the basis for determining whether NP and its ethoxylates are "toxic" under Paragraph 64(a) of CEPA 1999 have been critically evaluated by staff of Environment Canada.

The supporting documentation for the environmental assessment (Servos *et al.,* 2000) underwent an external scientific peer review, which was performed by:

C. Metcalfe, Environmental and Resource Studies, Trent University
D. Moore, Cadmus Group
K. Solomon, Centre for Toxicology, University of Guelph
G. Van Der Kraak, Department of Environmental Biology, University of Guelph

The environmental sections of this Assessment Report, summarizing the supporting documentation, were prepared by D.F.K. Rawn with assistance from N. Davidson and also reviewed by the following internal reviewers at Environment Canada:

K. Adare, Guidelines and Standards Division, Environment Canada
D. Dore, Chemicals Control Division Environmental Canada
D. Dubé, Chemicals Evaluation Division, Environment Canada
B. Ernst, Air and Toxic Issues, Environment Canada
J. Haskill, Renewable Resources, Environment Canada
B. Mander, Chemicals Control Division, Environment Canada
K. Potter, Guidelines and Standards Division, Environment Canada
L. Rutherford, Air and Toxic Issues, Environment Canada
R. Sutcliffe, Chemicals Evaluation Division, Environment Canada
N. Tremblay, Chemical Control Division, Environment Canada

Although NP/NPEs have toxicological properties that are similar to those of other APs/APEs,[1] other APs/APEs were not considered in this assessment. OP/OPEs, which are used in Canada to a lesser extent than NP/NPEs, are present in similar environmental compartments as NP/NPEs. Although this assessment was focused strictly on NP/NPEs, relevant data for OP/OPEs have been reviewed in the environmental supporting documentation (Servos *et al.,* 2000). Because of the toxicological and endocrine effects of these compounds on environmental organisms, their assessment is considered a priority, but the compounds are beyond the scope of this assessment.

The approach to the assessment of the effects of NP/NPEs on human health is necessarily restricted due to the extremely limited database on both exposure and effects for individual components of this complex mixture of a large number of congeners. For example, available data on exposure to NP/NPEs in media to which the general population in Canada is exposed (e.g., air, food, drinking water and consumer products) are insufficient to support other than bounding or reasonable worst-case estimates of intake for the entire class of substances. Moreover, potentially critical effects of NP/NPEs on human health have not been adequately investigated, since only a very limited number of members of this class of substances have been studied and as sensitive frameworks for testing and assessment of some key endpoints (e.g., potential for endocrine disruption) have not yet been developed.

In view of the limitations of the database, an interim screening approach has been adopted for the assessment of risks to human health. In this screening assessment, identified effect levels for NP/NPEs are compared with reasonable worst-case or bounding estimates of exposure for the entire class of substances. Weight of evidence for and adversity of observed effects have generally not been considered at this initial stage. Rather, the adequacy of these rather crude margins of exposure is considered in relation to intake from various sources, including environmental media and consumer products, primarily as a basis for identification of priorities for further work to permit a more defensible assessment of risks from all sources of exposure for the general population. This interim approach has been adopted in recognition that, while more informative data on health effects of these substances are likely to be forthcoming in the near term, the more robust data set on environmental organisms, some of which are directly exposed to discharges of these substances, is currently a more appropriate benchmark against which to assess risks in the general environment.

The search strategy that served as the basis for identification of relevant data for the human health assessment is outlined in Appendix A. In brief, effects-related studies for this screening assessment were identified primarily from several recent reviews (Talmage, 1994;

[1] The nomenclature for the various alkylphenols and alkylphenol ethoxylates discussed in this report is briefly explained in Section 2.1.1 and summarized in the List of Acronyms and Abbreviations.

U.K. Environment Agency, 1998; WHO, 1998). In addition, a number of on-line databases were searched to identify relevant data on exposure and effects of NP/NPEs that were not included in the reviews. Although secondary sources were used to identify many of the available data, the original reports for toxicological studies (except for acute toxicity and genotoxicity) identified in the reviews were acquired in order to confirm the results. In view of the relatively limited database for assessment of the toxicity of NP/NPEs, additional attempts were made to acquire data relevant to exposure and/or effects from representatives of industry, the provinces, and other Canadian federal and international agencies. It has not been possible to determine if studies of Industrial Bio-Test Laboratories Inc., which constitute a subset of the investigations summarized in a 1969 review by Smyth and Calandra, have been validated. While cited in this report, they do not contribute directly to the conclusions drawn (i.e., the critical effect levels were not derived therefrom); moreover, results of these investigations are consistent with those reported by others.

In view of the limited objectives of the screening assessment, the information considered in the health assessment has been restricted principally to that directly relevant to determination of the margin of exposure — i.e., data to serve as the basis of the reasonable worst-case or bounding estimates of exposure and effect levels from repeated-dose studies. Related data, such as those on pharmacokinetics, are not included herein, since they are considered inadequate to meaningfully inform the margin of exposure.

Sections of this Assessment Report and supporting documentation related to human health were prepared by the following staff of Health Canada:

M.E. Meek
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Sections of the supporting documentation on exposure were reviewed by R. Moody of the Product Safety Bureau, Health Canada, and by P. Lau of the Food Packaging Materials and Incidental Additives Section, Food Directorate, Health Canada. Sections of the supporting documentation on reproductive effects, including estrogenicity, were reviewed by M. Wade of the Environmental and Occupational Toxicology Division of Health Canada.

In order to address primarily adequacy of coverage, sections of the effects-related supporting documentation pertaining to human health were reviewed externally by:

F. Ratpan, Novacor
S. Sang, World Wildlife Fund Canada
J.P. Van Miller, Union Carbide

Adequacy of coverage and defensibility of conclusions of the health-related sections of the Assessment Report and the supporting documentation were considered in a written review by:

J. Christopher, California Environmental Protection Agency
M. Dourson, Toxicology Excellence for Risk Assessment
P. Ridgway, U.K. Health and Safety Executive
R. Rudell, Silent Spring Institute

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (April 1 to May 31, 2000) (Environment Canada and Health Canada, 2000). Following

consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and responses is available on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)). Due to the extensive literature available for NP/NPEs and NPECs, the Assessment Report does not include detailed descriptions of critical studies. These data are, however, reviewed and described in detail in the supporting documentation.

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
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or

Environmental Health Centre
Room 104
Health Canada
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2.0 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF "TOXIC" UNDER CEPA 1999

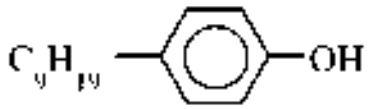
2.1 Identity and physical/chemical properties

2.1.1 Nomenclature

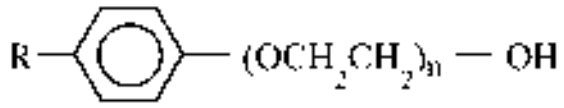
NP is a chemical intermediate composed of a phenol ring attached to a lipophilic straight or, more usually, branched nonyl group. NPEs belong to the larger group of compounds known as APEs and have the following general formula: $C_{15}H_{24}O+(CH_2CH_2O)_n$. The predominant positional isomer of monoalkylphenols is the *para* isomer, which usually comprises ≥90% of industrial formulations, while the *ortho* isomer comprises ≤10%. In the United States, the U.S. Environmental Protection Agency and the Chemical Manufacturers Association's Alkylphenols and Ethoxylates Panel have agreed that the commercial product that best represents "nonylphenol" is a chemical substance composed of branched C_9-alkylphenols with Chemical Abstracts Service (CAS) registry number 84852-15-3 (Hellyer, 1991). There may also be small amounts of 2,4-dinonylphenol in commercial nonylphenol preparations. CAS registry numbers for a variety of alkylphenols, ethoxylates and other derivatives are given in Talmage (1994). Considering the branching of the C_9-chain, there may be scores, if not hundreds, of individual NPE isomers in an industrial NPE formulation. Each NPE is conventionally described by its average ethoxylate (EO) chain length, which ranges between 1 and 100 for different formulations.

Structures of NPEs and associated degradation products are shown in Figure 1.

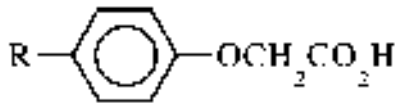
FIGURE 1 Chemical structures for NP, NPE, NP1EC and NP2EC



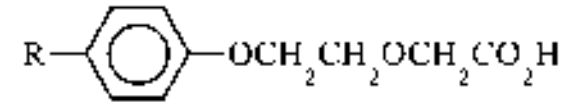
4-nonylphenol (NP)



R–C_9H_{19}, nonylphenol ethoxylates (NPE)



R–C_9H_{19}, nonylphenoxyacetic acid (NP1EC)



R–C_9H_{19}, nonylphenoxyethoxyacetic acid (NP2EC)

2.1.2 Physical and chemical properties

Some physical and chemical properties that have a bearing on the environmental persistence of NP and NPEs with average chain lengths of four (NP4EO) and nine (NP9EO) are summarized in Table 1. The properties of NP4EO and NP9EO are considered to be representative of NPEs and are presented because the available data set for these two compounds is the most complete.

TABLE 1 Properties of NP, NP4EO and NP9EO[1]

Property/specification	NP	NP4EO	NP9EO
CAS registry number	84852-15-3, 25154-52-3	7311-27-5, 9016-45-9	26027-38-3
Synonyms	4-nonylphenol, *p*-nonylphenol	Nonoxynol-4	Nonoxynol-9, Tergitol NP-9
Molecular formula	$C_{15}H_{24}O$	$C_{15}H_{24}O[C_2H_4O]_4$	$C_{15}H_{24}O[C_2H_4O]_9$
Molecular weight (g/mol)	220.3	396.2	617.6
Melting point (°C)	–8[2,3]	–40[4]	2.8[4]
Boiling point (°C)	295–320[1,3]		
Physical characteristics	colourless to pale straw (liquid)[1,3]	white to light amber liquid[5]	almost colourless liquid[6]
Specific gravity	0.953[7]	1.020–1.030 (25°C)[6]	1.057 (20°C)[4]
pK_a	10.7[8]		
Vapour pressure (Pa)	0.004 55 ± 0.003 5[8] 0.3[3]		
Solubility (mg/L)	5.4[9]	7.65[9]	"soluble"[5]
log K_{ow}	4.2–4.48[10,11,12]	4.24[10]	3.59[10]
Henry's law constant ($Pa \cdot m^3/mol$)	11.02[3,13]		0.000 24[5]

[1] From Reed (1978), except where noted. Other physical and chemical properties may be found in U.S. EPA (1985).

[2] Hüls, AG (1994).

[3] OECD (1997).

[4] Weinheimer and Varineau (1998).

[5] CIR (1983).

[6] WHO (1998).

[7] Enyeart (1967).

[8] Romano (1991).

[9] Ahel and Giger (1993a).

[10] Ahel and Giger (1993b).

[11] McLeese *et al*. (1981).

[12] World Wildlife Fund Canada (1996).

[13] U.K. Environment Agency (1997).

TABLE 2 Amount of NP and its ethoxylates produced, imported, exported and available for use in Canada in 1995 and 1996 (from Environment Canada, 1998)

	Amount (tonnes NP/NPE)	
	1995	**1996**
Produced in Canada	32 700	25 600
Imported to Canada	3 700	4 500
Exported from Canada	12 600	11 100
Available for use in Canada [1,2]	23 800	19 000

[1] Amount available for use = Amount produced + amount imported – amount exported. Results are based on survey responses received from 189 companies that reported involvement with NP/NPEs of 1000 kg per year or more.

[2] Both NP and NPEs are used as feedstock in the production of other products.

Specific gravity, viscosity and aqueous solubility increase with EO chain length. NPEs with a chain length greater than six are readily soluble in water. It should be noted, for example, that the pK_a of NP is 10.7 (Romano, 1991), which indicates that in most natural waters, virtually all NP is present in the undissociated form. The Henry's law constant and vapour pressure of NP and especially NPEs are low; therefore, partitioning to air is extremely limited.

NPECs are likely to be substantially, if not almost completely, ionized at the pH values of many natural waters (e.g., the pK_a of unsubstituted phenoxyacetic acid has been estimated as 5.12; NTP, 1998), and their log K_{ow} values are expected to be much lower than those of the corresponding ethoxylates (e.g., the log K_{ow} value of unsubstituted phenoxyacetic acid has been estimated as 1.34; Syracuse Research Corp., 1998).

2.2 Entry characterization

2.2.1 Uses, production and market trends in Canada

NP is produced by reacting phenol and mixed nonenes in the presence of a catalyst. It is used in the production of NPEs, as a monomer in polymer production and as an additive in polymer processing (U.K. Environment Agency, 1998). NPEs are manufactured by the ethoxylation of NP with ethylene oxide and used in the production of phenol/formaldehyde resins; in the production of tris(nonylphenyl)phosphite (TNPP) antioxidant for rubber and manufacture of lube oil additives; as a catalyst in the curing of epoxy resins; and in the manufacture of phenolic oximes (used in the extraction of copper from ores). The length of the EO chain is varied by controlling the reaction time or the ratio of NP to ethylene oxide.

Over 4500 companies operating in Canada were surveyed in 1997 under authority of Section 16 of the *Canadian Environmental Protection Act* (CEPA) to determine the uses of priority chemicals (Environment Canada, 1997b). Data were collected on the amount of NP and NPEs produced, imported, exported, shipped, acquired and used in Canada. A total of 189 companies responded that they were involved with NP and NPEs above the trigger quantity of 1000 kg per year (Environment Canada, 1997c).

The amount of NP plus NPEs available for use in Canada (domestic production plus imports minus exports) was 23 800 and 19 000 tonnes in 1995 and 1996, respectively (Table 2). It is not known how much of those totals refer to NP and how much to NPEs. NPEs were manufactured at three facilities in Canada in 1995 and 1996. They are used, in descending order, as feedstock, formulation, articles, chemical

aid, manufacturing aid and containers.[2] As reported in surveys of Canadian industry carried out under authority of Section 16 of CEPA, the total amount of NP used by industry in Canada in 1996 was 5000 tonnes, with the majority being used as chemical intermediates. The total reported use of NPEs in the same year was also 5000 tonnes (Environment Canada, 1997c).

In 1989, domestic demand for NP in Canada was 4500 tonnes: 3700 tonnes were from domestic production, 1800 tonnes were imported and 1000 tonnes were exported (Camford Information Services Inc., 1990). In that year, 1000 tonnes were used in ethoxylated textile specialties, 1600 tonnes in ethoxylated pulp mill specialties, 500 tonnes in miscellaneous ethoxylates, 500 tonnes for TNPP and 900 tonnes for miscellaneous uses, including pesticides and lube oil (Camford Information Services Inc., 1990).

Although forecasts for demand of NP and NPEs in Canada were not available, the growth for NP in the United States was 2% per year in the period 1988–1997 and was forecast at 1–2% per year from 1998 through 2002 (Anonymous, 1998).

Because of the surfactant properties of NPEs, NPE-containing products have many industrial, commercial, institutional and household uses in Canada, including lubrication, defoaming, assisting in dyeing, as emulsifiers, controlling deposits and cleaning machinery and materials, scouring fibres, as wetting and de-wetting agents and in product finishing. NPE-containing products are used in many sectors in Canada, including textile processing, pulp and paper manufacturing, metal processing, petroleum refining, oil and gas recovery, power generation, food and beverage processing, plastics manufacture, and the building and construction industry, as well as in various cleaning products, paints, resins and protective coatings (Talmage, 1994; Maguire, 1999). As well as being used in industry, a variety of cleaning products, degreasers and detergents are also available for institutional and domestic use. Consequently, there are many routes of entry into the environment for these substances during the course of their manufacture, use and disposal.

Two hundred and eleven pesticide products containing NP and/or NPEs were identified for current use in Canada. Forty percent of these products contain less than 1% NP or NPE, 85% of these products contain less than 10% NP or NPE and 95% of these products contain less than 20% NP or NPE. The NP

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[2] Glossary of terms (from Environment Canada, 1997b):

Article — incorporated into a consumer product or "manufactured article."

Chemical aid — a substance that is added to a reaction mixture to aid in the manufacture, synthesis or purification of a chemical or process stream (e.g., process solvents, catalysts, inhibitors, buffers, flocculation agent, etc.).

Container — manufacture of bottles, pails and other containers.

Feedstock — used as feedstock or chemical intermediate and becomes chemically transformed into another chemical.

Formulation — incorporated into a formulated product or packaged as a product, other than a consumer product or manufactured article for resale.

Manufactured article — a consumer product or an article for which its final use depends in whole or in part on the physical shape or design of the article. For instance, vinyl film or tubing containing a listed substance would be considered a manufactured article, whereas plastic granules that are intended for extrusion would not. Except for consumer products for the retail market, fluid formulations would not be considered to be manufactured articles. Although companies were required to report the quantities of substances they consumed making manufactured articles, they were not required to report actual quantities of the actual "manufactured articles."

Manufacturing aid — a substance that aids the manufacturing process (e.g., lubricants, metalworking fluids, coolants, hydraulic fluids, degreasers).

and NPEs appear only as formulants in these pesticides, primarily as emulsifiers, surfactants, wetting agents, etc. The application rate of these products varies considerably, depending on their use (Moore, 1999).

It is not known if NP is used to mark fuel oil for taxation purposes in Canada; however, this has been identified as a use pattern in the United States (Reed, 1978).

NPEs have been prohibited since 1997 as an active ingredient in soil supplements that are regulated under the *Fertilizers Act* (Webster, 1998).

A range of other applications, some of which appear to have limited potential for release to the environment, nonetheless represent direct sources of exposure for humans. Uses that may result in residues of NP and NPEs in foods include the use of NP and its ethoxylates as a "spreader" in several pesticide formulations, as a dispersant/emulsifier in vegetable and fruit waxes, in detergents and disinfectants used on foods and in various food packaging applications (World Wildlife Fund Canada, 1996). NP is also a contaminant and breakdown product of TNPP, used as a polymer resin in food contact packaging (The Society of the Plastics Industry, Inc., 1998a), and has been reported to leach from polyvinyl chloride (PVC) polymer tubing into water passed through the tube (Junk *et al*., 1974) and from PVC bottles into food simulants (Gilbert *et al*., 1986). A wide range of consumer products contain NP and NPEs. Cosmetic products such as skin creams, eye and face makeup, hair care products, deodorants and bath products, as well as cleaning products and paints, may be direct sources of exposure to these substances. Nonoxynol-9 (NP9EO) is also used as a spermicide in contraceptive foams, jellies and creams (McIntyre, 1996; World Wildlife Fund Canada, 1997; WHO, 1998). Specific information on the percent composition of NP/NPEs in various consumer products is presented in Table 3.

2.2.2 Sources and releases

2.2.2.1 Natural sources

There are no known natural sources of NP and NPEs. Their presence in the environment is, therefore, solely a consequence of anthropogenic activity.

2.2.2.2 Anthropogenic sources

Releases of NP and NPEs to the environment can occur at various points in the product life cycle — namely, during primary production of NPEs, manufacture of NPE-containing products, product use and disposal of the product to wastewater treatment, septic system or landfill.

Over 4500 companies operating in Canada were surveyed in 1997 under authority of Section 16 of CEPA to determine their releases of priority chemicals to the environment (Environment Canada, 1997b). Ranges of releases in 1996 from 65 companies in Canada involved in primary NPE production, manufacture of NPE-containing products or industrial use are shown in Table 4. It is not known how much of these totals refers to NP and how much to NPEs. The total release of NP and NPEs combined in 1996 from industrial manufacture and use was 96.5 tonnes (Environment Canada, 1997c). The largest industrial releasers were (1) formulators and distributors of surfactants and (2) industrial users of cleaning products, degreasers and detergents, which each released between 25 and 60 tonnes of NP and NPEs in 1996. Together, these two groups of industries accounted for the majority of total releases from industrial sources. Producers of paints, protective coatings, resins and adhesives released between 5.000 and 9.999 tonnes per year. Releases of between 0.100 and 4.999 tonnes of NP and NPEs in 1996 were reported for each of the following industries: formulators of industrial, institutional and domestic cleaning products, degreasers and detergents; pulp and paper mills; oil and gas recovery; producers of wastewater treatment products; formulators and distributors of products for the pulp and paper industry; and miscellaneous industries.

TABLE 3 Concentrations of NP and its ethoxylates in consumer products

Product	Average ethoxylate chain lengths	Range of concentrations[1]	Reference
Antiwrinkle preparation	8	>1 to 3%	McIntyre, 1996
Bath preparation	10, 12, 20, 40	>1 to 3%	McIntyre, 1996
Deodorant	10, 12, 14, 18	>1 to 3%	McIntyre, 1996
Eye makeup	Nonylphenol, 10, 15	>3 to 10%	McIntyre, 1996
Face makeup	10	0.1% or less	McIntyre, 1996
Fragrance	12, 14	>3 to 10%	McIntyre, 1996
Genital lubricant	9	>1 to 3%	McIntyre, 1996
Hair bleach	4, 6, 9, 49	>30 to 100%	McIntyre, 1996
Hair conditioner	10, 14, 23	>3 to 10%	McIntyre, 1996
Hair dye	1, 2, 4, 6, 9, 10, 49	>30 to 100%	McIntyre, 1996
Hair grooming products	4, 9, 10, 11, 12, 15, 23	>3 to 10%	McIntyre, 1996
Hair removal products	10	>0.1 to 0.3%	McIntyre, 1996
Hair shampoo	Nonylphenol, 4, 10, 12, 15	>10 to 30%	McIntyre, 1996
Hair straightener	10	>1 to 3%	McIntyre, 1996
Hair waving preparation	4, 9, 10, 11, 12, 14, 15, 23, 30	>3 to 10%	McIntyre, 1996
Manicure preparation	7, 14, 100	>30 to 100%	McIntyre, 1996
Skin cleanser	4, 8, 9, 10, 12, 14, 15	>3 to 10%	McIntyre, 1996
Skin moisturizer	4, 5, 6, 9, 10, 12, 14, 15	>3 to 10%	McIntyre, 1996
All-purpose spray cleaner	not specified[2]	<0.2 to 5%	World Wildlife Fund 1997
Stain remover	not specified[2]	<0.2 to 11%	World Wildlife Fund 1997
Liquid laundry detergent	not specified[2]	<0.2 to 28%	World Wildlife Fund 1997
Paints	8–9, 15–20	0.6 to 3%	WHO, 1998

[1] The concentrations reported for the cosmetics are approximate; they are reported as range numbers 1, 2, 3, 4, 5, 6 and 7, corresponding to ranges of concentrations of >30 to 100%, >10 to 30%, >3 to 10%, >1 to 3%, >0.3 to 1%, >0.1 to 0.3% and 0.1% or less, respectively.

[2] While the average EO chain length was not specified, the analytical method would have detected only NPEs with an EO chain length of between 4 and 10.

It is important to note that industrial releases do not indicate the total release of NP and NPEs to the Canadian environment. For instance, individual households and institutions using NPE-containing products were not contacted under the Section 16 survey, and these releases are, therefore, not reported. Nevertheless, these products are generally disposed of "down the drain" and are released to municipal water treatment facilities or septic systems. This source is likely to be significant to the NPE loading at wastewater treatment facilities.

2.3 Exposure characterization

2.3.1 Environmental fate

With regard to the behaviour of a chemical in the environment, it should be noted that there are many factors that influence its persistence, including its physical and chemical properties and ecosystem-specific properties, such as (for aquatic ecosystems) the nature and concentration of microbial populations, the nature and concentration of dissolved and suspended

TABLE 4 Releases of NP and its ethoxylates to various environmental media, by industry sector in Canada in 1996 (from Environment Canada, 1998) [1,2]

Industry sector	No. of sites [3]	Total (kg) released to				Total (kg, range) released from all sites
		Air	Stream	Waste-water	Landfill/ or deep well	
Formulators and distributors of surfactants	4		√			25 000–60 000
Industrial users of cleaning products, degreasers and detergents	3	√			√	25 000–60 000
Producers of paints, protective coatings, resins and adhesives	19		√			5000–9999
Formulators of industrial, institutional and domestic cleaning products, degreasers and detergents	22					100–4999
Pulp and paper mills	3	√		√	√	100–4999
Oil and gas recovery	2		√	√		100–4999
Production of wastewater treatment products [4]	2		√			100–4999
Formulators and distributors of products for the pulp and paper industry	6		√			100–4999
Miscellaneous	4					100–4999
Total	**65**					

[1] For reasons of confidentiality, only ranges are reported. Checkmarks (√) indicate releases to the compartments.

[2] Textile mills are under-represented. In 1996, approximately 227 textile mills operated in Canada; however, only 97 received the Section 16 survey, and, of these, only 22 responded that they were involved with NPEs above the 1000-kg trigger quantity. Releases of NPEs were reported to be zero by the 22 respondents.

[3] In some cases, several sites may be owned by one company.

[4] Products used in pulp and paper, steel, oil and gas, hydropower and wastewater treatment facilities.

material, temperature, degree of insolation, etc. In general, important physical, chemical and biological removal mechanisms for chemicals in aquatic ecosystems are, (i) volatilization and adsorption to suspended solids and sediment, (ii) chemical and photochemical degradation or transformation and (iii) uptake and transformation by microorganisms, respectively. The variation in the physical/chemical properties of NP/NPEs and their rapid conversion to other metabolites make their environmental fate extremely complex.

2.3.1.1 Air

NP and NPEs are not expected to readily volatilize into air and are expected to degrade rapidly in the atmosphere. Dachs *et al*. (1999) detected NP (sum of 11 isomers) in all

atmospheric samples collected from the urban and coastal regions of the Lower Hudson Estuary and predicted that NP may volatilize out of water into the air in areas where NP concentrations are elevated in surface waters, although the Henry's law constant is low. The U.K. Environment Agency (1998) has estimated a half-life of 0.3 days for the reaction of hydroxyl radicals with NP in the atmosphere, indicating that it would be unlikely for any NP in air to be transported to remote regions. NPEs are far less volatile than NP, and thus it is expected that they would not partition to the atmosphere. Because of the presence of NPEs in aerially applied pesticide formulations, however, there is a need to determine their atmospheric chemistry, photochemistry and fate.

2.3.1.2 Water and sediment

2.3.1.2.1 Degradation in water in laboratory tests

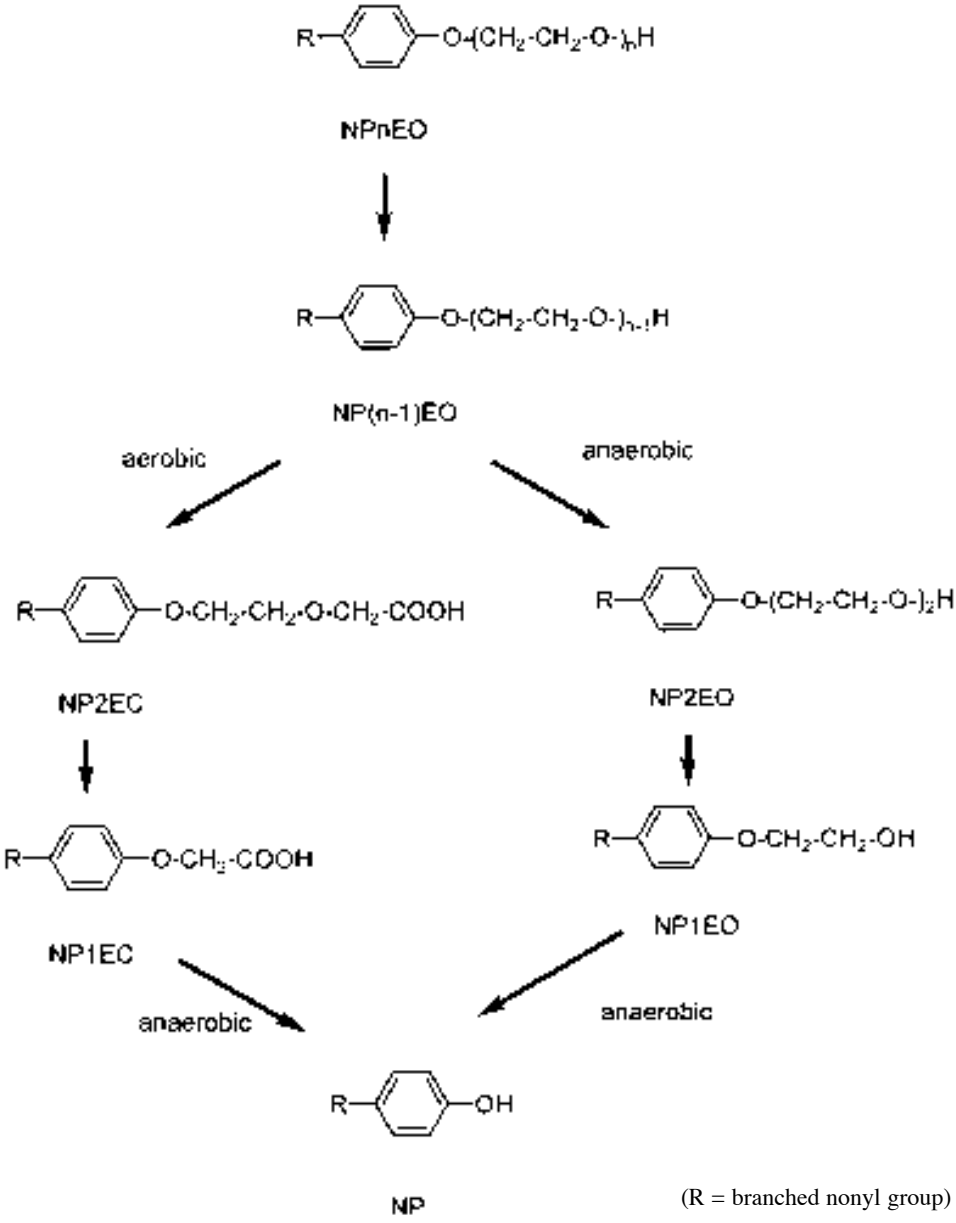
Although there are some conflicting reports in the literature, in general NPEs and NP are not readily biodegradable using standard test methods. Substantial biodegradation will occur after a period of acclimation. NPEs are, therefore, inherently biodegradable, and the mechanism involves stepwise loss of ethoxy groups to lower NPE congeners, followed by the production of NPEC and NP, depending upon experimental conditions (Rudling and Solyom, 1974; Maki *et al*. 1994). The degradation pathway is shown in Figure 2. This pathway is an oversimplification because it does not include NPnEC where $n > 2$ or NPEs with carboxyl groups attached to the nonyl chain. The intermediate and final products of metabolism are more persistent than the parent NPEs, but it is believed that such chemicals will also be ultimately biodegraded. Branching of the nonyl group in NP and NPEs retards biodegradation, as does increase in length of the EO chain. APs and APEs are more persistent than alkylbenzene sulfonates and alcohol ethoxylates (Kravetz *et al*., 1991; Maguire, 1999). It should also be noted that the use of high concentrations of chemicals in biodegradability tests may result in artificially high persistence data if the chemical poisons the test organisms. This possibility has been suggested to account for some differences in results for the biodegradability of NPEs (e.g., U.K. Environment Agency, 1997).

2.3.1.2.2 Degradation in municipal wastewater treatment plants

It has been noted that full-scale municipal wastewater treatment plants (MWWTPs) can provide greater efficiencies for the removal of NPEs than can bench-scale systems, which may be due to a greater variety of microbial populations and nutrients in the former (Holt *et al*., 1992). In general, primary biodegradation of NPEs in MWWTPs is readily achievable, but ultimate biodegradation is not. Substantial differences in treatment efficiencies for NPEs and their degradation products exist among MWWTPs. These differences have been attributed to the load of NPEs in influent streams and MWWTP design and operating conditions, including temperature of treatment. In some locations, more persistent products such as NP and lower-chain NPEs have been observed in MWWTP final effluents and receiving waters. In addition, substantial concentrations of NP and lower-chain NPEs are found in sludges from MWWTPs. The application of NP-containing sludges to agricultural land may result in potential exposure in terrestrial environments.

In general, primary biological degradation of NPEs is the major pathway and occurs more rapidly in MWWTPs than in natural environments because of the higher concentration of microorganisms in MWWTPs compared with natural environments. Most municipalities in Canada have some type of wastewater treatment. MWWTPs play a significant role in the transformation and degradation of NP and NPEs before their entry into the environment. More than 60% of the higher-chain APEs that enter MWWTPs exit as stable metabolites (e.g., APs and short-chain APEs) in either their effluents or their sludges (Ahel *et al*., 1994a).

FIGURE 2 Biological degradation pathway for NPEs



In general, once APEs, including NPEs are released to municipal wastewater systems, several transformations can occur. APEs with more than eight EO units (most common commercial products) are readily degraded in effluent treatment systems with >92% efficiency (Brunner *et al*., 1988; Kubeck and Naylor, 1990; Ahel *et al*., 1994a,b; Naylor, 1995). Under aerobic and anaerobic treatment conditions, the biodegradation mechanism involves an initial loss of ethoxy groups, leading to the production of NP1EO and NP2EO and their carboxylate derivatives NP1EC and NP2EC (as well as NPnEC, where n > 2, and CAPECs, alkyphenols with carboxylate groups on both the alkyl and ethoxylate chains and CAPEs, alkylphenols with carboxylated alkyl chain) and the final product, NP. The wastewater treatment, therefore, results in

chemical transformation to compounds that are more persistent, toxic and estrogenic than the parent NPEs. Structurally analogous metabolites are formed by the degradation of OPEs and other APEs in MWWTPs. Additionally, there is evidence for the halogenation of some of these products in MWWTPs that use chlorine for disinfection (Maguire, 1999).

Di Corcia *et al*. (1998) studied CAPECs experimentally and in effluents. These APE metabolites were found at higher concentrations than CAPEs and persisted in experimental media for more than five months. CAPECs represented 63% of the total APE metabolites present in MWWTPs at concentrations of 58 μg/L (Di Corcia *et al*., 1998). Ding *et al*., (1996) reported CAPECs in MWWTPs effluents at concentrations ranging from 0.9 to 1.1 μg/L.

Discharges from MWWTPs provide the two major routes for environmental release of NPEs and their degradation products. The first route is by discharge of the final treated effluent to nearby receiving waters. The second major environmental release route for nonylphenolics is via sewage treatment processes and adsorption onto sludge. NP (in particular) and NP1EO and NP2EO are more lipophilic than the parent NPEs and tend to accumulate in sludges and sediments, while NPECs (which are more water soluble and can substantially, or completely, ionize at the pH of most natural waters) are generally found in the final effluents, sometimes at much higher concentrations than other nonylphenolic compounds. NP, NP1EO and NP2EO, however, also have been found in effluents and receiving waters. Most Canadian MWWTPs employing secondary or tertiary treatment utilize the activated sludge process (an anaerobic digestion process), which results in the sorption of NP, the dominant nonylphenolic substance, onto sludge. Up to 95% of the nonylphenolic composition of digested sludge may be attributed to NP. Sludge is disposed of in three ways — by incineration, by landfilling and by spreading on agricultural soils. Although there has generally been little research on the fate of nonylphenolics in sludge disposed of by any of these three techniques, some studies have examined the fate of NP in landfills (Maguire, 1999).

The final effluent composition is dependent on the treatment process(es) used in the facility. Where only primary treatment is used, the effluent composition reflects the short hydraulic retention time, and ethoxylated products (i.e., NPnEO, where n = 3–20) are dominant (82%), with minor components of NP (3%), NP1EO and NP2EO (12%), and NP1EC and NP2EC (3%). Secondary-treated effluent composition is substantially different from that of primary-treated effluent (Figure 3). Higher-chain NPEs make up only 28% of the nonylphenolic compounds in secondary-treated effluent, whereas metabolites make up the rest (Figure 3). Carboxylic acid metabolites (i.e., NP1EC and NP2EC) account for about 46% of the secondary-treated effluent composition, while NP1EO and NP2EO make up 22% and NP accounts for only 4% (Ahel *et al*., 1994a) (Figure 3). Buildup of NP, however, has been observed in activated sludge and digested sludge from MWWTPs utilizing secondary or tertiary treatment systems (Giger *et al*., 1987) (Figure 4). Additionally, some production of NP1EO and NP2EO was observed in the digested sludge.

Birch (1991) and Watkinson and Holt (1991) noted that a critical control parameter for the treatment of NPEs in MWWTPs with activated sludge plants is the sludge retention time (SRT). This parameter dictates the necessary growth rate for the competent organisms within the total microbial population. When the growth rate of the organisms is less than the SRT, the competent organisms are washed out of the system, and little treatment of the specific substance takes place. The growth rate of organisms is influenced by temperature, and thus a combination of decreasing SRT and decreasing temperature will result in a less effective biodegradation system. Watkinson and Holt (1991) noted that the normal range of SRTs for activated sludge plants would appear to be in the range 6–20 days. Ahel *et al*. (1994b) noted

FIGURE 3 Concentration of NP, lower-chain NPEs and NPECs in various types of municipal wastewater treatment plant effluents (Windsor = primary treatment; Burlington = secondary treatment; Galt, Guelph and Edmonton = tertiary treatment) (data from Bennie, 1998a)

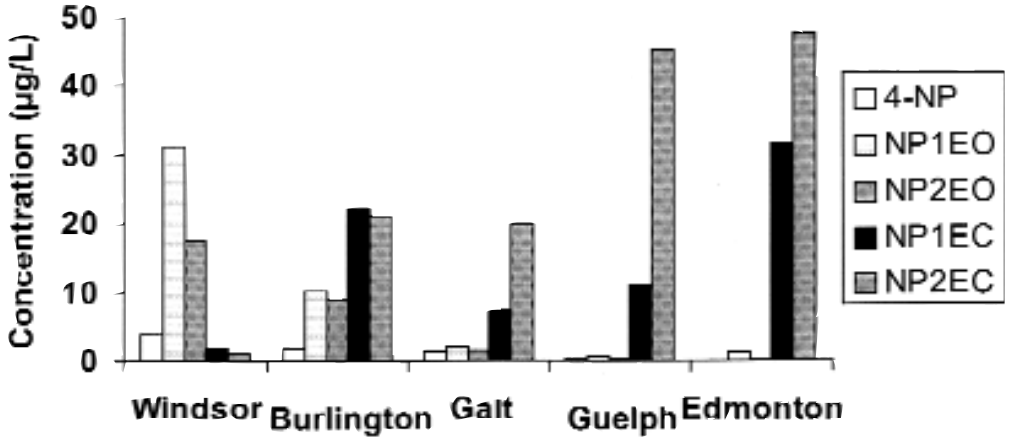
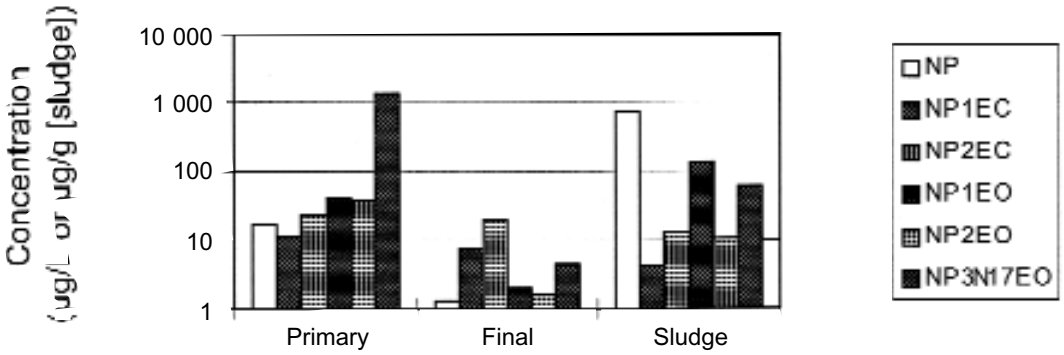


FIGURE 4 Distribution of NP, NPEs and lower-chain NPECs in effluent and sludge from a tertiary-treated municipal wastewater treatment plant. Sample taken September 1997, representing the mean of eight 24-hour composites (Water Technology International Corp., 1998b)



that the highest NPE elimination rates were achieved in the MWWTPs characterized by low sludge loading rates and nitrifying conditions. This was confirmed in a limited study of two Canadian MWWTPs (Water Technology International Corp., 1998b). It should also be noted that there may be substantial differences in treatment efficiencies of NPEs between dedicated industrial wastewater treatment facilities and MWWTPs. Field and Reed (1996) reported that industrial wastewater treatment can be characterized by higher temperatures, increased hydraulic residence times and greater degrees of acclimation than that of MWWTPs. Because MWWTPs operate at ambient temperatures, more seasonal variation in effluent composition would be expected from MWWTPs than from industrial effluents.

2.3.1.2.3 Degradation in water and sediment

Primary biodegradation of higher-chain NPEs is generally faster than ultimate degradation of more persistent products, such as NP1EO, NP2EO, NP1EC, NP2EC and NP (Ahel *et al*., 1994b). Microbial acclimation to such chemicals is required for optimal degradation efficiencies (Maguire, 1999). Photodegradation of NP and lower-chain NPEs is also expected to be important. In aquatic ecosystems, it appears that parent NPEs are not persistent, although some degradation products may have moderate persistence, especially under anaerobic conditions. It should be noted that the U.K. Environment Agency (1997) estimated a biodegradation half-life of about 150 days for NP in surface water. Based on the limited data available, NP and the lower NPEs and NPECs are expected to be persistent in groundwater. The recent results of Heinis *et al*. (1999) indicate that NP can be moderately persistent in sediments. It is expected that the more water soluble (and ionized) carboxylate derivatives NP1EC and NP2EC will largely remain in the aqueous phase.

2.3.1.3 Soil

Although there are relatively few studies of NP and NPEs in soil, NP has been found to persist in landfills under anaerobic conditions; however, it does not appear to be persistent in soil under aerobic conditions (Marcomini *et al*., 1991). Based on results of laboratory biodegradation studies, Hughes *et al*., (1996) reported that NP9EO would be expected to biodegrade in soil under aerobic conditions. The U.K. Environment Agency (1997) estimated a half-life of about 30 days for primary biodegradation of NP in soil and of 300 days for ultimate mineralization. Studies conducted by Water Technology International Corp. (1998a) demonstrated similar results in Canadian soils. When sludge was added to soil, the concentration of NP initially increased, followed by a decrease to below detection limits within 120 days.

Sewage sludges are commonly applied to soils in Canada. Studies on the persistence of NP in soils indicate that NP can be rapidly degraded to carbon dioxide by soil microorganisms (Topp, 1999). NP, at concentrations as high as 250 mg/kg, was rapidly mineralized by soil organisms in cultivated agricultural soils at 4°C, temperate, non-cultivated soils and arctic soils. The lack of a lag phase in the mineralization indicated that the soil contained active microflora, conditioned to mineralize other natural phenols in soils. A study conducted at the Guelph Turfgrass Institute by Bennie *et al*. (1998) demonstrated a rapid disappearance of initial concentrations of 5.5 mg NP/kg soil in sludge-treated soil plots. NP concentrations were undetectable after 90 days. The NPEs may be degraded to NP in the soils, therefore resulting in the non-linear disappearance of NP in the soils after sludge application. Bokern *et al*. (1998) concluded that the uptake of NP from soil was slow and that NP was quickly mineralized by soil microorganisms.

2.3.2 Environmental distribution

Fugacity modelling was carried out to provide an overview of key reaction, intercompartment and advection (movement out of a system) pathways for NP and its overall distribution in the environment. Fugacity modelling for NPEs was not considered appropriate, given the tendency of surfactants of this type to accumulate at media interfaces. A steady-state, non-equilibrium model (EQC Level III fugacity model, Version 1.01; May 1997) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). Values for input parameters were as follows: molecular weight, 220 g/mol; aqueous solubility, 6 mg/L; vapour pressure, 0.3 Pa; log K_{ow}, 4.3; melting point –8°C. A "low half-lives" scenario and a "high half-lives" scenario were constructed to "bracket" the half-lives suggested by data referred to in this Assessment Report. The following values were used in the modelling: half-life in air, 5–17 hours; half-life in water, 1700–5500 hours; half-life in soil, 550–1700 hours; and half-life in sediment, 17 000–55 000 hours.

The results of this modelling indicate that NP partitions differently depending on the medium to which it is released. For example, if emitted into air only, more than two thirds of the NP that remains at steady state is predicted to be present in air (67–76%), with lower fractions in water (12%), sediment (8-12%) and soil (3-8%). When NP is released to water, the model predicts that most of it is present in water (49–59%) and, to a lesser extent, sediment (41–50%), with a negligible proportion (<1%) in air and soil. If released to soil only, virtually all (>99%) of the NP is predicted to be present in the soil compartment.

2.3.3 Environmental concentrations

Concentrations of NP and NPEs measured in environmental samples are summarized in Table 5, based on Canadian data when such data are available. A limited number of studies have reported the environmental occurrence of NP and NPEs in Canada. Together with available unpublished data, the reported environmental concentrations of NP and NPEs in effluents, sludges, surface waters and aquatic sediments are listed in Appendix A of the environmental supporting document (Servos *et al*., 2000). Concentrations of NP and NPEs found in Canadian sediments, effluents and sludges in Canada are similar to those found in other countries (Servos *et al*., 2000).

2.3.3.1 Air

No data were identified on concentrations of NP and its ethoxylates, or related compounds, in Canadian air. Dachs *et al*. (1999) detected NP (11 isomers) in all samples of ambient air from urban and coastal areas of the Lower Hudson Estuary. Concentrations of NP in air of the New York–New Jersey Bight ranged from 2.2 to 70 ng/m^3. No data on the levels of NPEs in ambient air were identified, although, based on the fact that they are far less volatile than NP, it is expected that they would not partition to the atmosphere.

2.3.3.2 Water and effluents

In general, NPEs are found at high concentrations (maximum concentration 8811 μg/L) in untreated or partially treated industrial (e.g., textile mills) and municipal effluents in Canada. Untreated effluents typically have elevated NP3–17EO concentrations and relatively high levels of NP and NP1,2EO (Table 5). Treatment significantly reduces the concentration of NP3–17EO in final effluents. The levels of NP3–17EO, NP1,2EO and NP in final effluents can, therefore, vary dramatically, depending on the type and degree of treatment. Well-treated effluents typically have very low levels of NP3–17EO. As higher-chain-length NPEs move through the treatment system, they are degraded to lower-chain-length NPEs and NPECs and ultimately to NP, which itself can be further degraded or sorbed to particles or sludges. Although NP1EO and NP2EO are created during treatment, concentrations of these transformation products are generally reduced in well-treated effluents. In contrast, NP1EC and NP2EC can increase in concentration with increased degree of treatment (Figure 3). The nature of the inputs and type and degree of treatment strongly influence the concentrations and relative proportions of NPEs released in final effluents. The relative distribution and concentrations of NPEs in influent, final effluent and sludges are, therefore, very different (Figure 4).

As the EO chain length decreases, a corresponding decrease in water solubility is observed. NP is, therefore, generally associated with organic particles, sludges in the treatment system and ultimately sediments in the environment. NPECs, however, are considerably more water soluble than the corresponding NPEs and are present in the aqueous phase of final effluent.

In Canadian fresh water, concentrations of NP ranged from non-detectable (<0.02 μg/L) to 4.25 μg/L (mean 0.20 μg/L; median <0.02 μg/L) (42 sites; n = 126) (Bennie *et al.* 1997; Bennie, 1998a) (Table 5). Highest freshwater concentrations of NP were observed in areas in close proximity to MWWTP discharges,

Table 5 Ranges of concentrations of NPEs in the Canadian environment (total number of sites, total number of samples)

Environmental compartment	Site type		NP	NP1EO	NP2EO	NP3–17EO	NP1EC	NP2EC
Effluents (μg/L)	Textiles	untreated	2.68–13.33 (2,5)	37.17–257.09 (2,5)	106.31–591.98 (2,5)	798.42–8811.24 (2,5)	<0.45 (1,2)	<0.45 (1,2)
		on-site secondary treatment	0.09–3.56 (2,4)	1.12–4.10 (1,2)	0.93–3.92 (1,2)	2.07–315.45 (2,3)	0.74–5.2 (2,4)	<0.45–55.13 (2,4)
		going to MWWTP	0.23–25.62 (9,14)	0.74–69.15 (10,14)	0.64–284.51 (10,14)	50.18–5767.65 (10,14)	<0.45–1.90 (5,7)	<0.45–2.80 (5,7)
	Pulp and paper	prior to 1998	<0.02–26.20 (14,33)	<0.02–3780.00 (13,32)	<0.02–67.84 (14,33)	–	–	–
		after 1998	<0.10–4.3 (19,19)	<0.10–6.90 (3,3)	<0.10–35.60 (3,3)	5.90–28.80 (3,3)	<1.00–10.13 (15,15)	<1.00–32.32 (15,15)
	MWWTP	primary	<0.02–62.08 (8,21)	0.07–56.13 (10,26)	0.34–36.33 (10,26)	4.81–735.20 (8,22)	1.17–11.00 (3,7)	1.01–5.20 (3,7)
		secondary	0.12–4.79 (21,54)	<0.02–43.37 (20,46)	<0.02–32.62 (20,46)	1.00–52.82 (16,36)	2.15–74.97 (14,34)	2.15–45.40 (14,34)
		tertiary	<0.02–3.20 (7,37)	0.30–26.4 (7,37)	0.25–12.45 (7,37)	0.40–18.00 (6,35)	2.15–48.58 (6,34)	2.15–59.46 (6,34)
		lagoon	0.75–2.15 (5,5)	0.34–0.90 (5,5)	0.03–0.90 (5,5)	1.00–2.10 (4,4)	2.15–2.6 (4,4)	2.15–3.00 (4,4)
Aquatic (μg/L)	Rivers		<0.02–4.25 (25,90)	<0.02–2.30 (12,51)	<0.02–2.45 (12,51)	0.11–17.56 (3,27)	0.44–3.17 (1,37)	0.81–4.30 (1,37)
	Lakes		<0.02–0.06 (5,5)	<0.02–5.07 (4,4)	<0.02 (4,4)	–	–	–
	Harbours		<0.02–0.98 (12,31)	<0.02–10.29 (12,26)	<0.02–10.43 (12,26)	–	–	–
Benthic (μg/g)			<0.02–72.20 (23,58)	<0.02–38.12 (6,14)	<0.02–6.02 (6,14)	0.02–0.17 (1,4)	–	–
Soil/sludge (μg/g)			0.74–1260 (30,107)	2.90–1825.29 (28,90)	1.52–297.21 (28,90)	0.43–215 (28,90)	<0.30–8.70 (17,66)	<0.30–26.0 (17,66)

pulp mill discharges, large population centres or regions of heavy industry. The different types of sites sampled included rivers, lakes (primarily Great Lakes) and harbours. In rivers across Canada, the concentrations of NP ranged from <0.02 to 4.25 μg/L, although Carey *et al.* (1981) reported values up to 2600 μg/L in Canagagigue Creek in Elmira, Ontario. These latter values were not considered representative because they were associated with an industrial spill into this small creek. NP concentrations in lakes ranged from <0.02 to 0.06 μg/L, and NP concentrations in harbours were between <0.02 and 0.98 μg/L. The maximum NP1EO concentration in rivers (2.30 μg/L) was lower than those observed in lakes (5.07 μg/L) or harbours (10.3 μg/L); however, the maximum NP2EO level in rivers (2.45 μg/L) was higher than that in lakes, which was below the detection limit (<0.02 μg/L) (Table 5). The maximum NP2EO concentration observed in harbours was 10.4 μg/L. Levels of NP3–17EO detected in two rivers in southern Ontario ranged from 0.11 to 17.6 μg/L (mean 1.41 μg/L; median 0.39 μg/L; n = 27 at three sites).

Concentrations of NP in untreated textile mill effluents ranged from 2.68 to 13.3 μg/L (Table 5). NP levels in effluent from on-site treated textile mills ranged from 0.09 to 3.56 μg/L. NP concentrations in textile mill effluents that discharge through a municipal treatment facility were between 0.23 and 25.6 μg/L (Bennie, 1998a). NP1EO and NP2EO concentrations in final effluents from textile mills were dependent on type of effluent treatment. Highest concentrations were observed in effluents that were not subject to treatment (Bennie, 1998a). Higher-chain NPEs were found at higher concentrations (2.07–8811 μg/L) than NP or the lower-chain NPEs in textile mill effluents (Table 5).

Pulp mill effluent samples taken in the years 1990–1993 showed that NP concentrations were quite variable (Bennie, 1998a). Due to recent changes to reduce the use of NPEs in Canadian pulp and paper mill processes, NP concentrations in final effluent from pulp and paper mills were divided into those values obtained prior to 1998 (<0.02–26.2 μg/L) (Bennie, 1998a) and those obtained more recently (<0.10–4.3 μg/L) (Lee and Peart, 1999) for this assessment. Lee and Peart (1999) reported NP1EO, NP2EO and NP3-17EO concentrations in pulp and paper mill effluents ranging from <0.10 to 6.90 μg/L, from <0.10 to 35.6 μg/L for NP2EO and from 5.90 to 28.8 μg/L, respectively (Table 5).

NP was below method detection limits (<0.02 μg/L) in two effluent samples from a major Canadian oil refinery (Bennie, 1998a).

MWWTPs equipped with primary, secondary and tertiary treatment systems have been sampled across Canada (Bennie, 1998a; Lee *et al.*, 1998; Water Technology International Corp., 1998b). Final effluents contained concentrations of NP that ranged from <0.02 to 62.1 μg/L, from 0.12 to 4.79 μg/L and from <0.02 to 3.20 μg/L for primary, secondary and tertiary treatment systems, respectively (Table 5). MWWTPs that use a lagoon system had NP effluent concentrations ranging from 0.75 to 2.15 μg/L (Bennie, 1998a; Water Technology International Corp., 1998b). Bennie *et al.* (1998) measured NP concentrations in raw sewage from nine communities in eastern Canada (0.69–156 μg/L). The highest concentrations (>100 μg/L) were associated with two cities where textile mill inputs to the municipal treatment system were significant. NP1EO concentrations in MWWTP effluents ranged from <0.02 to 56.1 μg/L, with highest concentrations observed in effluents from primary treatment systems. NP2EO concentration trends were similar (<0.02–36.3 μg/L), with the highest maximum concentrations observed in primary effluents. NP3–17EO concentrations in final effluents from primary treatment plants were greater than secondary, and, similarly, a decrease in concentration in final effluent from tertiary MWWTPs was observed relative to secondary treatment effluents. NP1,2EC concentrations ranged from 1.01 to 75.0 μg/L in effluents from MWWTPs, with maximum concentrations occurring in effluents from facilities with secondary or tertiary treatment.

2.3.3.3 Sediments

The water-soluble NPEs and NPECs are present in the aqueous phase (Table 5). In contrast, the hydrophobic transformation products of NPE degradation — NP and NP1,2EO — are generally sorbed to sediments. Most of the APE concentration data in Canadian sediments are for NP. Very few data for the NPEs are available in the literature. A recent study by Shang *et al*. (1999) on the distribution of NPEs in marine sediments from the Strait of Georgia observed a shift from the dominance of NPEs with 8–10 EO units in commercial products to NP and NP1EO in sediments. These authors also concluded that NPEs were relatively persistent in aquatic sediments.

NP concentrations in sediments from the Great Lakes basin and the upper St. Lawrence River ranged from below detection levels (<0.02 μg/g dry weight [dw]) to 72.2 μg/g dw (Lee and Peart, 1995; Bennie *et al*., 1997; Bennett and Metcalfe, 1998; Bennie, 1998a) (Table 5). NP concentrations measured in sediment from the upper and lower reaches of the Fraser River and the Thompson River sub-basin ranged from <0.02 to 0.57 μg/g (Brewer *et al*., 1998). The highest NP concentrations in the Great Lakes data set are associated with Hamilton Harbour samples taken near the discharge of the MWWTP at Burlington, Ontario. The mean Canadian NP sediment concentration was determined to be 4.46 μg/g, with a median value of 0.21 μg/g (n = 58 at 23 sites).

NP1EO concentrations in sediment from the upper St. Lawrence River and Great Lakes basin ranged from <0.02 to 38.12 μg/g dw, with mean levels of 3.13 μg/g dw and a median of <0.03 μg/g dw (n = 14 at six sites) (Bennie *et al*., 1997; Bennie, 1998a). In the same study, NP2EO concentrations in sediment ranged from <0.02 to 6.02 μg/g dw, with a mean of 0.51 μg/g dw and a median of <0.02 μg/g dw (n = 14 at six sites). NP3–17EO sediment concentrations measured at one site in Ontario ranged from <0.02 to 0.17 μg/g dw (mean 0.05 μg/g dw; median 0.02 μg/g dw; n = 4) (Bennie, 1998a). No NPEC concentration data were identified in Canadian sediments.

2.3.3.4 Sludges

Lee and Peart (1995), Lee *et al*. (1997, 1998), Bennie (1998a), Bennie *et al*. (1998) and Water Technology International Corp. (1998a) determined NP concentrations in sludge samples from MWWTPs across Canada. Levels ranged from 0.74 to 1260 μg/g dw, with a mean concentration of 299.28 μg/g dw (n = 107 at 30 sites); the median value was 217.27 μg/g dw. The highest values were associated with MWWTPs that utilize anaerobic secondary sludge digestion processes. NP1EO and NP2EO were reported in sludge at concentrations ranging from 2.9 to 1825 μg/g dw and from 1.5 to 297 μg/g dw, respectively. NP2EO in sludge is usually present at much lower concentrations than NP1EO, but in some samples concentrations of NP2EO were slightly higher. NP3–17EO concentrations ranged from 0.43 to 215 μg/g dw (mean 49.58 μg/g dw; median 47.60 μg/g dw; n = 90 at 28 sites). NP1EC concentrations were reported to be between <0.30 and 8.70 μg/g dw (mean 2.53 μg/g dw; median 2.26 μg/g dw; n = 66 at 17 sites), while the range of NP2EC concentrations was reported to be <0.30–26.0 μg/g dw (mean 9.27 μg/g dw; median 9.56 μg/g dw; n = 66 at 17 sites).

Lee *et al*. (1997, 1998) reported concentrations in digested sludge from nine MWWTPs ranging from <0.5 to 25 μg/g dw for NP1EC and from <0.5 to 38 μg/g for NP2EC. Detectable levels of NP1EC (2.8–6.6 μg/g dw) and NP2EC (7.1–23 μg/g dw) were found in sludge from two Canadian MWWTPs (Water Technology International Corp., 1998b).

2.3.3.5 Soil

There are essentially no data available for APE concentrations in Canadian soils. A reference sample collected during a sludge addition study was found to have concentrations below detection limits (<0.03 μg/g dw) (Water Technology International Corp., 1998a). Bennie (1998b) reported a concentration of NP of 2.72 mg/kg and traces of NPEs in sludge-amended soil. Following the aerial application of 0.47 L NP/ha in a pesticide formulation to 40 ha of forest,

concentrations in all soil samples collected for up to 62 days were below the limit of detection (0.1 ppm) (Sundaram *et al*., 1980).

The concentrations of NP, NP1EO and NP2EO in sludge-amended soil in Switzerland immediately after the application of sewage sludge were 4.7, 1.1 and 0.1 mg/kg, respectively. After 320 days, residual concentrations were 0.5, 0.1 and 0.01 mg/kg for NP, NP1EO and NP2EO, respectively (Marcomini *et al*., 1989).

2.3.3.6 Biota

There are no published data on NP levels in fish or other aquatic biota in Canada; however, NP levels in a limited number of specimens have been determined in an unpublished study (Bennie, 1998a). Two carp (*Cyprinus carpio*) samples from Hamilton Harbour had non-detectable levels (<0.02 μg/g) of NP, while a third carp sample contained 0.02 μg/g (whole tissue wet weight). Nine rainbow trout (*Oncorhynchus mykiss*) taken from western Lake Ontario had non-detectable levels (<0.02 μg/g) of NP, but a tenth fish contained 0.043 μg/g (whole tissue wet weight). Liver and fat samples from five different beluga whales (*Delphinapterus leucas*) collected on the St. Lawrence River shore were analysed for NP. NP levels in all five liver samples were below detection (0.02 μg/g), but three of the five fat samples contained detectable NP concentrations (0.02–0.12 μg/g wet weight) (Bennie, 1998a). Concentrations of NP, NP1EO and NP2EO were as high as 1.6, 7.0 and 3.0 mg/kg, respectively, in four composite samples of fish (chub [*Leuciscus* (*Squalus*) *cephalus*], barbel [*Barbus barbus*] and rainbow trout) collected from the Glatt River in Switzerland; concentrations in a single sample of wild duck (*Anas boscas*) ranged from not detected to 1.2, 2.1 and 0.35 mg/kg dw for NP, NP1EO and NP2EO, respectively (Ahel *et al*., 1993). In five samples of mussels, *Mytilus edulis*, exposed *in situ* for 7 weeks to water from a surfactant manufacturer's wastewater outlet in Sweden, levels of NP, NP1EO, NP2EO and NP3EO were up to 0.40, 0.28, 0.13 and 0.04 mg/kg fresh weight, respectively (Wahlberg *et al*., 1990).

2.3.3.7 Drinking water

Clark *et al*. (1992) measured the concentration of NP1–7EO in a single drinking water sample in the United States. The concentration of each NPE measured was between 0.062 and 0.129 μg/L (Clark *et al*., 1992). Three drinking water samples in Italy contained concentrations of NPEs of 0.061–0.120 μg/L (Crescenzi *et al*., 1995). Concentrations of NP and NP1–3EO in an unspecified number of tap water samples collected in Barcelona, Spain, ranged from below the limit of detection (not specified) to 0.25 μg/L (Guardiola *et al*., 1991).

2.3.3.8 Food

The concentration of NP in one sample of fresh pork loin purchased from a local market in Toronto, which was cooked, was 0.53 mg/kg, while the level in one sample of cured pork was 0.34 mg/kg (Ramarathnam *et al*., 1993).

2.3.3.9 Consumer products

NP and NPEs are components in a wide range of consumer products, including cosmetics, cleaners and paints. The NP/NPE concentrations and EO chain lengths present in a number of these products are summarized in Table 3. Cosmetics notifications submitted by manufacturers to Health Canada (McIntyre, 1996) indicate that NP and NPEs are used in a large number of cosmetic products applied to the skin and hair. While the concentrations reported are approximate, some cosmetic products are reported to contain in excess of 30% by weight (Table 3). The World Wildlife Fund Canada (1997) analysed 31 common brand-name soaps and cleaning products available on the Canadian market (laundry detergents, stain removers, dishwashing soap, surface cleaners, bathroom cleaners, fabric softeners, oven cleaners and shampoo/hand soap)

for NPEs with a chain length between 4 and 10 inclusive. Seven of these products contained detectable concentrations of NPEs (the limit of detection was 0.2% w/w); two were liquid laundry detergents, two were stain removers and three were surface cleaners (Table 3). NPEs are typically found in paints at concentrations between 0.6% and 3% (WHO, 1998). NPEs are also the active ingredient in vaginal spermicides (Talmage, 1994).

2.3.4 Levels in human tissues and fluids

In a study conducted in Switzerland, adipose samples from 25 human cadavers thought to be non-occupationally exposed (4 collected in 1983–84 and 21 in 1994) were analysed for NP and NP1EO and NP2EO. The tissue concentrations of NP (which ranged from 19.8 to 84.4 ng/g lipids) and NP1EO and NP2EO (which were below the limit of detection [5 ng/g lipids] in all samples) were all within the range of background contamination found in the analytical "blank" samples. Müller (1997) indicated that all reasonable precautions had been taken to minimize contamination during analysis. NPEs with a chain length of 7–10 were identified but not quantified in urine samples from three non-occupationally exposed Canadian human subjects (Charuk *et al.*, 1998).

2.4 Effects characterization

2.4.1 Ecotoxicology

Although the studies reported in the literature have used many species, different test methods and different chemicals, there is a consistent pattern in the toxicity reported for NP and NPEs. NP is acutely toxic to fish (LC_{50} values 17–1400 μg/L), invertebrates (LC_{50} values 20–3000 μg/L) and algae (LC_{50} values 27–2500 μg/L). Chronic toxicity values (No-Observed-Effect Concentrations, or NOECs) are as low as 6 μg/L in fish and 3.9 μg/L in invertebrates. There is an increase in the toxicity of NPEs with decreasing EO chain length. NPECs are less toxic than the corresponding NPEs and have acute toxicities similar to those of NPEs with 6–9 EO units. NP and NPEs have been reported to cause a number of estrogenic responses in a variety of aquatic organisms. The relative estrogenic potency determined in several different *in vitro* systems is in the order NP > NP1EO = NP2EO > NP1EC = NP2EC > NP9EO. APEs bind to the estrogen receptor, resulting in the expression of several responses in both *in vitro* and *in vivo* systems, including the induction of vitellogenin. The threshold for vitellogenin induction in fish is 10 μg/L for NP. The estrogenic responses appear to be at least additive and should, therefore, be considered as a group. APEs also affect the growth of testes, alter normal steroid metabolism, disrupt smoltification and cause intersex (ova-testes) in fish.

2.4.1.1 Toxicity via atmospheric exposure

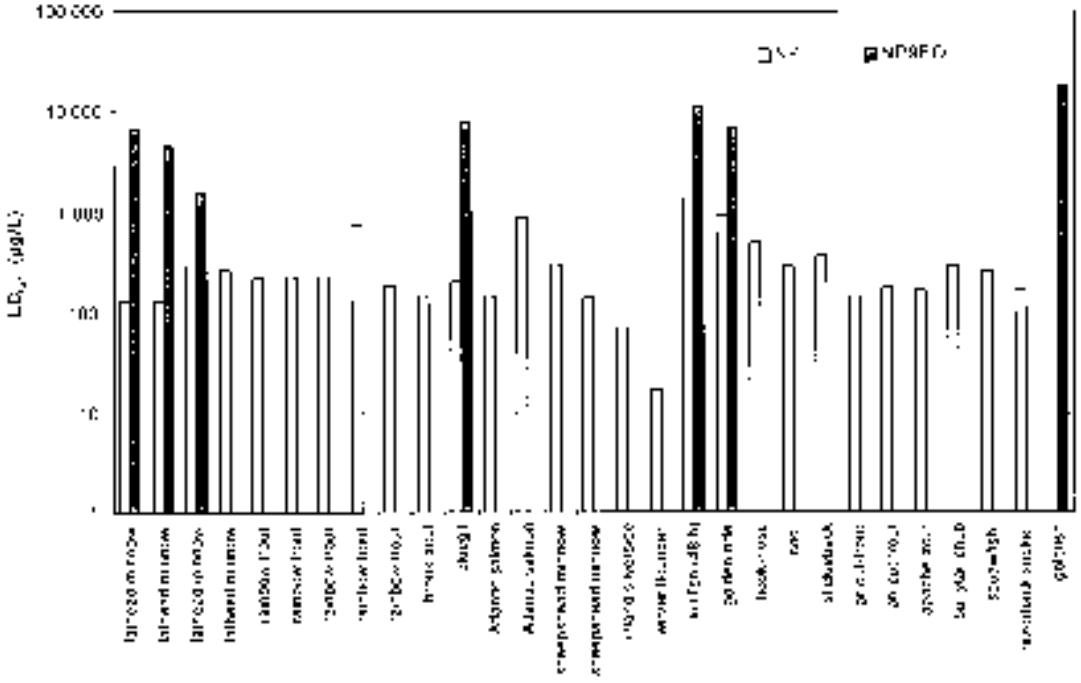
No data were identified on the toxicity of NP and its ethoxylates, or of other APs and their ethoxylates, to organisms via atmospheric exposure in Canada.

2.4.1.2 Toxicity via aquatic exposure

Most of the data in the literature have examined the effects of NP, although there are some data on the toxicity of NPEs and NPECs to freshwater organisms. There are relatively few toxicity data for marine organisms.

To assist in the assessment and interpretation of the data, a level of confidence (I–III) was associated with each of the studies based on the methodologies used and reported, the availability of supporting information (e.g., measured concentrations, water quality, etc.) and the availability of the original reports. Emphasis has been placed on studies that used individual compounds rather than mixtures or commercial preparations. This review of toxicity is focused on NP and its associated polyethoxylates (NPEs) and carboxylates (NPECs). The review presented by Talmage

FIGURE 5 Acute toxicity of NP and NP9EO to various fish species



gr-cut-trout = Greenback cutthroat trout; lah-cut-trout = Lahontan cutthroat trout

(1994) included many commercial products and mixtures of a wider variety of APEs.

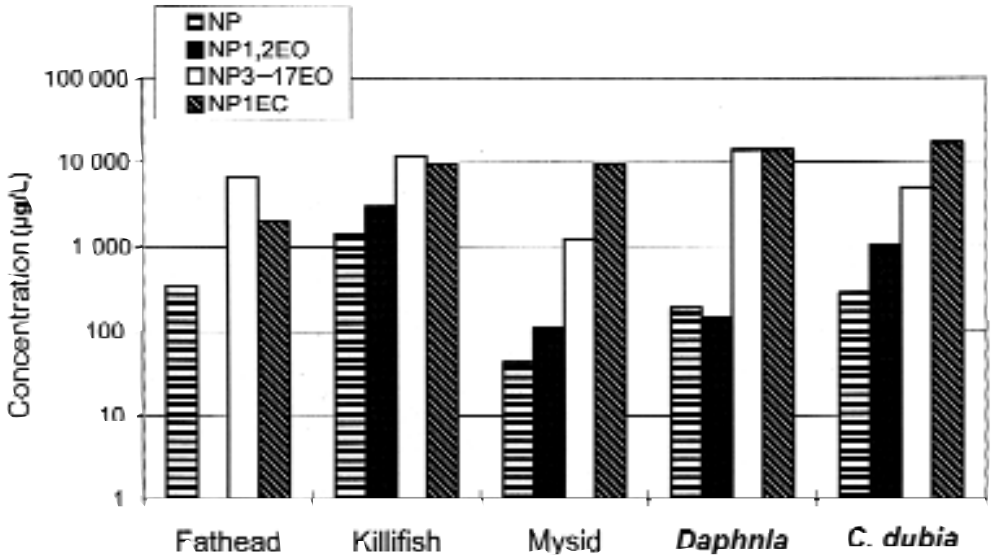
Early studies were focused on commercial products containing a variety of APEs. The majority of recent studies in the literature have focused on NP, OP or their respective polyethoxylates with 9 or 10 EO units (e.g., NP9EO, OP10EO). Although there are numerous studies on APEs in the literature, few have specifically examined the relationship between structure (EO chain length) and toxicity. In general, the toxicity of APEs in most organisms increases as the length of the EO chain decreases.

NPE toxicity increases as EO chain lengths decrease. During biodegradation, a reduction of NPE chain length is observed; however, this process simultaneously reduces total APE concentrations and thereby lowers toxicity. In a die-away study, Yoshimura (1986) also observed a net reduction in toxicity despite the degradation of NPEs to more toxic, lower-molecular-weight constituents (e.g., NP1EO). It is, therefore, important to measure the specific chemical composition of the matrix of interest to be able to adequately evaluate the potential toxicity of APEs.

2.4.1.2.1 Nonylphenol

The 96-hour LC_{50} for NP has been determined for at least 18 different species of fish, with reported values ranging from 17 to 1400 μg/L, although most of the values range from 100 to 300 μg/L (Figure 5). The 96-hour LC_{50}s for fathead minnow (*Pimephales promelas*), reported in several validated studies, ranged from 128 to 300 μg/L (Holcombe *et al*., 1984; Ward and Boeri, 1991b; Brooke, 1993; Naylor, 1995; Weeks *et al*., 1996) (Figure 6). Reported 96-hour LC_{50}s for rainbow trout were similar, 190–920 μg/L (Brooke, 1993; Dwyer *et al*., 1995; Naylor, 1995). *Ceriodaphnia dubia* had a 96-hour EC_{50} of 69 μg/L and a 7-day NOEC of 134 μg/L, based on reproduction, for

FIGURE 6 Relative toxicity of NP, NPEs and NPECs in fathead minnow (*Pimephales promelas*, 96-hour LC_{50}), killifish (*Oryzias latipes*, 48-hour LC_{50}), mysid shrimp (*Mysidopsis bahia*, 96-hour LC_{50}), *Daphnia magna* (48-hour LC_{50}) and *Ceriodaphnia dubia* (7-day LC_{50})



NP (Weeks *et al*., 1996). The NOEC (growth) in mysid shrimps, *Mysidopsis bahia*, was found to be 3.9 µg/L (Ward and Boeri, 1991c). Forty-eight-hour LC_{50}s for *Daphnia magna* ranged from 93 to 470 µg/L (Ankley *et al*., 1990; Brooke, 1993; Comber *et al*., 1993; Naylor, 1995) (Figure 6). Twenty-one-day NOECs of 24 µg/L (Comber *et al*., 1993) and 116 µg/L (Brooke, 1993) have been reported for *Daphnia magna*, based on reproduction. Additionally, 96-hour LC_{50}s of 20 µg/L (Brooke, 1993) and 170 µg/L (England and Bussard, 1994) have been reported for the freshwater amphipod, *Hyalella azteca*. LC_{50}s for NP in dragonflies, *Ophiogomphus* sp., and snails, *Physella virgata*, were also in the same range, >768 µg/L and 774 µg/L, respectively (Brooke, 1993).

NPE toxicity to algae is similar to results observed for other organisms. Ninety-six-hour EC_{50}s based on growth for NP in *Selenastrum capricornutum* (410 µg/L) and for the marine alga, *Skeletonema costatum* (27 µg/L), were reported by Ward and Boeri (1990a,b). A 72-hour EC_{10} value of 500 µg/L in *Scenedesmus subspicatus* was reported by Hüls, AG (1996). Weinberger and Rea (1981, 1982) calculated a 24-hour LC_{50} for *Chlorella pyrenoidosa* of 1500 µg NP/L, while they saw effects on growth at concentrations as low as 25 µg/L. The photosynthetic activity (Moody *et al*., 1983) and the ultrastructure of cell membranes (Weinberger and Rea, 1981) of *Chlamydomonas reinhardii* were inhibited by 500 µg NP/L. Prasad (1989) observed inhibition of frond production after 2 days of exposure to >500 µg/L in pond weed (*Lemna minor*). Reduced growth and photosynthetic activity were reported at NP concentrations between 125 and 500 µg/L. Similar effects also were reported for *Salvinia molesta* exposed to NP (Prasad, 1989).

Studies conducted in sediment–water exposure systems with NP determined a 14-day LC_{50} for the midge, *Chironomus tentans*, of 75 µg/L based on interstitial water concentrations and a NOEC (growth and survival) of 20 mg/kg based on sediment concentrations (England and Bussard, 1993). Kahl *et al*. (1997) reported a NOEC of 42 µg/L and a Lowest-Observed-Effect Concentration (LOEC) of 91 µg/L for life cycle tests with the midge, which evaluated survival,

growth, emergence and fecundity. Tadpoles, *Rana catesbiana*, had a 30-day LC_{50} of 260 mg/kg and a NOEC of 155 mg/kg in sediment (Ward and Boeri, 1992; Weeks *et al*., 1996). The LC_{50} was similar after 10, 20 and 30 days of exposure.

Studies have been performed to examine effects of NP on bacteria. An EC_{10} for oxygen consumption by the bacterium, *Pseudomonas putida*, was >10 000 µg NP/L (Knie *et al*., 1983), while an EC_{50} for *Photobacterium phosphoreum* (Microtox) occurred at 60 600 µg NP/L (Dorn *et al*., 1993).

Results from large littoral enclosure studies were conducted in triplicate with NP at nominal concentrations between 3 and 300 µg/L (Liber *et al*., 1998a,b; O'Halloran *et al*., 1998; Schmude *et al*., 1999). There were no effects on zooplankton observed in the enclosures treated with NP at the lowest exposure concentration, 5 µg/L (O'Halloran *et al*., 1998). Periphyton growth was not affected at any treatment level (O'Halloran *et al*., 1998). Snails and clams (*Pisidium*) were the most affected macroinvertebrates in exposed enclosures, with significantly reduced abundances (up to 100%) in the 243 µg/L treatment during the 2-year duration of the study (Schmude *et al*., 1998). Oligochaetes and chironomid midges also were reduced in the 243 µg/L treatment but recovered within 6 weeks. Only minor effects on snails and oligochaetes were observed in the 76 µg/L treatment, and no effects were seen on macroinvertebrates in the 5 or 23 µg/L treatment (Schmude *et al*., 1999). Juvenile bluegill sunfish (*Lepomis macrochirus*) added to the enclosure had reduced survival in the highest treatment, 243 µg/L.

2.4.1.2.2 Nonylphenol ethoxylate, diethoxylate and polyethoxylates

The toxicity of NPEs decreases with increasing EO chain length in a wide variety of species, including fish, invertebrates, algae and soil microorganisms (Figure 6). The LC_{50}s and EC_{50}s for NP9EO are much higher than those reported for NP in fish, invertebrates and algae. LC_{50} values ranging from 2500 to 12 500 µg/L have been reported for the higher EO chains in fathead minnows and rainbow trout (Marchetti, 1965; Calamari and Marchetti, 1973; Unilever Research Laboratories, 1977; Dorn *et al*., 1993).

In invertebrates, the 48-hour LC_{50} of NP9EO in *Daphnia magna* was reported as 14 000 µg/L by Dorn *et al*. (1993). The 48-hour LC_{50} for the marine amphipod, *Mysidopsis bahia*, was 900–2000 µg/L for NP9EO (Hall *et al*., 1989; Patoczka and Pulliam, 1990), 2570 µg/L for NP15EO and >100 000 for NP40EO and NP50EO (Hall *et al*., 1989). The 96-hour LC_{50} for NP10EO was determined in a number of crustaceans and clams and was generally >10 000 µg/L (Swedmark *et al*., 1971, 1976). Low toxicity (19 300–>100 000 µg/L) relative to NP was observed for NP12EO in shrimp, crabs and molluscs (Portmann and Wilson, 1971; Van Emden *et al*., 1974; Waldock and Thain, 1991). Eggs and larvae of the mussel, *Mytilus edulis*, were more sensitive than adults. Collyard *et al*. (1994) also demonstrated a 2- to 3-fold decrease in toxicity in the amphipod, *Hyalella azteca*, with age of the organisms exposed to NPE.

Twelve species of marine algae were tested using branched NPEs (Igepal). All showed total or some growth inhibition at concentrations above 100 000 µg/L (Ukeles, 1965). In the algae, the reported 96-hour EC_{50} of NP9EO for *Selenastrum capricornutum* ranged from 12 000 to 50 000 µg/L (Lewis, 1986; Dorn *et al*., 1993).

A few studies have also shown effects of NPEs on bacteria, although generally bacteria appear to be less sensitive than other biota to APs and APEs. *Photobacterium phosphoreum* toxicity (EC_{50}) decreased with increasing EO chain length for NPEs (Ribosa *et al*., 1993). Cserhati *et al*. (1991) tested several species of soil bacteria in agar cultures and found that at high concentrations, NPEs inhibited growth, while at low concentrations, NPEs stimulated the growth of some bacteria.

2.4.1.2.3 *Nonylphenoxyacetic acid and nonylphenoxyethoxyacetic acid*

Yoshimura (1986) reported 48-hour LC_{50}s in killifish (*Oryzias latipes*) for NP1EC and NP2EC of 9600 and 8900 μg/L, respectively. These values are slightly lower than the values reported for NP8.4EO/NP8.9EO (11 200–14 000 μg/L) but much higher than that reported for NP (1400 μg/L) (Yoshimura, 1986). Similar results for NP1EC were observed in fathead minnows. In another study, LC_{50}s for NP1EC (2000 μg/L) and NP9EO (6600 μg/L) were reported in fathead minnows (Williams *et al*., 1996). A similar trend was seen in *Daphnia magna*, *Mysidopsis bahia* and *Ceriodaphnia dubia* for NP1EC in recent studies by the Chemical Manufacturers Association (Naylor *et al*., 1997). Maki *et al*. (1998) measured 48-hour LC_{50}s in *Daphnia magna* for NP2EO (115–198 μg/L) and NP2EC (990 μg/L). These data suggest that the NPECs are much less toxic than the corresponding NPEs.

2.4.1.3 Toxicity to terrestrial plants and animals

There are only limited data available on the toxicity of NP to plants, and there are no data in the published literature on other APs and APEs. The concentration causing 50% growth reduction in cell suspension cultures of 14 species ranged from 0.05 mM (11 mg/L) to more than 1.00 mM (220 mg/L) (Bokern and Harms, 1997). NP was also toxic to plant roots. *Lupinus hartwegii* showed a 50% growth reduction at 0.1 mM (22 mg/L) (Bokern *et al.,* 1998). The growth of *Lupinus polyphyllus* root cultures also was inhibited but did not reach 50% growth reduction at 1 mM (220 mg/L) NP. The uptake of NP from soil was slow, and NP was quickly mineralized by soil microorganisms. NP accumulated in several species of plants and was metabolized to hydroxylated and conjugated derivatives.

The earthworm, *Apporectodea calignosa*, tested by Krogh *et al*. (1996) and reported by the U.K. Environment Agency (1998), had a 21-day EC_{10} (reproduction) of 3.4 μg/g in soil for NP. There are no toxicity data available for soil-dwelling organisms for the other NPE metabolites. NP accumulation in several species of plants was minimal, and NP was metabolized to hydroxylated and conjugated derivatives. Terrestrial plants appear to be relatively insensitive to the effects of NP and NPEs (Bokern *et al*., 1998).

2.4.1.4 Effects of alkylphenols and alkylphenol polyethoxylates on endocrine function

APs and APEs have been reported to cause a number of estrogenic responses in a variety of aquatic organisms. These responses occur at concentrations similar to those at which chronic effects are reported in aquatic biota. Experiments in several different *in vitro* systems have indicated similar relative potencies among NPEs. NP was found to be ~100 000 times less potent than estradiol (E_2). NP2EO and NP1EC were only slightly less potent than NP in inducing vitellogenin in trout hepatocytes. Addition of EO units to NPEs reduced the potency, such that NP9EO was an order of magnitude less potent *in vitro* (Jobling and Sumpter, 1993) (Table 6). APEs bind to the estrogen receptor, resulting in the expression of several responses, including the induction of vitellogenin in both *in vitro* and *in vivo* systems.

One of the functions of endogenous estrogens in fish is to stimulate the liver to produce vitellogenin, a large phospholipoprotein (Chen, 1983). It is released into the bloodstream and sequestered by developing oocytes for production of egg yolk (Wallace, 1985; Tyler *et al*., 1988a,b; Tyler, 1991). In maturing female fish, vitellogenin is a major constituent of blood proteins; in male fish, it is not normally present in appreciable amounts. If male fish are exposed to estrogens, however, vitellogenin can be produced at similar levels to those found in maturing females. Although the implications of the induction of vitellogenin for the reproductive function of fish are not fully understood, it has been used as a very sensitive indicator of exposure of fish to exogenous estrogens. Jobling *et al*. (1996) determined the potency of NP2EO and NP1EC to be only slightly less than that of NP in rainbow trout. Jobling *et al*. (1996) also

Table 6 Summary of relative toxicity and relative estrogenicity based on endocrine disrupting effects [1]

Chemical	Relative potency to E_2 Vg induction, trout hepatocytes [2]	Vg induction in rainbow trout (µg/L) [3]	Relative potency to E_2, YES assay [4]	Relative potency to E_2, YES assay [5]	Relative potency to E_2, YES assay [6]	Relative binding to E_2 receptor; K_d (M) [7]	Binding to trout ER [8]	Relative estrogenicity to NP (selected for assessment)	Relative toxicity (based on acute and chronic data)
NP	9.0 E–6	10	2.0 E–4	1.4 E–4	8.9 E–5	5.0 E–5	2.54 E–4	1	1
NP1EO					2.0 E–6		5.23 E–6	0.67	0.5
NP2EO	6.0 E–6			6.6 E–6		0	3.93 E–5	0.67	0.5
NPnEO (≥9)	2.0 E–7			0				0 (0.02)	0.005
NP1EC	6.3 E–6		8.0 E–6	4.0 E–5	0	2.0 E–4	1.68 E–4	0.63	0.005
NP2EC				4.0 E–5				0.63	0.005
OP	3.7 E–5	3	1.8 E–3	6.6 E–4		1.1 E–5	6.37 E–4	4.1	1
OP1EC								0.63	0.005
OP2EC								0.63	0.005

[1] Abbreviations used: E_2 = 17β-estradiol; ER = estradiol receptor; Vg = vitellogenin; K_d = distribution constant, YES = yeast estrogen screen.

[2] Jobling and Sumpter (1993).

[3] Jobling *et al*. (1996).

[4] Burnison (1998).

[5] Routledge *et al*. (1998).

[6] Metcalfe (1999).

[7] White *et al*. (1994).

[8] Van Der Kraak (1999).

demonstrated that NP2EO and NP1EC had similar potency for *in vivo* induction of vitellogenin in rainbow trout. The threshold for vitellogenin induction in fish is 10 μg/L for NP (Jobling *et al*., 1996). The induction of mRNA in rainbow trout was recently reported at 1 μg NP/L (Fent *et al*., 1999). The estrogenic responses appear to be at least additive (Soto *et al*., 1994; Sumpter and Jobling, 1995) and should, therefore, be considered as a group. The threshold for expression of intersex (ova-testes) in killifish was <50 μg NP/L (Gray and Metcalfe, 1997). APEs also affect the growth of testes in fish, alter normal steroid metabolism and disrupt smoltification (Madsen *et al*., 1997; Ashfield *et al*., 1998; Fairchild *et al*., 1999). There is currently considerable debate resulting from the inconsistency in relative potency reported for estradiol receptor binding, yeast estrogen screen (YES) assay and vitellogenin induction in trout hepatocytes. Additional research is required to fully understand the potential estrogenic effects of APs and APEs on the environment. The significance of estrogenic responses to the individual or population is also not known. A thorough discussion of current research into effects of APEs on endocrine function was presented in the environmental supporting documentation (Servos *et al*., 2000; Servos, 1999b).

2.4.2 Bioaccumulation in the environment

Bioaccumulation of APs and APEs has been studied in a number of algae, plants, invertebrates and fish species, both in the laboratory and under field conditions. Bioconcentration factors (BCFs) of APs and APEs determined in the laboratory and bioaccumulation factors (BAFs) measured in the field are similar and represent a low to moderate tendency to bioaccumulate (Table 7). This is expected based on a measured log K_{ow} of 4.48 (Ahel and Giger, 1993b) for NP. OECD (1997) predicted a theoretical BCF of 1280 based on K_{ow}. Metabolic rate and excretion could alter the actual value considerably from the theoretical value, resulting in lower BAFs measured in both laboratory and field studies. The available literature suggests that the ability of NP and NPEs to bioaccumulate in aquatic biota in the environment is low to moderate. BCFs and BAFs in biota, including algae, plants, invertebrates and fish, range from 0.9 to 4120 for NP. There are relatively few data available for NPEs, but, based on their structure, they are not expected to bioaccumulate (Table 7).

2.4.3 Effects in experimental mammals and humans

Identified information on effects of NP and NPEs in laboratory animals and humans is summarized in this section. As noted in Section 1.0 and in Appendix A, relevant studies were identified primarily from several recent reviews (Talmage, 1994; U.K. Environment Agency, 1998; WHO, 1998), as well as searches of on-line databases. For endpoints such as acute toxicity and genotoxicity (i.e., those that were not critical to the limited objectives of this screening assessment), the information presented in this section was derived principally from the above reviews; in contrast, the effect levels for those effects resulting from repeated exposures to NP/NPEs that were considered potentially relevant to development of the margins of exposure were confirmed from the primary sources. Weight of evidence for and adversity of effects were generally not considered in this screening exercise.

In view of the limited objective of this screening assessment, presentation in the sections below is limited to an overview of the nature of the identified data on toxicity of NP/NPEs, with emphasis on the magnitude of the effect levels from repeated-dose studies potentially relevant to development of the margins of exposure, rather than full descriptions of protocol and results of available studies. More detailed information is presented in tabular form in the health-related supporting documentation. Information included herein is also restricted principally to that considered to be directly relevant to determination of the margin of exposure.

TABLE 7 Bioaccumulation of NP and NPEs in aquatic organisms

Chemical	Species		BCF	BAF	$t_{1/2}$	Reference	Comments
NP	fathead minnow	*Pimephales promelas*	271		1.4 days	Ward and Boeri, 1991a	
NP	fathead minnow		344		1.2 days	Ward and Boeri, 1991a	
NP	fathead minnow		741			Brooke, 1993	
NP	rainbow trout	*Oncorhynchus mykiss*	24–98		0.8 days	Lewis and Lech, 1996	
NP	rainbow trout			6		Ahel *et al*., 1993	1
NP	rainbow trout				0.49– 5.8 hours (α) 40.2–99.0 hours (ß)	Coldham *et al*., 1998	
NP	Atlantic salmon	*Salmo salar*	75–235 280 (k_1/k_2)		4 days	McLeese *et al*., 1981	
NP	bluegill sunfish	*Lepomis macrochirus*	220			Brooke, 1993	
NP	bluegill sunfish			87		Liber *et al*., 1998b	
NP	carp	*Cyprinus carpio*	0.9–2.2			CITI, 1992	
NP	threespine stickleback	*Gasterosteus aculeatus*	1250			Ekelund *et al*., 1990	2
NP	chub	*Leuciscus* [*Squalus*] *cephalus*		7		Ahel *et al*., 1993	1
NP	barbel	*Barbus barbus*		15			
NP	alga	*Cladophora glomerata*		487		Ahel *et al*., 1993	1
NP	aquatic plant	*Fontinalis antipyretica*		54			
NP	aquatic plant	*Potamogeton crispus*		32		Ahel *et al*., 1993	
NP	mussel	*Mytilus edulis*		340		Granmo *et al*., 1991	1
NP	mussel		2740/4120			Ekelund *et al*., 1990	1
NP	mussel		1.4–7.9 10 (k_1/k_2)		0.3 days	McLeese *et al*., 1980	
NP	shrimp	*Crangon crangon*	110			Ekelund *et al*., 1990	1
NP1EO	rainbow trout	*Oncorhynchus mykiss*		3		Ahel *et al*., 1993	
NP1EO	barbel	*Barbus barbus*		19		Ahel *et al*., 1993	
NP1EO	chub	*Leuciscus* [*Squalus*] *cephalus*		1		Ahel *et al*., 1993	
NP1EO	mussel	*Mytilus edulis*		170		Granmo *et al*., 1991	
NP1EO	alga	*Cladophora glomerata*		10		Ahel *et al*., 1993	1
NP1EO	aquatic plant	*Fontinalis antipyretica*		2		Ahel *et al*., 1993	
NP1EO	aquatic plant	*Potamogeton crispus*		2		Ahel *et al*., 1993	
NP2EO	rainbow trout	*Oncorhynchus mykiss*		0.8		Ahel *et al*., 1993	
NP2EO	barbel	*Barbus barbus*		37		Ahel *et al*., 1993	
NP2EO	chub	*Leuciscus* [*Squalus*] *cephalus*		2		Ahel *et al*., 1993	
NP2EO	mussel	*Mytilus edulis*		100		Granmo *et al*., 1991	
NP2EO	alga	*Cladophora glomerata*		23		Ahel *et al*., 1993	1
NP2EO	aquatic plant	*Fontinalis antipyretica*		3		Ahel *et al*., 1993	1
NP2EO	aquatic plant	*Potamogeton crispus*		10		Ahel *et al*., 1993	1
NP3EO	mussel	*Mytilus edulis*		60		Granmo *et al*., 1991	

Comments:

1. Staples *et al*. (1998) calculated wet weight equivalent BAF based on 95% water, in algae and 85% in fish.

2. Caution because not corrected for >80% of radioactivity as metabolites.

For various endpoints, the toxicity of this class of substances generally decreases as the number of EO units increases (Talmage, 1994). In the following sections, information on NP, NP4EO, and NP9EO for which there are a considerable amount of data, is presented separately, followed by information on the remaining NPEs.

2.4.3.1 Effects in laboratory animals and *in vitro*

2.4.3.1.1 Nonylphenol

Identified data for NP include studies of acute toxicity, several repeated-dose toxicity studies in rats by the oral route, several genotoxicity tests in bacteria and mammalian cells, a multigeneration reproductive study in rats and several *in vitro* and *in vivo* assays of estrogenic activity.

The acute toxicity of NP is relatively low, with oral LD_{50} values in the rat between 580 and 1620 mg/kg-bw. Dermal LD_{50} values in rabbits were >2000 mg/kg-bw. NP was moderately to severely irritating to rabbit skin and eye (U.S. EPA, 1992a,b,c; WHO, 1998).

In short-term and subchronic studies with rats, toxic effects reported following oral exposure to NP included histopathological changes in the liver and kidney. The Lowest-Observed-Effect Level (LOEL) for NP in male rats exposed for 28 days was 25 mg/kg-bw per day, based on increased relative liver weight; in the same 28-day study, a No-Observed-Effect Level (NOEL) of 400 mg/kg-bw per day (highest dose tested) was reported for females (Richards, 1989). In a 90-day study in rats exposed by the oral route, absolute ovary weight and mean body weight were reduced in females and relative kidney weight was increased and mean body weight was reduced in males at 2000 ppm (approximately 129–149 mg/kg-bw per day) (Cunny *et al*., 1997).

No chronic toxicity studies with NP were identified, with the exception of the multigeneration study described below.

Genotoxicity data identified were restricted to a small number of *in vitro* studies. NP was consistently negative in bacterial tests of mutagenicity (WHO, 1998), although it induced DNA damage in human sperm, lymphocytes and MCF-7 breast cancer cells exposed *in vitro* (Banerjee and Roy, 1996; Anderson *et al*., 1997).

In a multigeneration study in which rats were exposed to NP in the diet, the LOEL was 200 ppm in diet (equivalent to a mean dose of approximately 12–18 mg/kg-bw per day in males, 16–21 mg/kg-bw per day in non-lactating females or 27–30 mg/kg-bw per day in lactating females), based on an increase in renal medullary tubular dilation and cyst formation in males in all generations (F_0–F_3) and in F_3 females. There were also increases in gestation length and in percent abnormal sperm morphology observed in the F_2 generation at this dietary level, as well as at the 650 ppm and at 2000 ppm, but these 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. No developmental effects were reported at any dietary level; however, a range of effects on endocrine-regulated endpoints, including delayed vaginal opening, was observed at 650 and 2000 ppm (NTP, 1997; Chapin *et al*., 1999).

In reproductive toxicity studies, histological changes in the seminiferous vesicles of the testes of rats were observed following oral exposure to 100 mg NP/kg-bw per day for 10 days (de Jager *et al*., 1999a,b), though this was accompanied by compound-related mortality at doses that did not cause deaths in several other studies. Reductions in relative testis, epididymis, seminal vesicle and prostate weights were reported in rat pups exposed to 0.8 mg NP/kg-bw per day intraperitoneally in the first 15 days after birth (Lee, 1998); however, this information is not considered directly relevant to the margin of exposure, owing to the lesser relevance of this route of administration.

In a number of *in vivo* and *in vitro* studies, NP has been weakly estrogenic. NP increased uterine weight in immature or ovariectomized rats and in mice following oral administration of 50 mg/kg-bw per day and above and following subcutaneous and intraperitoneal administration (Lee and Lee, 1996; Shelby *et al*., 1996; CMA, 1997; Coldham *et al*., 1997; Laws and Carey, 1997; Odum *et al*., 1997). Several other effects indicative of estrogenic activity have been observed in rats following the subcutaneous administration of NP *in vivo*, including endometrial proliferative response (Soto *et al*., 1991; Cotroneo *et al*., 1997) and stimulation of uterine vascular permeability (Milligan *et al*., 1998). Colerangle and Roy (1996) reported an increase in cell proliferation in the mammary gland of rats exposed to 0.01 mg NP/day by subcutaneous minipump; however, this effect was not reproducible in two subsequent studies (Odum *et al*., 1999a,b). NP was 1000–100 000 times less potent than estradiol in stimulating estrogenic activity (Lee and Lee, 1996; Milligan *et al*., 1998). In *in vitro* studies, NP activated the estrogen receptor with a potency 5000–7000 times less than that of 17ß-estradiol (Routledge and Sumpter, 1996; Gaido *et al*., 1997; Odum *et al*., 1997). In MCF-7 human breast cancer cells, cell proliferation was stimulated by NP at concentrations between 0.1 and 10 μM (22 and 2203 mg/L) (White *et al*., 1994; Villalobos *et al*., 1995; Blom *et al*., 1998).

2.4.3.1.2 Nonylphenol-4-polyethoxylate

Identified data for NP4EO (Nonoxynol-4) include studies of acute toxicity, repeated-dose toxicity studies in rats and dogs by the oral route, several genotoxicity tests in bacteria and mammalian cells *in vitro* and in mice *in vivo* and two *in vivo* assays of estrogenic activity in rats.

The acute toxicity of NP4EO is low, with oral LD_{50} values in the rat between 4290 and 7400 mg/kg-bw and an oral LD_{50} of 5000 mg/kg-bw in guinea pigs. The dermal LD_{50} in rabbits is greater than 2000 mg/kg-bw. NP4EO was non-irritating to severely irritating to rabbit skin following exposure to undiluted compound. Irritation of the eye was reported to be minimal to severe (corrosive) following exposure of rabbits to undiluted NP4EO and slight following exposure to 10% diluted compound (Talmage, 1994; WHO, 1998).

In subchronic (90-day) studies with rats and dogs, toxic effects observed following oral exposure to NP4EO included an increase in liver to body weight ratio and a decrease in body weight gain in the first 4 weeks only. The LOEL was 200 mg/kg-bw per day, with a NOEL of 40 mg/kg-bw per day (Smyth and Calandra, 1969).

In a 2-year oral chronic study with rats, a LOEL of 200 mg/kg-bw per day was reported based on reduced weight gain, which the authors concluded was due to decreased food consumption. In a similar study with dogs, the LOEL was 200 mg/kg-bw per day based on an increase in alkaline phosphatase activity in serum and an increase in relative liver weight. In both cases, the NOEL was 40 mg/kg-bw per day (Smyth and Calandra, 1969).

No evidence of genotoxicity was reported in tests of reverse mutation at the histidine locus in bacteria or in unscheduled DNA repair studies in rat primary hepatocytes with NP4EO. NP4EO did not induce micronuclei in the bone marrow cells of mice following intraperitoneal injection in one study (WHO, 1998).

No evidence of estrogenic activity was observed in rats *in vivo* as evidenced by a lack of the stimulation of uterine growth following oral exposure of ovariectomized females to NP4EO at doses up to 1000 mg/kg-bw per day for 4 consecutive days in two studies (Berke and Mitchell, 1995; Williams *et al*., 1996).

2.4.3.1.3 Nonylphenol-9-polyethoxylate

Identified data for NP9EO (Nonoxynol-9) include studies of acute toxicity, repeated-dose toxicity studies in rats and dogs by the oral route and in rats by the intraperitoneal and intravaginal routes, an immunotoxicity test in mice by the

intraperitoneal route, several genotoxicity tests in bacteria and mammalian cells *in vitro* and in rats and mice *in vivo*, reproductive and developmental studies in rats following oral, intrauterine, intravaginal and dermal exposure and an *in vivo* assay of estrogenic activity.

The acute toxicity of NP9EO is relatively low, with oral LD_{50} values between 1410 and 5600 mg/kg-bw in the rat and between 620 and 4400 mg/kg-bw in rabbits, mice and guinea pigs. Dermal LD_{50} values in rabbits were ≥2830 mg/kg-bw. NP9EO was reported to be minimally to severely irritating to rabbit skin and moderately to severely irritating to the rabbit eye (Smyth and Calandra, 1969; WHO, 1998).

Oral and dermal LD_{50} values for NP9.5EO were greater than 3000 mg/kg-bw in the rat and rabbit. The compound was slightly irritating to rabbit skin and minimally to severely irritating to the rabbit eye (WHO, 1998).

In subchronic (90-day) studies with rats and dogs, toxic effects reported following oral exposure to NP9EO included reduced polysaccharide in the liver, increased relative liver weight and decreased weight gain, which may have been related to a decrease in food intake (Smyth and Calandra, 1969). The LOEL for NP9EO was 50 mg/kg-bw per day in the rat based on reduced polysaccharide in the liver. Effects on the liver were observed following the administration of 50 mg/kg-bw per day to female rats intraperitoneally for 5 days or intravaginally for 5–20 days (Chvapil *et al*., 1982a). When NP9EO was administered intravaginally, effects were also seen in the kidney. In a study with mice, NP9EO did not affect thymus-dependent humoral immunity or leukocyte counts when administered intraperitoneally for 24 days (Caren and Brunmeier, 1987).

No evidence of carcinogenicity was reported in 2-year chronic oral toxicity studies of NP9EO with rats and dogs. The only effect reported was an increase in relative liver weight in dogs at 88 mg/kg-bw per day (Smyth and Calandra, 1969).

In studies of genotoxicity, NP9EO did not induce mutation in bacteria or mammalian cells, although it did increase cell transformation in mammalian cells in one of three studies (Long *et al*., 1982). In single studies, intraperitoneal exposure to NP9EO did not induce cell proliferation in peritoneal cells in rats or abnormalities in germ cells in mice (Buttar *et al*., 1986; Jinxi *et al*., 1992).

In rats exposed orally to NP9EO on gestational days 6 through 15, litter size was decreased and pre-implantation loss and incidence of skeletal tissue deformities were increased, but only at maternally toxic doses (i.e., 250 and 500 mg/kg-bw per day, based on decreased maternal weight gain) (Meyer *et al*., 1988).

There have been several investigations of effects following intravaginal and intrauterine administration, presumably because of NP9EO's common use as an active ingredient in spermicidal formulations. Irritation and inflammation of the vaginal epithelium were observed in rats, rabbits and monkeys following intravaginal exposure to NP9EO (Talmage, 1994; Patton *et al*., 1999). Effects including reduced number of pregnancies, reduced number of viable embryos and live fetuses and increased resorptions were reported in the absence of maternal toxicity when 0.50 mg was injected directly into the uterus of pregnant rats (Stolzenberg *et al*., 1976). The number of live fetuses was significantly reduced when pregnant rats were exposed to 25 mg NP9EO/kg-bw per day intravaginally on gestational day 4, 5, 8 or 9 (Buttar, 1982), and the number of implantations per uterus was significantly reduced following exposure to 50 mg/kg-bw per day on gestational day 3 or 7 (Tryphonas and Buttar, 1982). No teratogenic effects were reported at intravaginal doses up to 25 mg/kg-bw (Buttar, 1982).

No dose-related reproductive or teratogenic effects were reported in rats following dermal exposure to up to 500 mg NP9EO/kg-bw per day administered on gestational days 6–15 (Meyer *et al*., 1988).

When immature female rats were administered NP9EO for 3 days by gavage, there was no reported effect on uterine weight, indicating a lack of estrogenic activity, at doses up to 1000 mg/kg-bw per day (Williams *et al*., 1996).

2.4.3.1.4 Other nonylphenol polyethoxylates

Identified data for other NPEs include acute toxicity studies, repeated-dose toxicity studies in rats and dogs by the oral route for NP6EO, NP15EO, NP20EO and NP30E, a small number of genotoxicity studies (mostly in bacteria) for NP5EO, NP10EO, NP12EO and NP20EO, a reproductive and developmental study for NP10EO in mice and for NP30EO in rats by the oral route, and an in vitro estrogenic activity study for NP2EO and NP12EO.

In NPEs with chain lengths up to 40 (excluding 4 and 9), acute oral LD_{50}s in the rat range from 1300 to 15 900 mg/kg-bw; acute dermal LD_{50}s in rabbits were above 1800 mg/kg-bw. Skin irritation in rabbits ranged from non-irritating to severely irritating, with lower chain lengths generally being more irritating. Eye irritation to rabbits was minimal to severe in most studies with NPEs, with NP30EO and NP40EO being non-irritating. NP6EO was non-sensitizing in guinea pigs (Younger Laboratories 1961a,b; Union Carbide, 1992; WHO, 1998).

In subchronic studies with NP6EO and NP15EO, the LOEL was 40 mg/kg-bw per day in rats and 1000 mg/kg-bw per day in dogs following oral exposure, based on an increase in relative liver weights. No effects were noted in rats following oral exposure to NP20EO and NP30EO at doses up to 5000 mg/kg-bw per day or in dogs following oral exposure to NP30EO at doses up to 1000 mg/kg-bw per day. The LOEL in dogs for NP20EO was 40 mg/kg-bw per day based on an increase in the incidence of focal myocardial necrosis or degeneration (Smyth and Calandra, 1969).

In studies of genotoxicity, NP5EO, NP10EO and NP20EO did not induce mutation in bacteria (CIR, 1996; WHO, 1998). In single studies, NP12EO did not induce unscheduled DNA repair in primary rat hepatocytes *in vitro* or produce micronuclei in bone marrow cells of mice following intraperitoneal injection (WHO, 1998).

No reproductive or developmental effects were observed following oral exposure during gestation to 600 mg NP10EO/kg-bw per day in mice (Hardin *et al*., 1987) or up to 1000 mg NP30EO/kg-bw per day in rats (Meyer *et al*., 1988).

NP2EO stimulated the transcription of the estrogen receptor and cell proliferation in human breast cancer cells *in vitro* (White *et al*., 1994) and activated the estrogen receptor in yeast with a potency 500 000 times less than that of estradiol (Routledge and Sumpter, 1996). NP12EO did not demonstrate any estrogenic activity in an estrogen-inducible strain of yeast (Routledge and Sumpter, 1996).

2.4.3.2 Effects in humans

2.4.3.2.1 Nonylphenol

No data were identified on the effects of NP in humans.

2.4.3.2.2 Nonylphenol-4-polyethoxylate

Nonoxynol-4 application (10% in mineral oil) to the skin on the back resulted in faint to moderate erythema in 36 of 111 volunteers. Three of these reactions were classified as allergic contact dermatitis; however, in a 30-minute retest, there was evidence of a mild allergic response in only one of these three subjects (Jordan, 1995).

No further data were identified on the effects of NP4EO in humans.

2.4.3.2.3 Nonylphenol-9-polyethoxylate

Data in humans are limited to studies of effects following exposure to spermicides containing NP9EO (Nonoxynol-9).

In several studies, the use of NP9EO-containing spermicides has been reported to cause vaginal irritation and/or burning and genital ulceration in some females; irritation of the urinary tract has also been reported in some males and females following exposure (Chvapil *et al*., 1982b; Rekart, 1992; Roddy *et al*., 1993; Weir *et al*., 1995; Saborio *et al*., 1996, Stafford *et al*., 1998). Allergic contact dermatitis reactions to NP9EO in an antiseptic preparation and a condom were also reported (Dooms-Goossens *et al*., 1989; Fisher, 1994).

Following the intravaginal application of 150 mg NP9EO for 14 consecutive days by 10 women, the only significant effect reported was a reduction in serum cholesterol; no effects on liver function or hematological parameters were observed (Chvapil *et al*., 1982b). In another study, 12 women applied 2.5 g of cream containing 5.0% NP9EO intravaginally (yielding an applied dose of 125 mg) for 14 consecutive days. There were no significant differences in levels of proteins, lipids, triglycerides or serum enzymes in blood samples collected before, during (day 8) and after (day 15) exposure (Malyk, 1981).

The association between spermicide use and congenital malformations has been examined in a number of historical cohort and case–control studies (reviewed in Manjuck, 1989; Talmage, 1994; WHO, 1998). While there were statistically significant increases in overall malformations or in trisomies in relation to spermicide use in a small number of the available studies, no increase was observed in the majority of studies (which were generally larger and had better characterization of exposure and/or better adjustment for possible confounders). Further, the relative risks in most of the positive studies were relatively low (i.e., less than 2). Hence, based on these reviews, the weight of evidence for congenital malformations appears to be quite limited, with almost no indication of consistency, specificity or strength of association. There is also little evidence of an exposure–response relationship (although a gradient of exposure was not investigated in most studies, and the exposure characterization was somewhat crude in all of the available studies).

2.4.3.2.4 Other nonylphenol polyethoxylates

Contact dermatitis and contact photosensitivity have been reported in humans following exposure to NP6EO, NP10EO and NP12EO in consumer products (Nethercott and Lawrence, 1984; Meding, 1985; Michel *et al*., 1994; Wilkinson *et al*., 1995).

No further data were identified on the effects of NPEs of chain lengths other than four or nine in humans.

2.4.4 Abiotic atmospheric effects

Ozone Depletion Potential, Global Warming Potential and Photochemical Ozone Creation Potential were not calculated for NP/NPEs. NP/NPEs are not expected to readily volatilize into air and are expected to degrade rapidly in the atmosphere.

3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor (AF). A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

In Canada, the releases of NP and NPEs occur solely via anthropogenic activity. The largest source of this group of compounds appears to be effluent from textile mills, pulp and paper mills and MWWTPs. A second major source is sludge from MWWTPs, to which the compounds are adsorbed. Environmental effects are expected to be greatest in the aquatic environment in regions near effluent release points. NP is expected to partition into sediments in aquatic environments and exist in the sludge fraction of treated effluents.

3.1.1.1 Aquatic

Assessment endpoints include abundance, growth and survival of fish, invertebrates and algae. Additional endpoints include reproductive effects on invertebrates and fish. Although NPEs are associated with endocrine disrupting properties, the outcome of this assessment is based primarily on chronic toxicity. A discussion of the endocrine effects and a comparison between these two endpoints, however, have been included in this assessment. Both marine and freshwater species were used in aquatic risk characterizations, depending on species sensitivity.

3.1.1.2 Terrestrial

Assessment endpoints in the terrestrial environment are based on chronic toxicity data from one earthworm study. These were the only data available for terrestrial organisms.

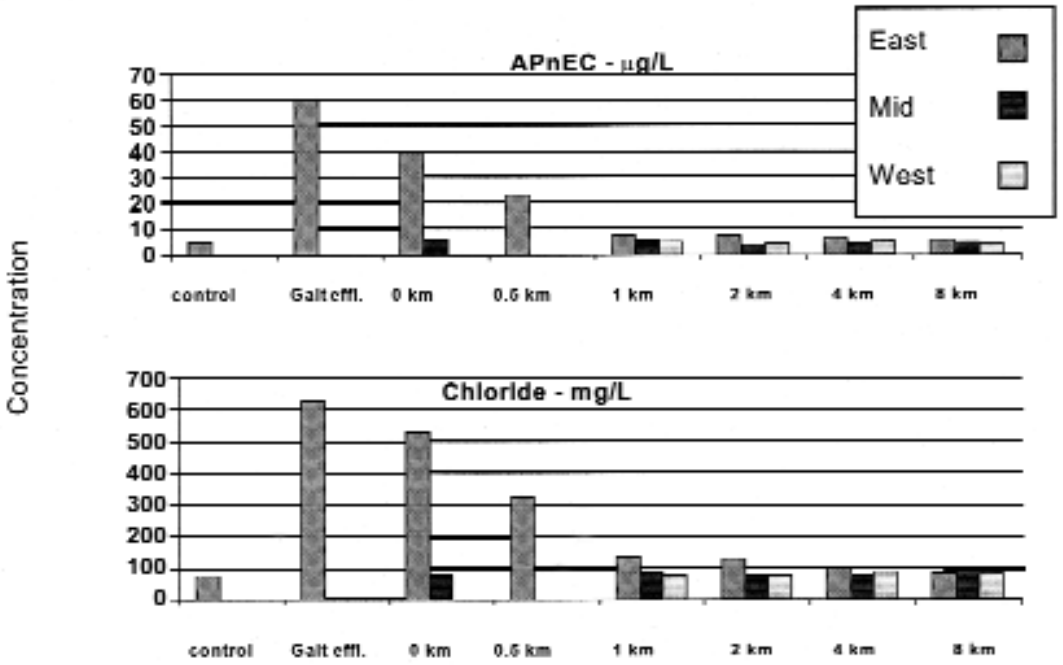
3.1.1.3 Atmospheric

Air was not considered to be a compartment of concern; therefore, a risk characterization in this compartment was not performed.

3.1.2 Environmental risk characterization

Significant releases of NPEs occur in industrial and municipal effluents in Canada. The emphasis of this risk characterization is, therefore, on the exposure from effluents. NPEs are released as complex mixtures whose composition may differ considerably, depending on the type of effluent and environmental compartment. NPEs are released at relatively constant concentrations as effluents (e.g., municipal effluents), with only minor seasonal variability; this, therefore, results in a relatively continuous exposure of aquatic organisms. However, changes in effluent dilution in the receiving environment will alter the exposure both spatially and temporally at most sites. Unfortunately, there are limited

FIGURE 7 Concentrations of alkylphenols relative to chloride concentrations in the Grand River



data available with which to confirm dilution at most sites, and there are considerably fewer data available for ambient surface waters, especially for the major metabolites. The available environmental data were used to validate the exposure predicted from effluent concentrations.

Sediment toxicity data are available only for NP and not for the other metabolites. Therefore, the relative aquatic toxicity factors for NP were used as a surrogate for NPEs. Although the application of sludges from MWWTPs to agricultural soils represents a major route of exposure, soil toxicity data again were available only for NP. The relative toxicity, therefore, was estimated from the available literature on NP.

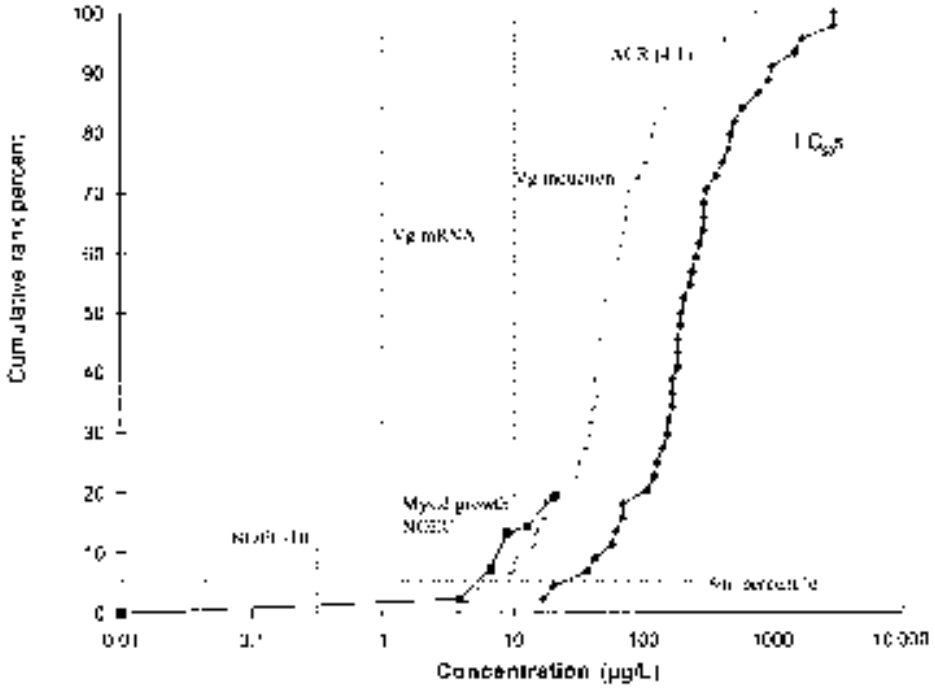
3.1.2.1 Overview of approach for determination of risk quotients

Because NPEs occur as complex mixtures in the environment and have different toxicities and estrogenic potencies, the approach used in this assessment was to first assess each chemical separately, then assess the complex mixtures found in the environment.

In the hyperconservative assessment, the EEV was taken to be the maximum effluent or environmental concentration. The ENEV for the hyperconservative assessment was determined by taking the most sensitive endpoint (e.g., LC_{50}, NOEC, etc.) and applying an AF (Table 8) to account for uncertainty in extrapolating from laboratory to field conditions and interspecies and intraspecies variations in sensitivity, or other identified uncertainties. Effluents released directly from textile mills from all sites were considered, even though many of these effluents received subsequent treatment in municipal treatment systems.

In aquatic environments, the conservative EEV was the maximum concentration of the final effluent (textile mills, municipal treatment systems and pulp and paper mills) that is discharged from each site directly to the environment (no additional treatment), diluted by a factor of 10. Although many sites have dilution

FIGURE 8 Assessment endpoints for NP



factors greater than 10 outside of the immediate mixing zone, especially in ocean or lake sites, there have been instances of lesser dilution. Therefore, a dilution factor of 10 was considered appropriate for this assessment. The case for lesser dilution was observed at the Galt Treatment Plant in the Grand River, studied by Bennie *et al.* (1998) (Figure 7). In this case, the effluent remained on one side of the river for up to 8 km downstream of the outfall. There was very little degradation of the NPEs and NPECs in the river water over the 8 km, and the decreased concentrations downstream were attributed to physical dilution, not chemical degradation. The ENEV for the conservative approach was based on a more realistic CTV together with an AF (Table 8). In the conservative risk characterization for sediment, concentration data for all locations were used, rather than the worst-case scenario data. Concentration data in sludge-applied soil were used as the EEV in the conservative risk characterization for the terrestrial environment for NP, whereas the concentrations in the sludge alone were considered in the hyperconservative approach.

A distributional assessment was performed only for the aquatic system, because it was the environmental compartment of main concern. In this assessment, rather than using one of the most sensitive studies to determine the ENEV, an assessment of all of the available literature was used to determine an ENEV. The ENEV was based on an assessment of the distribution of acute and chronic effects reported in the literature. The EEV used was the mean diluted effluent concentration for each site, rather than the maximum value observed. As a means of graphically displaying the relationship between the EEVs and ENEVs, the distribution of the exposure data was plotted as a cumulative rank percent (Figure 8).

Although there is considerable information on the acute toxicity of NP, there are few data available on its chronic toxicity, and there are relatively few data available for the other APs/APEs. Based on an assessment of the data, giving weight to the studies with highest confidence and for which the same species were tested, an acute to chronic ratio (ACR) of 4:1 was

Table 8 Most sensitive organisms in each trophic level for NP

Trophic level	Water (fresh/ marine)	Exposure length	Species	Endpoint	CTV (µg/L)	Hyper-conservative AF	Hyper-conservative ENEV (µg/L)	Conser-vative AF	Conser-vative ENEV (µg/L)	References
Fish	F	acute	Fathead minnow (*Pimephales promelas*)	96-hour LC_{50}	128	100	1.28	50	2.6	Brooke, 1993
	F	chronic	Rainbow trout (*Oncorhynchus mykiss*)	91-day NOEC	6.0	10	0.60	10	0.60	Brooke, 1993
	M	acute	Winter flounder [1] (*Pleuronectes americanus*)	96-hour LC_{50}	17	100	0.17	50	0.34	Lussier *et al.*, 1996
	M	chronic	no primary study available							
Invertebrates	F	acute	*Daphnia magna*	48-hour EC_{50} (immobilization)	190	100	1.9	100	1.9	Comber *et al.*, 1993
	F	acute	*Hyalella azteca*	96-hour LC_{50}	20.7	100	0.21	50	0.42	Brooke, 1993
	F	chronic	Zooplankton	NOEL (protect all species)	5	10	0.5	10	0.5	O'Halloran *et al.*, 1998
	F	chronic	*Daphnia magna*	21-day NOEC (reproduction)	24	10	2.4	10	2.4	Comber *et al.*, 1993
	F	chronic	*Daphnia magna*	21-day LC_{50}	100	100	1.0	100	1.0	
	M	acute	Mysid shrimp (*Mysidopsis bahia*)	96-hour LC_{50}	43	100	0.43	100	0.43	Ward and Boeri, 1990c
	M	chronic	Mysid shrimp (*Mysidopsis bahia*)	28-day NOEC (survival and reproduction)	6.7	10	0.67	10	0.67	Ward and Boeri, 1991b
				28-day NOEC (length)	3.9	10	0.39	10	0.39	
Algae	F		Algae (*Scenedesmus subspicatus*)	72-hour EC_{50} (biomass)	56.3	100	0.56	100	0.56	Kopf, 1997
				72-hour EC_{10} (biomass)	3.3	10	0.33	10	0.33	
				72-hour EC_{50} (growth rate)	323	100	3.23	100	3.23	
				72-hour EC_{10} (growth rate)	25.1	10	2.51	10	2.51	
	F		Algae (*Selenastrum capricornutum*)	96-hour EC_{50} (growth)	410	100	4.1	100	4.1	
				96-hour NOEC	92	10	9.2	10	9.2	Ward and Boeri, 1990a

Table 8 (continued)

Trophic level	Water (fresh/ marine)	Exposure length	Species	Endpoint	CTV (µg/L)	Hyper-conservative AF	Hyper-conservative ENEV (µg/L)	Conser-vative AF	Conser-vative ENEV (µg/L)	References
	M		Algae (*Skeletonema costatum*)	96-hour EC_{50} (cell growth)	27	100	0.27	100	0.27	Ward and Boeri, 1990d
				96-hour NOEC	10	10	1.0	10	1.0	
Sediment invertebrate	F	chronic	Midge (*Chironomus tentans*)	14-day NOEC (growth and survival)	20 mg/kg	10	2.0 mg/kg	10	2.0 mg/kg	England and Bussard, 1993
Sediment amphibian	F	chronic	Tadpole (*Rana catesbiana*)	30-day LC_{50}	260 mg/kg	100	2.6 mg/kg	100	2.6 mg/kg	Ward and Boeri, 1992
				30-day NOEC (survival, sublethal effects, weight)	155 mg/kg	10	15.5 mg/kg	10	15.5 mg/kg	
Soil invertebrate			Earthworm (*Apporectodea caligniosa*)	21-day EC_{10} (reproduction)	3.44 mg/kg	10	0.34 mg/kg	10	0.34 mg/kg	Krogh *et al.*, 1996
				21-day EC_{50} (reproduction)	13.7 mg/kg	10	1.37 mg/kg	10	1.37 mg/kg	

[1] Key study – winter flounder inconsistently lower than other 19 species of fish tested. Safety factor 50 chosen because more than three trophic levels reported in literature.

determined. This value was applied to the acute toxicity curves to determine a chronic toxicity endpoint (Figure 8).

To generate the chronic toxicity curve, the acute toxicity data available for NP were first plotted as a cumulative rank percent. The acute data were then converted by applying an ACR of 4:1. Using the slope of these data after a log probit transformation, a value of 10 μg/L was determined as the concentration at which 95% of species are protected; i.e., the EC_{50} is exceeded in less than 5% of species. An AF of 10 was applied to take into consideration uncertainty associated with species differences and reported sublethal responses. The resulting ENEV for NP was 1 μg/L. The limited data available suggest that a similar ACR for the other APs/APEs may be appropriate; therefore, an ACR of 4:1 was assumed to apply to all metabolites.

The ENEVs for the metabolites, other than NP, were determined by estimating the relative toxicity of the metabolites to NP, considering all of the available literature in the assessment, using the distributional approach. Greater weight was placed on stronger studies and those that compared the toxicity of various metabolites directly. The relative toxicity was then applied to the ENEV of NP, which was considered to have a much larger and more reliable data set for toxicity. This approach allowed for a more consistent assessment of the relative influence of the NPE metabolites.

The detection limits for environmental concentrations vary considerably among studies, over time and over matrices for the various metabolites. In the hyperconservative assessment, values less than the detection limit were taken as the reported detection limit for each sample. This was considered very conservative and in line with the preliminary screening philosophy of hyperconservative assessment. The detection limit for NP in some samples was higher than the ENEV, but it was felt that the uncertainty of the real environmental values warranted this conservative approach at this stage. In the conservative and distributional approaches, one-half of the reported detection limit was used to calculate mean concentrations, because this was considered to be a more realistic estimate.

3.1.2.2 Additivity of effects

Since NP and NPEs exist together in mixtures in environmental samples, the combined impact of the mixture was examined. Although there is no direct evidence in the literature, it has been assumed that the lower-chain-length NPEs (NP1EO, NP2EO) and NPECs (NP1EC, NP2EC) have a mode of action similar to that of NP and that their effects are additive. The longer-chain-length NPEs (e.g., NP9EO) may differ from NP, because the mechanism of action is likely a physical surfactant effect. In addition to examining the exposure and toxicity of each metabolite individually, a toxic equivalency approach was applied, which factored in contributions from NP as well as the lower-chain-length (1,2) NPEs and NPECs to determine the overall potential risk of the group. The toxicity of each metabolite relative to NP was determined from the available literature, as indicated in Table 6. The EEV_{TEQ} was calculated by multiplying the exposure concentration (C_X) of each compound by its relative potency (RP_X). The sum of values for each compound was determined to be the total EEV_{TEQ}. NP was used as a reference compound, because there were considerably more data available on the toxicity of this compound, which provided a better reference point.

$$\text{Total } EEV_{TEQ} = \Sigma (C_X \times RP_X)$$

The Toxic Equivalency Quotient (TEQ) was, therefore, calculated as follows:

$$TEQ = \frac{EEV_{TEQ}}{ENEV_{NP}}$$

This report is structured to evaluate the risk associated with each metabolite individually, followed by an assessment of the mixture.

3.1.2.3 Aquatic environment

There is a relatively large database on the occurrence of NPEs in the Canadian environment and in effluents, although the majority of the data are for NP. Occurrence data have been reported in surface waters and sediments from streams, lakes and harbours, and considerable data also are available for municipal, textile, pulp mill and refinery effluents. Although NPEs with an average of 9–10 EO units are the major product used, they degrade to NPEs or NPECs with fewer EO units and ultimately to NP. The composition of these chemicals, therefore, varies considerably in effluents and in the environment.

There are many studies reporting acute and chronic effects of NP, fewer studies reporting the toxicity of NPEs and only a few studies that included the NPECs (see Section 2.4; Servos, 1999a). Unfortunately, few of these studies compared all of the NP, NPEs and NPECs together in a consistent way in the test organism species. Although studies reported in the literature have used many species, different test methods and different chemicals, there is a consistent pattern in the toxicity reported. The relative toxicity of the various metabolites was determined using comparisons of the published toxicity data. Emphasis was placed on high-quality studies that reported acute and chronic data in a single species using standard methodologies.

NP is relatively toxic to fish (17–1400 μg/L), invertebrates (20–3000 μg/L) and algae (27–2500 μg/L). There is an increase in the toxicity of NPEs with decreasing EO chain length, such that NP is 200 times more toxic than NP9EO. NPECs are less toxic than the corresponding NPEs and have acute toxicities similar to those of NPEs with 6–9 EO units. The relative toxicities differ from the relative estrogenicities (Table 6). NPEC is much less acutely toxic relative to NP but has only a slightly lower relative estrogenic potency. Because the relative potency of the various metabolites is based on *in vitro* or trout hepatocyte studies, not whole-organism studies, caution in interpretation is necessary (Table 6).

3.1.2.3.1 Risk characterization for nonylphenol (NP)

The toxicity data set for NP is relatively large, particularly for freshwater fish, for which 19 acute studies are available. The most sensitive acute and chronic effects reported for freshwater and marine species of fish, invertebrates and algae are summarized in Table 8.

Hyperconservative approach

In the hyperconservative approach, the 96-hour LC_{50} of 17 μg/L in winter flounder (*Pleuronectes americanus*) (Lussier *et al.*, 1996) was the CTV; the CTV was divided by an AF of 100 because it was an acute LC_{50} value, which resulted in an ENEV of 0.17 μg/L (summarized in Table 9). The EEV was the maximum concentration, without dilution, at each type of site.

The hyperconservative quotient was calculated as follows for a primary MWWTP effluent:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{62.08\ \mu\text{g/L}}{0.17\ \mu\text{g/L}}$$

$$= 365$$

Similar calculations were performed for all other types of sites. When the EEV was compared with the ENEV for each effluent, the resulting EEV/ENEV quotient exceeded one for most of the undiluted effluents (Table 10). All textile mill effluents had quotients greater than one. Four of 14 pulp mills sampled prior to 1998 and 5 of 19 sampled more recently had quotients greater than one for NP. Most (38 of 41) MWWTP effluents also exceeded a quotient of one. Since there were quotients greater than one for each type of site, a conservative assessment of the environmental concentrations of NP relative to chronic toxicity endpoints was considered necessary for textile mills, MWWTPs and pulp and paper mills.

Table 9 Summary of the selected endpoints

Compound	Assessment level [1]	Endpoint	Species	CTV (µg/L)	AF	ENEV (µg/L)	Reference
NP	1	96-hour LC_{50}	Winter flounder (*Pleuronectes americanus*)	17	100	0.17	Lussier *et al.*, 1996
	2	NOEC (growth)	Mysid shrimp (*Mysidopsis bahia*)	3.9	10	0.39	Ward and Boeri, 1991c
	3	Chronic effects in less than 5% of species	Based on plotted acute data and applying an acute to chronic ratio of 4:1	10	10	1	
NP1EO	1	48-hour LC_{50}	Mysid shrimp (*Mysidopsis bahia*)	110	100	1.1	Hall *et al.*, 1989
	2	48-hour LC_{50}	Mysid shrimp (*Mysidopsis bahia*)	110	100	1.1	Hall *et al.*, 1989
	3	Chronic effects in less than 5% of species	Based on relative toxicity to NP's ENEV	1/0.5		2	
NP2EO	1	48-hour LC_{50} (from NP1EO)	Mysid shrimp (*Mysidopsis bahia*)	110	100	1.1	Hall *et al.*, 1989
	2	48-hour LC_{50} (from NP1EO)	Mysid shrimp (*Mysidopsis bahia*)	110	100	1.1	Hall *et al.*, 1989
	3	Chronic effects in less than 5% of species	Based on relative toxicity to NP's ENEV	1/0.5		2	
NP9EO	1	48-hour LC_{50}	Mysid shrimp (*Mysidopsis bahia*)	900	100	9.0	Hall *et al.*, 1989
	2	48-hour LC_{50}	Mysid shrimp (*Mysidopsis bahia*)	900	100	9.0	Hall *et al.*, 1989
	3	Chronic effects in less than 5% of species	Based on relative toxicity to NP	1/0.005		200	
NP1EC	1	NOEC	Fathead minnow (*Pimephales promelas*)	1000	10	100	Williams, 1997
	2	NOEC	Fathead minnow (*Pimephales promelas*)	1000	10	100	Williams, 1997
	3	Chronic effects in less than 5% of species	Based on relative toxicity to NP's ENEV	1/0.005		200	
NP2EC	1	LC_{50}	*Daphnia magna*	990	100	9.9	Maki *et al.*, 1998
	2	NOEC (from NP1EC)	Fathead minnow (*Pimephales promelas*)	1000	10	100	Williams, 1997
	3	Chronic effects in less than 5% of species	Based on relative toxicity to NP's ENEV	1/0.005	10	200	

[1] 1 = hyperconservative assessment; 2 = conservative assessment; 3 = distributional assessment.

Table 10 Number of Canadian effluent sites where risk quotients exceeded one for NPEs, using a hyperconservative assessment (total number of sites, total number of samples)

Environmental compartment	Sites		NP	NP1EO	NP2EO	NP9EO	NP1EC	NP2EC	TEQ
Effluents	Textiles	untreated	2 (2,5)	2 (2,5)	2 (2,5)	2 (2,5)	0 (1,2)	0 (1,2)	2 (2,5)
		on-site treatment	2 (2,4)	1 (1,2)	1 (1,2)	2 (2,3)	0 (2,4)	1 (2,4)	2 (2,4)
		going to MWWTP	9 (9,14)	10 (10,14)	10 (10,14)	10 (10,14)	0 (5,7)	0 (5,7)	10 (10,15)
	Pulp and paper	prior to 1998	4 (14,33)	13 (13,32)	4 (14,33)	–	–	–	14 (14,33)
		after 1998	5 (19,19)	2 (3,3)	2 (3,3)	2 (3,3)	0 (15,15)	2 (15,15)	6 (19,19)
	MWWTP	primary	8 (8,21)	10 (10,26)	10 (10,26)	7 (8,22)	0 (3,7)	0 (3,7)	10 (10,26)
		secondary	19 (21,54)	17 (20,46)	17 (20,46)	8 (16,35)	0 (14,34)	12 (14,34)	21 (21,54)
		tertiary	6 (7,37)	7 (7,37)	7 (7,37)	3 (6,34)	0 (6,34)	5 (6,34)	7 (7,37)
		lagoon	5 (5,5)	5 (5,5)	4 (5,5)	0 (4,4)	0 (4,4)	0 (4,4)	5 (5,5)
	Refinery		0 (2,1)						

Conservative approach

The winter flounder (a marine species) is more sensitive to NP than 18 other fish species reported in the literature by almost a factor of 10 (Figure 5). The consistency of the other acute toxicity data in fish suggested that this value was hyperconservative. In the conservative assessment, the CTV of the 28-day NOEC (length) for the mysid shrimp, *Mysidopsis bahia* (Ward and Boeri, 1991c), was divided by an AF of 10 to derive an ENEV of 0.39 μg/L (Table 9). An AF of 10 was considered appropriate because the ENEV was based on a NOEC and because there were considerable supporting data for at least three trophic levels.

The EEV was taken as the maximum concentration of effluent from each type of site, divided by a dilution factor of 10. The consideration of dilution, even using a conservative value of 10:1, dramatically decreased the number of effluents that resulted in an EEV/ENEV quotient of greater than one (Table 11). However, the conservative risk quotient exceeded a value of one in receiving water concentrations associated with several textile, municipal wastewater and pulp and paper mill effluents based on predicted concentrations. Three of 8 primary-treated municipal wastewater effluents, 1 of 21 secondary-treated municipal wastewater effluents, none of the tertiary- or lagoon-treated municipal wastewater effluents, 1 of 19 pulp and paper mill sites after 1998 and 3 of 14 pulp and paper mill sites prior to 1998 exceeded a quotient of one for NP. One of the two untreated textile mill sites exceeded a quotient of one, but neither of the two textile mills with on-site treatment had quotients greater than one for NP (Table 11). Several surface waters, including rivers that receive municipal or pulp mill effluents and harbours, also had risk quotients greater than one. Therefore, a distributional assessment was conducted.

Distributional approach

The ENEV for NP was taken to be 1 μg/L for protection of aquatic biota in the distributional approach (Figure 8). A further check on the appropriateness of the value 1 μg NP/L showed that NOECs for chronic effects in fish and invertebrates are reported in the range of 3–10 μg/L. Histological and biochemical responses also have been seen in the same concentration range. The induction of vitellogenin mRNA in rainbow trout has been reported at 1 μg/L. Therefore, the ENEV of 1 μg NP/L takes into account the uncertainty associated with species differences and extrapolation between laboratory and field studies, as well as reported molecular and histological responses.

Approximately 40% of the MWWTPs have mean concentrations of NP above 1 μg/L, although these are predominately effluents from primary (minimal) MWWTPs. However, if a dilution factor of 10 is applied, only five sites exceeded 1 μg/L for all sectors (Figure 9). The exceedances are usually less than a factor of 2 and included an untreated textile mill, three primary treated MWWTPs, a pulp mill effluent sampled prior to 1998 and a receiving water sample collected immediately downstream of a large MWWTP (Table 12). Based on recent data used in this assessment, NP alone may be at levels of concern to aquatic biota in areas immediately adjacent to industrial or municipal effluents. However, it is important to recognize that NP is only a single component of the APs/APEs released into the environment.

3.1.2.3.2 Risk characterization for nonylphenol polyethoxylates (NP1EO, NP2EO)

The acute 48-hour toxicity value of NP1EO for the mysid shrimp, *Mysidopsis bahia*, of 110 μg/L (Hall *et al*., 1989) was taken to be the hyperconservative CTV. This value was divided by an AF of 100, resulting in a hyperconservative and conservative ENEV of 1.1 μg/L (Table 9). An AF of 100 was used because acute toxicity data rather than chronic data were used and because

Table 11 Number of Canadian effluent and freshwater sites where risk quotients for NPEs exceeded one using a conservative assessment (total number of sites, total number of samples)

Environmental compartment	Sites		NP	NP1EO	NP2EO	NP9EO	NP1EC	NP2EC	TEQ
Effluents	Textiles	untreated	1 (2,5)	2 (2,5)	2 (2,5)	2 (2,5)	0 (1,2)	0 (1,2)	2 (2,5)
		on-site treatment	0 (2,4)	1 (1,2)	1 (1,2)	2 (2,3)	0 (2,4)	0 (2,4)	1 (2,4)
		going to MWWTP	na	na	na	na	na	na	na
	Pulp and paper	prior to 1998	3 (14,33)	12 (13,32)	4 (14,33)	–	–	–	7 (14,33)
		after 1998	1 (19,19)	2 (3,3)	2 (3,3)	0 (3,3)	0 (15,15)	0 (15,15)	3 (19,19)
	MWWTP	primary	3 (8,21)	9 (10,26)	9 (10,26)	5 (8,22)	0 (3,7)	0 (3,7)	9 (10,26)
		secondary	1 (21,54)	13 (20,46)	12 (20,46)	0 (16,35)	0 (14,34)	0 (14,34)	7 (21,54)
		tertiary	0 (7,37)	6 (7,37)	5 (7,37)	0 (6,34)	0 (6,34)	0 (6,34)	3 (7,37)
		lagoon	0 (5,5)	0 (5,5)	0 (5,5)	0 (4,4)	0 (4,4)	0 (4,4)	0 (5,5)
Aquatic	Rivers		2 (25,90)	6 (12,51)	3 (12,51)	2 (3,27)	0 (1,37)	0 (1,37)	4 (25,90)
	Lakes		0 (5,5)	2 (4,4)	0 (4,4)	–	–	–	1 (5,5)
	Harbours		1 (12,31)	9 (12,26)	4 (12,26)	–	–	–	7 (12,31)
Benthic			5 (24,58)	1 (6,14)	1 (6,14)	0 (1,4)	–	–	5 (24,58)
Soil/sludge			18 (30,107)	8 (28,90)	3 (28,90)	0 (28,90)	0 (17,66)	0 (17,66)	18 (30,107)

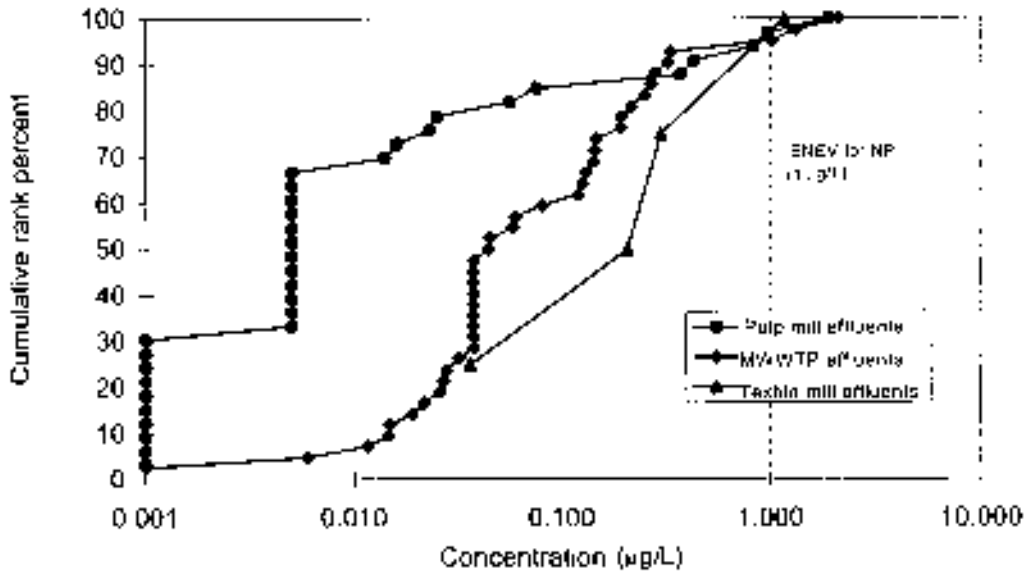
na = not applicable; – = not available

TABLE 12 Number of Canadian effluent and freshwater sites where risk quotients for NPEs exceeded one using a distributional assessment (number of exceedances/total number of sites)

Environmental compartment	Sites		NP	NP1EO	NP2EO	NP9EO	NP1EC	NP2EC	TEQ
Effluents	Textiles	untreated	1/2	2/2	2/2	2/2	0/1	0/1	2/2
		on-site treatment	0/2	0/1	0/1	0/2	0/2	0/2	0/2
		going to MWWTP	na	na	na	na	na	na	na
	Pulp and paper	prior to 1998	1/14	2/13	2/14	–	–	–	4/14
		after 1998	0/19	0/3	1/3	0/3	0/15	0/15	1/19
	MWWTP	primary	3/8	2/10	1/10	0/8	0/3	0/3	5/10
		secondary	0/21	1/20	0/20	0/16	0/14	0/14	1/21
		tertiary	0/7	0/7	0/7	0/6	0/6	0/6	0/7
		lagoon	0/5	0/5	0/5	0/4	0/4	0/4	0/5
Aquatic	Rivers		1/25	1/12	0/12	0/3	0/1	0/1	2/25
	Lakes		0/5	1/4	0/4	–	–	–	1/5
	Harbours		0/12	1/12	1/12	–	–	–	4/12

na = not applicable; – = not available

FIGURE 9 Environmental concentrations of NP in pulp mill, municipal wastewater treatment plant and textile mill effluents based on site averages and a dilution of 10:1



there were poor supporting data (Table 13). The ENEV value was considered appropriate for both NP1EO and NP2EO. An overview of available data suggests that the relative toxicity of both of these metabolites is similar and approximately half that of NP (e.g., killifish; Yoshimura, 1986). In the distributional approach, based on the more robust data on NP and assuming that the toxicity of NP1,2EO is about half that of NP, the ENEV for NP1,2EO was determined to be 2 μg/L.

Among the major degradation products of the higher-chain-length NPEs are NP1EO and NP2EO. Treatment systems, including MWWTPs, can, therefore, contain high levels of these metabolites, depending on the sources and the efficiency of degradation. Despite being less toxic than NP, these metabolites are found in higher concentrations, resulting in frequent exceedances of hyperconservative and conservative risk quotients, particularly for NP1EO (Tables 10 and 11). Almost all (9 of 10) primary-treated and more than half of both secondary- and tertiary-treated MWWTPs had conservative risk quotients greater than one, even after a dilution of 10:1 in the environment (Figure 10). In contrast, none of the wastewater lagoon systems (0 of 5) had exceedances. Textile mill effluents that are not treated can also exceed the ENEV by a considerable amount. Pulp and paper mill effluents seldom (less than 20%) exceed the ENEV for these metabolites and appear to have been reduced in recent years, although the recent data available for these compounds are limited (Figures 11 and 12). A variety of surface water concentrations frequently (65%) exceed the conservative ENEV. The presence of NP1EO and NP2EO in effluents, especially textile mill effluents and poorly treated municipal wastewater, represents a potential risk to the environment and was, therefore, considered further. When compared with a distributional ENEV of 2 μg/L, no pulp mills sampled after 1998 (n = 3) and only 3 of 42 (2 primary, 1 secondary) MWWTPs have mean concentrations of NP1EO greater than the ENEV. There was one pulp mill sampled after 1998 with elevated NP2EO and only one primary-treated MWWTP at levels above the ENEV of 2 μg/L (Table 12).

Table 13 Most sensitive aquatic organisms for NPEs and NPECs

Substance	Trophic level	Water (fresh/ marine)	Exposure length	Species	Endpoint	CTV (µg/L)	AF	ENEV (µg/L)	Reference	Confidence
NP1EO	Fish	F	acute	*Oryzias latipes*	48-hour LC_{50}	3000	100	3.0	Yoshimura, 1986	low
		F/M	chronic	NA [1]						
	Invertebrates	F/M	acute	NA						
		F	chronic	*Culex pipiens*	EC_{50} (emergence)	80 000	100	80	Maxwell and Piper, 1968	very low
	Algae	F/M	acute/chronic	NA						
NPnEO	Fish	F/M	acute/chronic	NA						
(mixture 1,2)	Invertebrates	M	acute	*Mysidopsis bahia*	48-hour LC_{50}	110	100	1.1	Hall *et al.*, 1989	moderate
		F	acute	*Ceriodaphnia dubia*	LC_{50}	626	100	6.26	Weeks *et al.*, 1996	high
		F	chronic	*Ceriodaphnia dubia*	7-day NOEC (reproduction)	280	10	28	Weeks *et al.*, 1996	high
	Algae	F/M	acute/chronic	NA						
NP2EO	Fish	F/M	acute	NA						
		F/M	chronic	NA						
	Invertebrates	F	acute	*Daphnia magna*	48-hour LC_{50}	148	100	1.48	Maki *et al.*, 1998	high
		F/M	chronic	NA						
	Algae	F/M	acute/chronic	NA						
		M								
NP9EO	Fish	F	acute	*Pimephales promelas*	96-hour LC_{50}	4600	100	46	Dorn *et al.*, 1993	high
		F	chronic	*Pimephales promelas*	7-day NOEC (growth)	1000	10	100	Dorn *et al.*, 1993	high
		M	acute (NP10EO)	*Gadus morhua*	96-hour LC_{50}	2500	100	25	Swedmark *et al.*, 1971	moderate
		M	chronic	NA						
	Invertebrates	F	acute	*Daphnia magna*	48-hour LC_{50}	14 000	100	140	Dorn *et al.*, 1993	high
		F	chronic	*Daphnia magna*	7-day NOEC (growth)	10 000	10	1000	Dorn *et al.*, 1993	high
		M	acute	*Mysidopsis bahia*	48-hour LC_{50}	900	100	9.0	Hall *et al.*, 1989	moderate
		M	chronic	NA						
	Algae	F	acute	*Selenastrum capricornutum*	EC_{50}	12 000	100	120	Dorn *et al.*, 1993	high
		F	chronic	*Selenastrum capricornutum*	NOEC (growth)	8000	10	800	Dorn *et al.*, 1993	high
		M	acute/chronic	NA						
NP1EC	Fish	F	acute	*Oryzias latipes*	48-hour LC_{50}	9600	100	96	Yoshimura, 1986	low
		F	chronic	*Pimephales promelas*	7-day NOEC (growth)	1000	10	100	Williams, 1997	moderate/ low
		M	acute/chronic	NA						
	Invertebrates	F	acute	*Daphnia magna*	48-hour LC_{50}	14 000	100	140	Naylor *et al.*, 1997	low
		F	acute	*Ceriodaphnia dubia*	96-hour LC_{50}	17 000	100	170	Naylor *et al.*, 1997	low
		F	chronic	*Ceriodaphnia dubia*	7-day NOEC (reproduction)	2200	10	220	Naylor *et al.*, 1997	low
		M	acute	*Mysidopsis bahia*	48-hour LC_{50}	9400	100	94	Naylor *et al.*, 1997	low
	Algae	F/M	acute/chronic	NA						
NP2EC	Fish	F/M	acute/chronic	NA						
	Invertebrates	F	acute	*Daphnia magna*	48-hour LC_{50}	990	100	9.9	Maki *et al.*, 1998	high
		F/M	chronic	NA						
	Algae	F/M	acute/chronic	NA						

[1] NA = no studies available.

FIGURE 10 Estimated environmental concentrations of NP, NP1EO+NP2EO, NP1EC+NP2EC and NP9EO near municipal wastewater treatment plants (primary, secondary and tertiary)

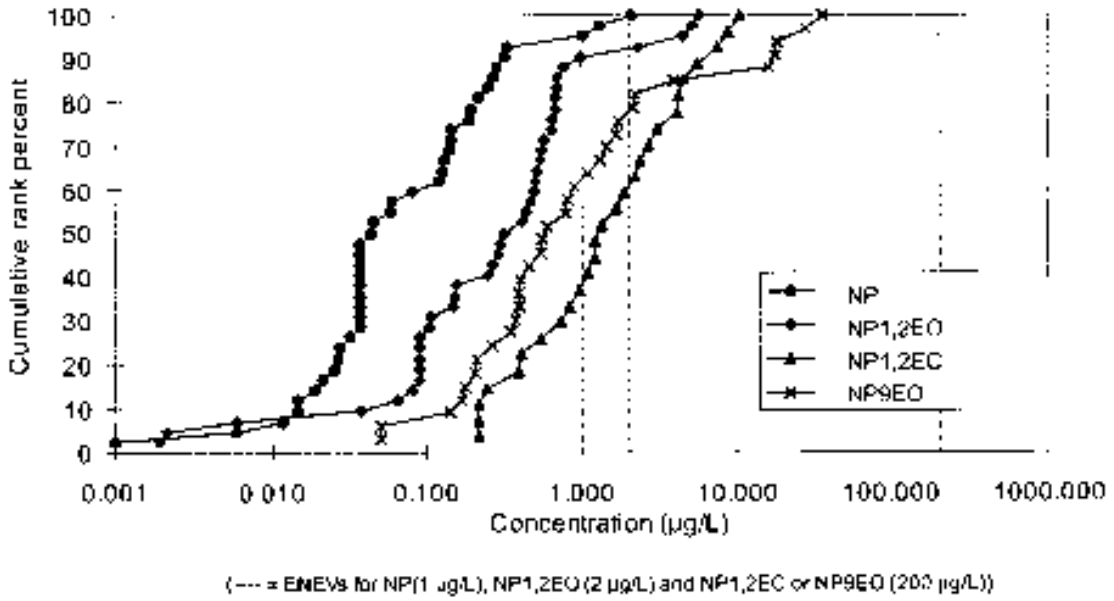
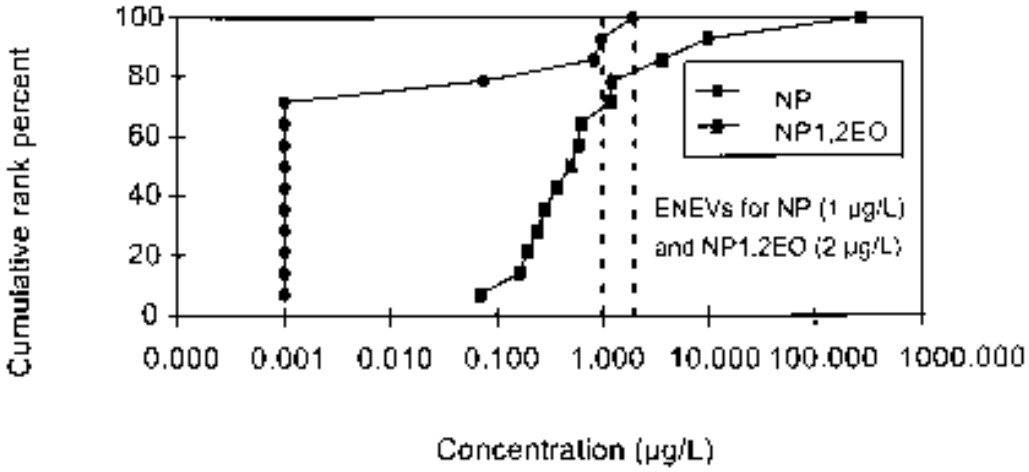


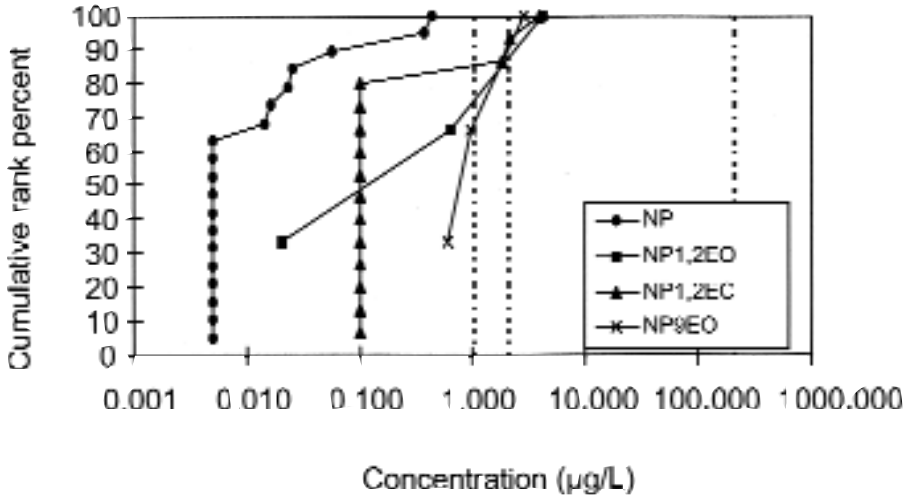
FIGURE 11 Estimated environmental concentrations of NP and NP1EO+NP2EO near pulp mills prior to 1998



3.1.2.3.3 Risk characterization for nonylphenol polyethoxylates (NP3–17EO)

NPEs with greater than 3 EO units were grouped together and treated as if they had the same toxicity as NP9EO. There are considerable acute and chronic toxicity data available for NP9EO and NP10EO, but few data for many of the other polyethoxylates. There are toxicity data available for several trophic levels, including fish, invertebrates and algae in freshwater and marine environments. The most sensitive reliable value is a 48-hour LC_{50} value in the mysid shrimp, *Mysidopsis bahia*, of 900 µg/L (Hall *et al.*, 1989) (Table 13). An AF of 100 was applied to that CTV, resulting in an ENEV of 9.0 µg/L. This value was applied to both the hyperconservative

FIGURE 12 Estimated environmental concentrations of NP, NP1EO+NP2EO, NP1EC+NP2EC and NP9EO near pulp mills after 1998



(…= ENEVs for NP (1μg/L), NP1,2EO (2 μg/L) and NP1,2EC or NP9EO (200 μg/L))

and conservative assessments (Table 9). The conservative approach considers dilution of effluents and is, therefore, more realistic.

Untreated or even on-site treated textile mill effluents had very high concentrations of NP9EO and consequently had high hyperconservative and conservative risk quotients (Tables 10 and 11). Primary municipal wastewater effluents also contain high levels of NP9EO, and five of eight sites have concentrations that are predicted to exceed a conservative risk quotient of one. MWWTPs are effective at reducing the concentrations of NP9EO in the final effluent, and none of the secondary- or tertiary-treated effluent or lagoons had predicted concentrations that would exceed the conservative risk quotient of one. The dilution of most of the primary-treated effluents is likely underestimated and would further reduce the predicted risk of these chemicals. Unfortunately, there are relatively few data available for pulp and paper mill effluents, but the three effluents for which data are available all have conservative risk quotients less than one. NP9EO concentrations in two of the three surface water sites sampled were greater than 9.0 μg/L. Only untreated textile effluents had mean NP3–17EO concentrations above the distributional ENEV (200 μg/L) (Table 12). This value (200 μg/L) was based on the ENEV of NP divided by the relative toxicity factor of 0.005 (Tables 6 and 9). The concentrations of NP9EO in treated effluents are not likely to pose a risk to the environment. However, untreated or partially treated effluents, particularly textile mill effluents, may pose a potential risk, especially if effluent dilution is low

3.1.2.3.4 Risk characterization for nonylphenol polyethoxycarboxylates (NP1EC, NP2EC)

A NOEC of 1000 μg/L for NP1EC in fathead minnow was reported by Williams (1997), and an AF of 10 was applied, resulting in an ENEV of 100 μg/L (Table 9). This value was used for both the hyperconservative and conservative approaches. Maki *et al*. (1998) reported an LC_{50} in *Daphnia magna* for NP2EC of 990 μg/L. Applying an AF of 100 resulted in an ENEV of 9.9 μg/L, and this value was used in the hyperconservative assessment (Table 9). The study on NP1EC is more robust and better documented than the study by Maki *et al*. (1998).

Since it is expected that NP1EC and NP2EC will have similar toxicities based on an overall assessment of the toxicity data, the values of Williams (1997) also were used as a conservative ENEV assessment for NP2EC.

NPECs can be created during effluent treatment, and concentrations in final effluent can be considerably higher than those in influent. Even in untreated effluents, the concentration of NP1EC does not appear to be high enough to result in chronic toxicity. The hyperconservative assessment resulted in some exceedances for NP2EC in wastewater effluents, particularly secondary and tertiary treatment (Table 10). When dilution is considered, no effluents in any sector have NPEC values that result in conservative risk quotients above one. Unfortunately, there are very few actual receiving water concentrations reported for these compounds. Despite the elevated concentrations of NPECs in treated final effluents, they have considerably lower toxicities; therefore, when considered alone, they do not represent a significant risk based on chronic toxicity.

3.1.2.3.5 Risk characterization for the combined effects of nonylphenol ethoxylates

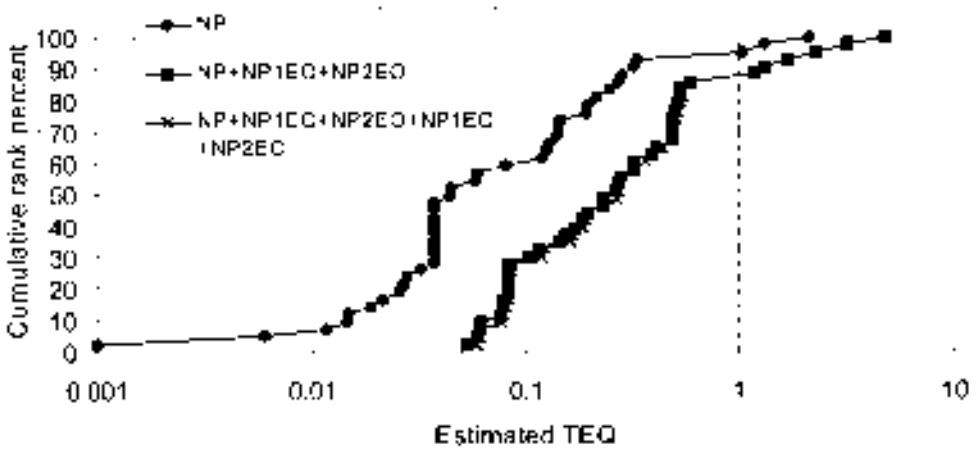
As observed in field measurements, NP and NPEs occur as complex mixtures, and the toxicities of the metabolites are expected to be additive. When NP is considered alone, only three sites have predicted concentrations in receiving waters that exceed a value of 1 μg/L. When NP1EO and NP2EO are considered in addition to NP, an additional four sites exceed the ENEV. The chronic toxicity of NPE mixtures in municipal effluents and receiving waters is dominated by the effects associated with NP1EO and NP2EO and, to a lesser extent, NP. In situations where the concentrations of NP9EO are high, the concentrations of NP1EO and NP2EO also are elevated and contribute significantly to the overall acute and chronic toxicity. Although the concentrations of NP1EC and NP2EC are often higher in municipal wastewater effluents, they contribute very little to the toxicity of the mixture because of their relatively low toxicity. Consideration of the additivity of NPEs slightly increased the number of sites that had conservative risk quotients greater than one (Table 11). Limited data indicate that untreated or partially treated textile mill effluents are likely to cause adverse effects on at least the most sensitive species in the receiving water because of the extremely high concentrations of NP3–17EO or its metabolites (NP1,2EO). NPEs also have the potential to exceed conservative ENEVs at a limited number of pulp mill and municipal effluents, particularly if effluent dilution is low or if there is little or no treatment.

In the distributional assessment, there was greater confidence in using the NP toxicity data together with the relative potencies for other metabolites to derive the TEQ than in using toxicity data for the metabolites alone. In the distributional assessment, the average effluent concentration at each site together with a dilution factor of 10 was used as the EEV. The combined TEQ results of the distributional assessment indicated levels of concern at 21 sites (2/2 untreated textile mills; 4/14 pulp mills prior to 1998; 1/19 pulp mills post-1998; 5/10 primary MWWTPs; 1/21 secondary MWWTPs; 2/25 river sites; 2/5 lake sites; and 4/12 harbour sites) (Table 12, Figure 13). The river, lake and harbour sites that exceeded the TEQ were typically adjacent to industrial sites or MWWTPs. The exceedance is usually due to the contribution of NP1EO.

3.1.2.3.6 Endocrine disruption in aquatic biota

Numerous studies have demonstrated the ability of APs/APEs to disrupt the normal function of the endocrine system of various organisms. These effects occur at a range of concentrations similar to those at which chronic effects occur in fish and invertebrates. Histological or biochemical responses have been reported at levels even lower than the NOEC for chronic toxicity. For instance, the threshold of NP for induction of vitellogenin in rainbow trout was reported as 10 μg/L, while the induction of mRNA for vitellogenin was reported at concentrations as low as 1 μg/L.

FIGURE 13 Estimated Toxic Equivalency Quotient (TEQ) of NPEs near municipal wastewater treatment plants



(----- = Risk Quotient = 1)

Recent reports by Miles-Richardson *et al*. (1999) suggest that in fathead minnows, histological and biochemical effects can occur at concentrations approaching or below 1 μg/L. However, the significance of these responses is not fully understood, and the effects on the organism or population have not been determined. Recent work by Brown *et al*. (1998) has demonstrated that NP can affect smoltification, resulting in reduced growth and survival in Atlantic salmon (*Salmo salar*) after very short term (24-hour) exposure to concentrations as low as 20 μg/L (nominal). Intersex in killifish has been demonstrated at 50 μg/L (Gray and Metcalfe, 1997). Vitellogenin induction is a biological response in fish that is mediated through binding of a chemical to the estrogen receptor. The threshold for this response is very similar to the LOEC for early life stage tests with rainbow trout and only slightly below the thresholds for *in vivo* responses such as intersex and impaired smoltification. Although potential effects mediated through the estrogen receptor have been identified both *in vitro* and *in vivo* for NP in fish, this is only one mechanism by which a chemical such as NP can potentially interact with endocrine systems. The application of a factor of 10 to the whole-organism vitellogenin induction in rainbow trout results in a hyperconservative ENEV of 1 μg/L, which would be similar to the threshold for induction of mRNA of vitellogenin in rainbow trout (Fent *et al*., 1999). A value of 1 μg/L seems justified for application to the EEV data for NP to determine if there is potential for endocrine-mediated responses in biota.

In the hyperconservative assessment, NP concentrations alone in final effluents are high enough in municipal effluents to cause concern for endocrine responses in 40% of the effluents. However, in the conservative assessment, when a dilution factor of 10 is applied, there are only three municipal effluent sites, one textile mill site and one pulp mill site that exceed a predicted aqueous concentration of 1 μg NP/L, and none that exceed a value of 10 μg/L (Figure 9). NP values were above 1 μg/L only in surface water immediately adjacent to industrial or municipal treatment sites. NP alone is unlikely to result in widespread effects mediated through the estrogen receptor in Canadian surface waters.

Similar to toxicity, the relative estrogenicity (RE) was used to determine a total estrogenic equivalency (EEV_{EEQ}) for the combination of NP and NPEs found as mixtures

in the environment using NP as the reference, as follows:

$$\text{Total } EEV_{EEQ} = \sum (C_X \times RE_X)$$

where:

- total EEV_{EEQ} = total estrogenic equivalency of a mixture based on estrogenicity of NP
- C_X = concentration of metabolite x in the mixture
- RE_X = relative estrogenicity of metabolite x compared with NP

As with acute and chronic toxicity, there are few data available on the relative estrogenicity of the other metabolites, and there is considerable discrepancy among the few existing studies. The relative estrogenicity of the metabolites differs considerably from their relative acute toxicity (Table 6). The data of Jobling and Sumpter (1993), based on vitellogenin induction in trout hepatocytes, were considered for relative potencies. Based on these data, both NP1,2EO and NP1,2EC are expected to be only slightly less estrogenic than NP. This contrasts with acute toxicity, where NP1,2EC are much less toxic than NP. Because of the prevalence of NP1,2EC in treated effluents, the estrogenic responses may be a concern. However, considerable debate has emerged on the relative estrogenicity of these compounds. NP1EC was slightly less potent than NP in rainbow trout estradiol receptor assays, while the potency of NP1EO was much lower than that of NP (Servos, 1999b; Van Der Kraak, 1999). In transfected yeast cell assays (YES, with hER), there is little or no binding of NP1,2EC to the estrogen receptor, suggesting a very low or zero potency. Mixtures of NP1,2EC did not cause ova-testes in killifish at concentrations similar to those that resulted in this response for NP (Metcalfe, 1999). Although this difference may be due to the characteristics of the *in vitro* assays, it does raise some uncertainty regarding the relative estrogenicity of these compounds. The discrepancies between potency estimates for NP1,2EC are particularly problematic. Although there remains debate the trout hepatocyte assay results of Jobling and Sumpter (1993), they are considered the best data currently available in the literature and were applied in this risk characterization. Caution must be used in interpretation of these results until the relative potency is validated in in vivo systems. NP1,2EO may exceed the threshold for endocrine responses in a few textile mill and municipal treatment effluents and receiving waters. NP1,2EC has the potential to cause estrogenic effects in most municipal and some pulp mill effluents. As many as 40% of receiving waters associated with municipal effluents (Figure 14) and a few pulp mill effluent exposed sites may have the potential for endocrine responses.

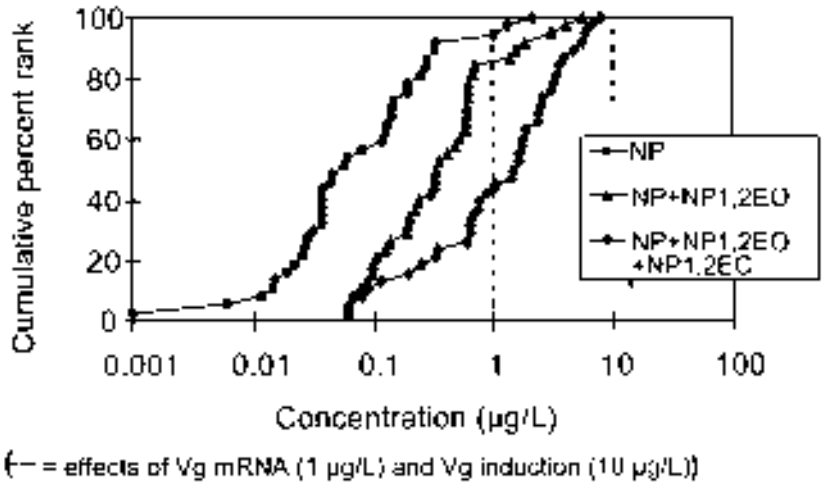
When considered alone, concentrations of NP would not exceed the threshold for estrogenic response, except in environments receiving primary treated municipal effluents; however, the dilution at these sites is also likely underestimated. If the effects of the NPEs are added to the effect of NP, then about 15% of the sites are expected to exceed the threshold of 1 μg/L. When the NPECs are also added, almost 60% of the municipal sites and a few of the pulp mill sites exceed the value of 1 μg/L. These effluents would be a cause for concern, as histological and biochemical responses may be expected. Many municipal effluents would be expected to cause vitellogenin induction, but they are not expected to exceed the threshold (10 μg NP/L for rainbow trout) in receiving waters after a 10:1 dilution, even when considered as a group.

There is considerable uncertainty associated with predicting estrogenic responses, particularly for NP1,2EC and NP1,2EO. If the relative estrogenic potency of NP1,2EC is much less than that reported by Jobling and Sumpter (1993), as is indicated by some of the *in vitro* data, there would be very few sites where the threshold for estrogenic-mediated responses would be exceeded.

3.1.2.4 Risk characterization for sediment

NP, NP1EO and NP2EO have a tendency to adsorb to sediments, whereas NPECs are more water soluble and tend to remain in the overlying

FIGURE 14 Estimated Estrogenic Equivalency (EEV_{TEQ}) of NPEs near municipal wastewater treatment plants



water (final effluent). NP is also moderately persistent in sediment; therefore, the effects of NP and NPEs are of primary interest for sediment-dwelling organisms. Unfortunately, there are no effects data available to benthic organisms for nonylphenolic compounds with the exception of NP. The CTV is the 14-day NOEC (growth and survival) for the midge, *Chironomus tentans*, of 20 μg/g (England and Bussard, 1993); dividing by an AF of 10 results in an ENEV of 2.0 μg/g (Table 8). The chironomid data were selected because they represented the sediment-exposed biota. There are many factors that can affect the bioavailability of NP in sediments, including sorption to organic matter, which will alter the expression of toxicity. Variability in the sediment characteristics makes it difficult to extrapolate directly from laboratory results to toxicity in the environment. NP can also bioaccumulate in the environment, with a BAF of approximately 10. This could result in slightly higher exposure of selected organisms. The toxicity in sediments for NPEs was estimated relative to NP using the aquatic toxicity factors and dividing the ENEV by the relative toxicity for NP (2.0 μg/g). This resulted in an ENEV for NP1,2EO of 4.0 μg/g.

The concentrations of NP in Canadian sediments are generally low (<1 μg/g), with the exception of industrial harbours and sites near the outfalls of MWWTPs. A comparison of the sediment concentrations with the ENEV of 2.0 μg/g shows risk quotients greater than one in about one-fifth of the sites (5 out of 24), generally in areas immediately adjacent to MWWTP outfalls (Table 11). There are fewer data available for NP1EO and NP2EO in sediments, but their concentrations are usually less than those of NP. At one of six sites, the concentrations of NP1EO and NP2EO exceeded the ENEV. Limited data on NP9EO suggest that they are found at very low concentrations in sediments. No sediment data were available for NP1EC or NP2EC, but, based on their high water solubility and much lower toxicity, they are not expected to pose a risk for chronic toxicity in sediments.

Exposure to NP and NP1,2EO in sediments downstream of industrial or municipal effluents may result in potential risk to aquatic biota. The pattern of NP and NPEs in sediment is very different from that of the aqueous phase. The more hydrophobic chemicals are more prevalent in sediment, which is in contrast to higher levels

of NP1,2EC in final effluents. The distribution and fate in river, harbour or lake sediments may also be very different from the distribution in water. For example, at Galt, Ontario, on the Grand River, the concentrations of NP decline rapidly with dilution downstream to 8 km. In contrast, the concentrations of NP in sediment increased at the 8-km site relative to locations close to the outfall (0 and 0.1 km). This is likely due to changes in the sediment composition, which shifts from hard rock and cobble at the outfall to higher organic content silts farther downstream. The potential effects of NP and NPEs in sediment can, therefore, be remote from the outfall, where dilution of the effluent is relatively high.

3.1.2.5 Risk characterization for the terrestrial environment

The earthworm, *Apporectodea calignosa*, tested by Krogh *et al*. (1996), had a 21-day EC_{10} (reproduction) of 3.4 μg NP/g in soil, which was taken to be the CTV. An AF of 10 was applied to the CTV to obtain an ENEV of 0.34 μg/g (Table 8). This ENEV was used in both the hyperconservative and conservative approaches. The difference between the approaches was that the concentration in raw sludge was used as the EEV in the hyperconservative assessment, while the concentration in sludge-applied soil was used as the EEV in the conservative assessment. There are no toxicity data available for soil-dwelling organisms for the other NPE metabolites.

NP is found in relatively high concentrations in sludge relative to other NPE metabolites. In general, concentrations of NP1EO are usually lower than concentrations of NP, although in a limited number of cases NP1EO concentrations were higher than those of NP. NP9EO and NP1,2EC concentrations are consistently low in sludge. NP is more hydrophobic than the other metabolites and is expected to be the most persistent in soils. The focus of the sludge application was, therefore, on NP. In the conservative assessment, the predicted soil concentrations after sludge application were estimated based on the sludge concentrations measured in MWWTPs and the application rates recommended by the Ontario Ministry of Environment and Energy and Ontario Ministry of Agriculture, Food and Rural Affairs (1996) (maximum 8 tonnes per hectare over 5 years). Sludge NP concentrations ranged from 10 to 1260 μg/g. The sludge is assumed to be applied and tilled to a depth of 15 cm, and 1 ha is assumed to weigh 2000 tonnes. When applied to the soil and tilled, the sludge concentrations are, therefore, diluted by a factor of 0.004.

In the conservative analysis, the risk quotients for NP in soils based on predicted concentrations immediately after application are usually greater than one (18 of 30 sludge sites), indicating a potential for chronic effects (Table 11). The predicted concentrations in soil are higher than the ENEV by less than a factor of 2 and are rarely in exceedance by a factor of 10. During risk management of sludge application to agricultural soils, consideration must be given to application rates, the concentration of NP and NPEs in the sludge and the duration of the potential exposure (i.e., degradation).

A distributional assessment for NP and NPEs in soil was not undertaken, since actual concentrations in soil in Canada were not available. Further evaluation on a qualitative basis suggests that NP alone degrades rapidly in soil. However, when sludges that contain both NP and NPEs are considered, the degradation of the NPEs to NP may contribute to maintaining higher levels of NP for longer periods than would be expected if only NP existed in the sludge. However, NP is not expected to persist in soils for extended periods of time (<90 days), and sludge applications are normally followed by a period of fallow.

3.1.2.6 Summary of risk by specific sector

3.1.2.6.1 Textile mill effluents

Textile mills are a major source of APEs and a concern for the environment. Raw textile mill effluents have very high levels of NP and NPEs (especially those with high EO chain lengths). At one of the monitored Canadian textile mills, in the past, effluents were discharged directly into

the environment. At another, on-site treatment is performed, although the system performs poorly. Very high levels of NP3–17EO (798–8811 μg/L), NP1EO and NP2EO (37–592 μg/L) and NP (2.7–13.3 μg/L) in receiving waters were measured at these two sites. Effluent concentrations measured at the point of release into water bodies were divided by a dilution factor (10) to estimate environmental concentrations. The distributional ENEV values were exceeded in all samples from these two sites. Two additional textile mill sites that have on-site secondary treatment systems were monitored. Results showed that these mills were not completely effective at eliminating the NP or NPEs. The concentrations of NP1,2EC in untreated textile mill effluents are very low. In most cases, the textile mills discharge into municipal treatment systems. Although these systems are very efficient at removing NPEs, significant amounts of NP and NPEs can potentially be released into the environment, even after treatment. The fate of NPE in textile mill effluents needs to be determined in both treatment systems and the environment, particularly at sites where there is little or no treatment.

3.1.2.6.2 Pulp and paper mill effluents

There has been a move within the pulp and paper industry to reduce or eliminate the use of NPEs from effluents, and there appears to have been a reduction in exposure over recent years. Pulp and paper mill effluents were, therefore, separated into samples collected prior to 1998 and those collected as part of a more recent study. Samples collected prior to 1998 commonly had detectable levels of NPEs and in one case had effluent concentrations in excess of 100 μg/L (Figure 11). Although concentrations of NPEs were low in samples collected after 1998 (Figure 12), there were only three sites sampled for these compounds, making it difficult to draw a conclusion. However, only a very few of the pulp mills studied had NP or NPEs in their effluents at concentrations high enough to be a concern for the environment.

3.1.2.6.3 Municipal treatment plant effluents

NP would not be expected to currently cause significant effects in the aquatic environment through exposure to treated effluents via water, although effluents from MWWTPs subject to primary treatment may be of some concern (Figure 10). However, NP is relatively insoluble in water and, therefore, bound to particles and sludges, which may result in exposure through alternative routes. Exposure of biota in sediment may occur at different locations compared with exposure of aquatic organisms (e.g., Galt–Grand River situation). NP was shown to represent a potential risk to sediment biota downstream of MWWTP outfalls.

Sludges that are applied to soils result in exposure of terrestrial biota. Considering the levels, which are only slightly above the ENEV, the rapid degradation in soil and low accumulation in plants, it is unlikely that land application of sludges under best management practices is a major concern. However, there are very few data available, and the potential roles of NP1EO and NP2EO need to be considered in terms of both their toxicity and their potential to prolong the exposure to NP in soils.

The higher-chain-length NPEs degrade not only to NP, but to a variety of lower-chain-length NPEs and NPECs in municipal treatment systems. These compounds can occur at relatively high concentrations and represent a risk for both chronic toxicity and estrogenic effects in the aquatic environment. Depending on the inputs and the degree and type of treatment at the plant, NP1EO and NP2EO can be found at levels that are expected to cause chronic toxicity. This is based on an assumption of a dilution of 10:1, which may be an underestimate, especially for primary-treated effluents or discharges to marine environments. However, during low-flow periods, many treated effluents discharge into aquatic environments with dilutions considerably less than 10, even approaching a factor as low as 2. Although instantaneous dilution estimates may be much higher, many environments may have much lower dilutions for significant distances from the

outfall because of entrapment or poor mixing of the effluent. The assessment of receiving waters, including a case study on the Grand River, confirms there is potential for significant exposure to both NP1EO and NP2EO considerable distances downstream of the outfall.

The NPECs are also formed as a result of the degradation of higher-chain-length NPEs and are considerably more water soluble. They can, therefore, increase in concentration during the course of treatment and can reach levels considerably higher than those of NP or NPEs in final effluent. Secondary- and tertiary-treated effluents can have relatively high concentrations of NP1EC and NP2EC, despite having extensive and efficient treatment systems. The toxicities of the NPECs are much lower than those of the corresponding NPEs, and, therefore, despite their higher concentrations, the NPECs do not represent a concern for chronic toxicity in municipal effluents (no municipal effluent had a conservative risk quotient of greater than one for NP1EC or NP2EC). In contrast, because the NPECs may be only slightly less estrogenic than NP, they could contribute to potential estrogenic responses, even in well-treated effluents. This is based on extrapolation of cell culture results, as there are few published *in vivo* data available on these compounds. Additionally, the significance of estrogenic responses at the whole-organism or population level has not been determined. Caution must, therefore, be used in interpreting the significance of these observations, and further work is needed to determine the significance for the Canadian environment. Although there are limited concentration data for CAPECs, they have been reported in MWWTP effluents and represent a large fraction of APE metabolites. Further research to determine their impacts on organisms is necessary to address this issue fully.

3.1.2.7 Summary of risk characterization

The major route of entry of NP and NPEs into the Canadian environment is through discharge of effluents. The composition of the mixture can differ considerably among the various effluents, depending on the source and the degree and type of treatment. Textile mill effluents represent a major source of release of NPEs to the environment. Untreated or partially treated textile mill effluents can have high NP9EO, NP1EO and NP2EO concentrations, which exceed the chronic effect level (ENEV). Although pulp and paper mill effluents currently have low levels of NP, there is evidence that, at least in the past, some sites had very high concentrations of NPEs in their final effluent. There appears to be a recent decrease in discharge of NPEs from pulp and paper mills, but there are very few data available with which to validate this conclusion (Figures 11 and 12). Municipal effluents are a significant source of NPEs and are widespread across the country. Untreated effluents can have high levels of NP, NP1EO and NP2EO, which may exceed thresholds for chronic effects (ENEV) in the aquatic environment, resulting in risk quotients exceeding one (Tables 10–12). Treated effluents have relatively low levels of high EO chain length NPEs. NP1EO and NP2EO may be present in final effluents at concentrations that may result in potential chronic toxicity. Although the dilution may be greater than predicted, it is likely that significant areas near outfalls are potentially impacted, and this is supported by measurement of NPEs in surface waters. Treated effluents can elevate the concentration of NPECs in final effluents, but, due to their low relative toxicity, NPECs are not expected to cause chronic toxicity in the environment. The potential for estrogenic responses in effluents is apparent, especially if the effects of the individual metabolites are considered to be additive (Figure 14). However, the significance of estrogenic responses is not fully understood. The concentration of NP is low in treated effluents, as it degrades and sorbs to sludge particles; however, the concentration of NP sorbed to sediments is expected to be higher. Despite a relatively low potential to bioaccumulate (Table 7), sediment-dwelling organisms may be exposed to NP directly, either through contact with water or sediment or through ingestion of sediment or food.

There is potential for chronic toxicity to occur in aquatic biota due to exposure to NPEs and their metabolites in a variety of effluents. This can be associated with different metabolites of NPEs, depending on the source and degree and type of treatment. It is important that all of the NPE metabolites, not only NP, be considered together to assess the potential for impacts in the environment.

Under current use patterns, NP/NPE releases in Canada can result in environmental concentrations that exceed the levels of concern. The significance of the potential effects of NP and NPEs and their widespread use and occurrence in effluents suggest that caution should be used with this group of compounds. Although other APEs, such as OPEs, have physical/chemical properties similar to those of NPEs, which make them attractive as replacements for NPEs, they also have similar toxicological properties and greater estrogenic properties. Therefore, the potential impact of replacement of NPEs with other APEs should be considered in risk management activities.

3.1.2.8 Uncertainties in the environmental risk characterization

There are a number of uncertainties associated with the environmental risk characterization that remain because of knowledge and data gaps in the current literature.

- The dilution of effluent by ambient river, harbour or lake water was assumed to be a factor of 10, and this is likely to vary considerably. Actual dilution factors may be much greater or considerably less than 10, and most almost certainly vary with seasonal flow conditions. The dilution factor can play a large role in the calculation of risk quotients for NP and NPEs. However, it is believed that a dilution factor of 10 is an appropriate value to represent the areas near outfalls.
- The assessment compared the exposure levels with the best information available on chronic and acute toxicity, as well as the potential impacts of NP and NPEs on reproductive and developmental toxicity. However, much of the information, especially on the endocrine-mediated mechanisms, is still evolving, and much of it still needs to be validated. Endocrine-mediated mechanisms of toxicity were deemed to be important to consider, but the lack of confidence, and in some cases uncertainty, in the interpretation of data was seen as a limitation in applying these data to determine environmental no-effect concentrations. The ENEVs in the distributional approach, at least for NP, based on chronic toxicity, were considered adequate to protect against endocrine-mediated effects. The problems associated with determination of the relative estrogenicity of the other metabolites, especially NP1,2EC, raise a number of uncertainties. Several key areas of research on the effects of NP and NPEs are required, which may have significance for the evaluation of whether adverse effects are occurring through endocrine-mediated mechanisms.
- Because NP and NPEs occur together in effluents and in the environment, and because their mode of action is likely the same, their combined impact or potential impact is important in determining the risk associated with complex effluents or environmental samples. Although the assumption of additivity seems appropriate (for both chronic and endocrine-mediated effects), it has not been validated for NP and NPEs.
- It is not known whether biological responses such as vitellogenin induction translate to an adverse effect in the organism or the population. However, vitellogenin induction and other endocrine-mediated responses do occur at concentrations that are likely to result in whole-organism responses, such as intersex and impaired smoltification. They also occur in the range of LOECs reported for early life stage tests in fish.
- Some metabolites of NPEs (e.g., NP) tend to partition to sediment. However, the effect of NP on sediment-dwelling organisms is poorly characterized. For instance, few studies exist on NP, and no studies show the relative effect of NP on benthic organisms compared with

the NPEs. Estimates of relative potency in sediment organisms were based on the relative potency of NP and NPEs in aquatic water column organisms.

- The lack of data on the concentration of NP and particularly NPEs in sediments associated with outfalls is a limitation of the current data sets. Fate, exposure and bioavailability of NP and NPEs associated with sediments are not well characterized, even though sediments could be a major route of exposure.
- Lack of data on the extent, persistence and effects of NP and NPEs in soils that receive sludge amendments is a limitation in evaluating the potential level of concern for this activity.
- NP and NPEs do not occur in the environment alone but usually occur in complex mixtures with other types of substances. The influence of these mixtures on the overall toxicity has not been well assessed. For example, it is known that MWWTP effluents in Canada and elsewhere contain natural and synthetic estrogens, which are expected to have similar estrogenic effects in the environment.

3.2 CEPA 1999 64(b): Environment upon which life depends

NP/NPEs are unlikely to volatilize out of water and into the air, except in localized areas where NP concentrations in the water are elevated. NP is likely removed from the atmosphere via reaction with hydroxyl radicals, indicating that it would be unlikely for any NP in air to be transported far from its source, to move from the troposphere to the stratosphere and contribute to ozone depletion, to contribute to ground-level ozone formation or to contribute to climate change. NPEs are less volatile than NP, and, therefore, it is expected that they would not partition to the atmosphere.

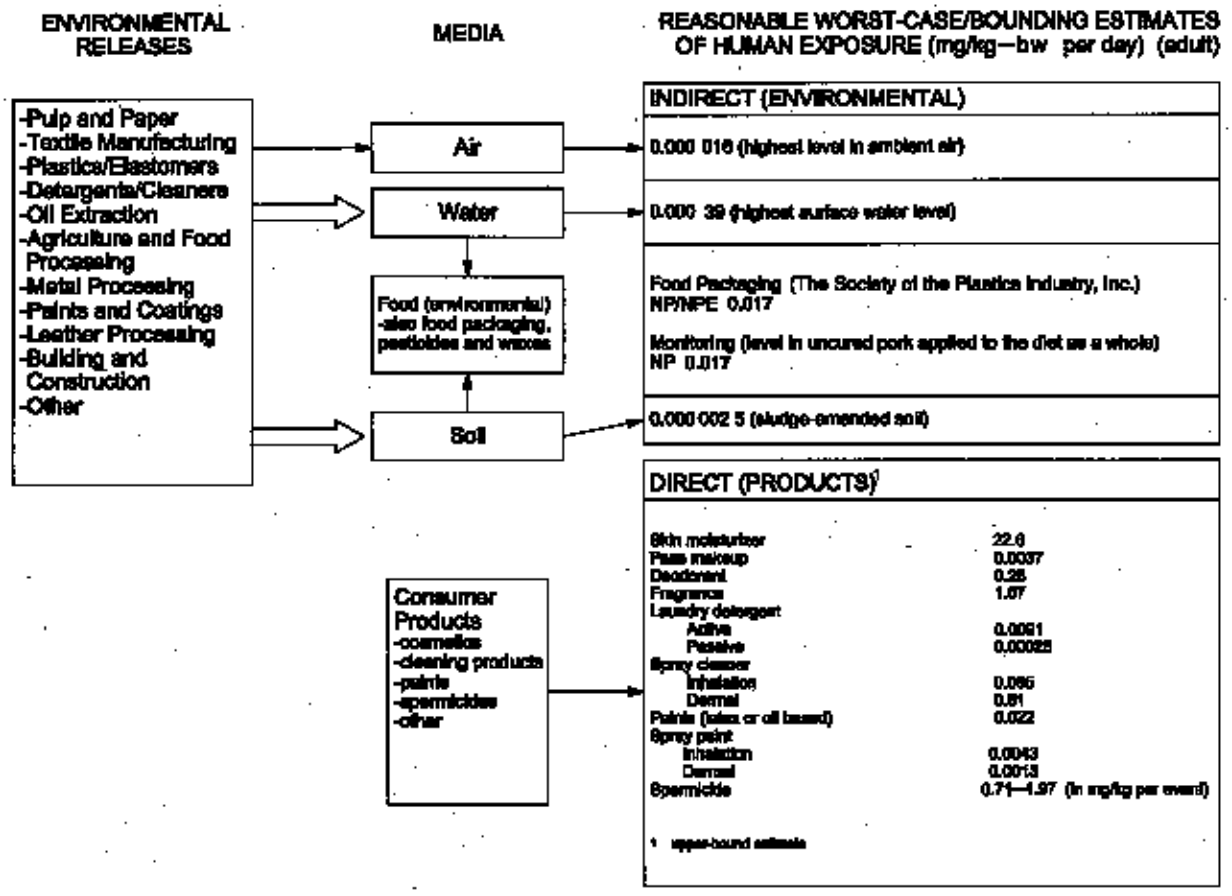
3.3 CEPA 1999 64(c): Human health

3.3.1 Estimates of potential exposure to nonylphenol and its ethoxylates

Estimation of potential exposure to NP/NPEs is complicated due to the numerous potential sources of exposure to these compounds, which include indirect exposure from releases to the environment from a wide range of industrial and domestic activities and direct exposure of humans from numerous consumer products that contain these compounds (Figure 15). In addition, NPEs are present in commercial products and in the environment as complex mixtures of a large number of isomers of various nonyl branching patterns and EO chain lengths. Analytical methods for measuring such mixtures are complex, and monitoring data for those media most relevant to human exposure are extremely limited (Section 2.3.3).

The limitations of the available monitoring data for NP and NPEs preclude the development of reliable estimates of typical exposure of the general population to these compounds. Instead, in this section, reasonable worst-case or bounding estimates of exposure to total NP/NPEs from various environmental media and consumer products have been developed, in order to characterize potential exposure from a variety of pathways. Because most of the consumer products for which suitable data are available are used primarily by adults, and since limitations of the available data are sufficient to preclude a very confident estimation of intake for even one age group, the estimated exposures have been derived for this age class only. (The differences among age classes in intake from a given medium, as a result of age-specific differences in intakes of environmental media and in body weight, would be small in relation to the variation in exposure from the various sources, in any case.) Reasonable worst-case or bounding estimates of intake of NP/NPEs by adult Canadians from various sources are summarized in Table 14.

FIGURE 15 Potential pathways of exposure to NP/NPEs for the general population



Since it is expected that NP1EC and NP2EC will have similar toxicities based on an overall assessment of the toxicity data, the values of Williams (1997) also were used as a conservative ENEV assessment for NP2EC.

NPECs can be created during effluent treatment, and concentrations in final effluent can be considerably higher than those in influent. Even in untreated effluents, the concentration of NP1EC does not appear to be high enough to result in chronic toxicity. The hyperconservative assessment resulted in some exceedances for NP2EC in wastewater effluents, particularly secondary and tertiary treatment (Table 10). When dilution is considered, no effluents in any sector have NPEC values that result in conservative risk quotients above one. Unfortunately, there are very few actual receiving water concentrations reported for these compounds. Despite the elevated concentrations of NPECs in treated final effluents, they have considerably lower toxicities; therefore, when considered alone, they do not represent a significant risk based on chronic toxicity.

3.1.2.3.5 Risk characterization for the combined effects of nonylphenol ethoxylates

As observed in field measurements, NP and NPEs occur as complex mixtures, and the toxicities of the metabolites are expected to be additive. When NP is considered alone, only three sites have predicted concentrations in receiving waters that exceed a value of 1 µg/L. When NP1EO and NP2EO are considered in addition to NP, an additional four sites exceed the ENEV. The chronic toxicity of NPE mixtures in municipal effluents and receiving waters is dominated by the effects associated with NP1EO and NP2EO and, to a lesser extent, NP. In situations where the concentrations of NP9EO are high, the

Table 14 Reasonable worst-case/bounding estimates of intake of NP and NPEs by adult Canadians

Exposure medium		Assumptions	Estimated intake (mg/kg-bw per day)	Comments	Margin of exposure [1]
Environmental media (indirect exposure)					
Air		- based on the maximum total concentration of NP (0.070 $\mu g/m^3$) measured in ambient air in coastal New York/New Jersey in 1998 (Dachs *et al.*, 1999) - assumes a 24-hour inhalation volume of 16.2 m^3/day by an average Canadian adult weighing 70.9 kg (EHD, 1998)	0.000 016	- NPEs are much less volatile and would not be expected to partition appreciably to air	7.5×10^5
Water		- based on maximum total NP1–17EO measured in surface waters across Canada between 1991 and 1998 (18.25 $\mu g/L$) in Canagagigue Creek upstream of Elmira wastewater control plant in Ontario (Bennie, 1998b) - assumes mean consumption of 1.5 L/day of tapwater consumed as drinking water plus that added to beverages by an average Canadian adult weighing 70.9 kg (EHD, 1998)	0.000 39	- levels measured in drinking water in very limited sampling from other countries were much lower (Section 2.3.3.7)	3.1×10^4
Soil		- based on content of NP+NP1EO+NP2EO in soil immediately after application of sewage sludge in Switzerland (5.9 mg/kg) (Marcomini *et al.*, 1989) - assumes mean intake of 30 mg/day of soil by an adult weighing 70.9 kg (EHD, 1998)	0.000 002 5	- levels in sludge-amended soil in other studies are somewhat lower	4.8×10^6
Food	**Packaging**	- based on the estimate of potential level of NP in the diet from food contact use of TNPP of 19.8 ppb (0.0198 mg/kg) (The Society of the Plastics Industry, Inc., 1998a) and of NPEs and NP in the diet from the use of NPEs in food contact applications of 0.504 ppm (mg/kg) and 0.89 ppb (0.000 89 mg/kg), respectively (The Society of the Plastics Industry, Inc., 1998b) - assumes mean consumption of 2.3 kg food/day by an average Canadian adult weighing 70.9 kg (EHD, 1998)	0.017	- these are considered reasonable worst-case estimates; for the principal food contact polymers containing TNPP/NPE, The Society of the Plastics Industry, Inc. estimated the extent of migration into the diet as a whole, based on the TNPP/NPE levels, food contact applications and, in the case of TNPP, migration estimates from studies that simulated or exaggerated the actual food contact uses of the polymers (using food simulating solvents and time and temperature conditions recommended by the U.S. Food and Drug Administration), and, in the case of NPE applications, assuming that 100% of the substance migrates into food (The Society of the Plastics Industry, Inc., 1998a,b)	706
	Monitoring	- based on the mean content of NP in duplicate samples of uncured cooked pork collected at a Toronto market (0.53 mg/kg) (Ramarathnam *et al.*, 1993) - assumes a total consumption of 2.3 kg food/day, all of which contains the above level of NP, by an average Canadian adult weighing 70.9 kg (EHD, 1998)	0.017	- these data do not include NPE - no information on whether samples were in contact with food packaging source of NP/NPEs - estimated mean intakes via food based on simple bioaccumulation models were much lower; based on a soil content of 5.9 mg/kg for NP+NP1EO+NP2EO (Marcomini *et al.*, 1989 [summarized in previous row]), log K_{ow} of 4.2 (approx. mean for these NP/NPEs [Section 2.0]), and assuming the resultant levels in food apply to the food group as a whole, estimated mean intake was 0.0015 mg/kg-bw per day based on regression models of bioconcentration in plants and biotransfer to beef and milk (Travis and Arms, 1988), and <0.000 40 mg/kg-bw per day based on a fresh weight bioconcentration factor of <0.006 for whole potatoes (Danish EPA, in U.K. Environment Agency, 1998)	698

Table 14 (continued)

Exposure medium	Assumptions	Estimated intake (mg/kg-bw per day)	Comments	Margin of exposure [1]
Subsistence populations	- based on maximum content of NP+NP1EO+NP2EO in composite sample of muscle from three fish species (5.78 mg/kg dw in *Barbus barbus*) and the content of NP+NP1EO+NP2EO in muscle of a mallard duck (3.65 mg/kg dw) from the Glatt Valley in Switzerland (where wastewater loadings were reportedly quite high) - assumes water content of 75% in fish and 67% in duck (U.S. EPA, 1997a) - assumes country food consumption recommended for high-use Amerindian populations of 500 g/capita per day for fish and 200 g/capita per day for small game (Coad, 1994), by an average Canadian adult weighing 70.9 kg (EHD, 1998)	0.014	- available data for Canada are quite limited; levels of NP in whole body of fish from Lake Ontario were much lower (max. 0.043 mg/kg fresh weight) (Bennie, 1998b)	857
Direct (consumer products)				
Skin moisturizer	- assumes a typical quantity of product used per event for "body lotion" of 8 g and a maximum event frequency of 2 times per day for users only (ECETOC, 1994) - based on the upper bound of the concentration of the range of >3 to 10% within which the concentration of NPE in skin moisturizer falls (McIntyre, 1996; see Table 3) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.10)\ (8\ g)\ (2/day)\ (1000\ mg/g)}{(70.9\ kg)}$	22.6	- assumes that the NP/NPEs contained in such "leave on" products are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	0.5
Face makeup	- assumes a typical quantity of product used per event for "foundation" of 0.265 g and a maximum event frequency of once per day for users only (U.S. EPA, 1997b) - based on the upper bound of the concentration of the range of 0.1% or less within which the concentration of NPE in face makeup falls (McIntyre, 1996; see Table 3) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.001)\ (265\ mg)\ (1/day)}{(70.9\ kg)}$	0.0037	- assumes that the NP/NPEs contained in such "leave on" products are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	3.2×10^3
Deodorant	- assumes a typical quantity of product used per event for "underarm deodorants" of 0.52 g and a maximum event frequency of 1.29 times per day for users only (U.S. EPA, 1997b) - based on the upper bound of the concentration of the range of >1 to 3% within which the concentration of NPE in deodorant falls (McIntyre, 1996; see Table 3) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.03)\ (520\ mg)\ (1.29/day)}{(70.9\ kg)}$	0.28	- assumes that the NP/NPEs contained in such "leave on" products are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	43
Fragrance	- assumes a typical quantity of product used per event for "colognes & toilet water" of 0.65 g and a maximum event frequency of 1.71 times per day for users only (U.S. EPA, 1997b) - based on the upper bound of the concentration of the range of >3 to 10% within which the concentration of NPE in fragrances falls (McIntyre, 1996; see Table 3) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.10)\ (650\ mg)\ (1.71/day)}{(70.9\ kg)}$	1.57	- assumes that the NP/NPEs contained in such "leave on" products are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	8

TABLE 14 (continued)

Exposure medium	Assumptions	Estimated intake (mg/kg-bw per day)	Comments	Margin of exposure [1]
Laundry detergent	**Active** (from exposure while hand washing delicate fabrics) - based on a maximum concentration of 28% NPE in liquid laundry detergent (World Wildlife Fund Canada, 1997) - assuming a frequency of use of once per week, a density of product of 1.13 g/cm^3, a dilution fraction of 1:540 and a film thickness on skin of 4.99×10^{-3} cm (Versar Inc., 1986) - the exposed surface area (2 hands and 1/4 of arms) is assumed to be 1547 cm^2 (Health Canada, 1995) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.28)\ (1.13\ g/cm^3)\ (1/7\ days)\ (1/540)\ (4.99 \times 10^{-3}\ cm)\ (1547\ cm^2)\ (1000\ mg/g)}{(70.9\ kg)}$	0.0091	- assumes that the NP/NPEs are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	
	Passive (exposure from detergent left on clothing, etc.) - based on a maximum concentration of 28% NPE in liquid laundry detergent (World Wildlife Fund Canada, 1997) - assuming a frequency of event of 365 days per year, a transfer factor of 0.1 and an amount of product deposited on fabric of 4×10^{-5} mg/cm^2 (Versar Inc., 1986) - the exposed surface area (whole body minus head and hands) is assumed to be 16 015 cm^2 (Health Canada, 1995) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.28)\ (1/day)\ (0.1)\ (4 \times 10^{-5}\ mg/cm^2)\ (16\ 015\ cm^2)}{(70.9\ kg)}$	0.00025	- assumes that the NP/NPEs are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	1.3×10^3
Household cleaner	**Inhalation** - based on a maximum concentration of 5% NPE in all-purpose spray cleaner (World Wildlife Fund Canada, 1997) - assuming a mass of 76 g is used per event, a 0.47-hour duration of exposure, an overspray fraction of 0.04, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 360 days per year (Versar Inc., 1986) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\ (76\ 000\ mg)\ (0.47\ hour)\ (0.04)\ (1.3\ m^3/hour)\ (360/365\ days)}{(70.9\ kg)\ (\ 20\ m^3)}$	0.065	- assumes that the NP/NPEs are absorbed across the lung to the same extent as via the gastrointestinal tract	
	Dermal - based on a maximum concentration of 5% NPE in all-purpose spray cleaner (World Wildlife Fund Canada, 1997) - assuming an event frequency of 360 days per year, an exposed surface area of 400 cm^2 (both palms), a product density of 0.88 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm (Versar Inc., 1986) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\ (360/365\ days)\ (400\ cm^2)\ (0.88\ g/cm^3)\ (2.1 \times 10^{-3}\ cm)\ (1000\ mg/g)}{(70.9\ kg)}$	0.51	- assumes that the NP/NPEs are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	21

Table 14 (continued)

Exposure medium	Assumptions	Estimated intake (mg/kg-bw per day)	Comments	Margin of exposure [1]
Latex or oil-based paints	- based on a maximum concentration of 3% NPE in latex paint (WHO, 1998) - assuming an event frequency of 7 days per year, an exposed surface area of 220 cm^2 (10% of face, hands and forearms), a film thickness on the hands of 9.81×10^{-3} cm and a product density of 1240 mg/cm^3 (Versar Inc., 1986) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.03)\ (7/365\ \text{days})\ (220\ cm^2)\ (9.81 \times 10^{-3}\ cm)\ (1240\ mg/cm^3)}{(70.9\ kg)}$	0.022	- assumes that the NP/NPEs are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	545
Spray paints	**Inhalation** - based on a maximum concentration of 3% NPE in paints (WHO, 1998) - assuming a mass of 460 g is used per event, a 0.17-hour duration of exposure, an overspray fraction of 0.73, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 1 event per year (Versar Inc., 1986) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.03)\ (460\ 000\ mg)\ (0.17\ hour)\ (0.73)\ (1.3\ m^3/hour)\ (1/365\ days)}{(70.9\ kg)\ (20\ m^3)}$	0.0043	- assumes that the NP/NPEs are absorbed across the lung to the same extent as via the gastrointestinal tract	
	Dermal - based on a maximum concentration of 3% NPE in paints (WHO, 1998) - assuming an event frequency of 1 event per year, an exposed surface area of 190 cm^2 (10% of both hands and forearms), a film thickness on the skin of 6.55×10^{-3} cm and a product density of 0.9 g/cm^3 (Versar Inc., 1986) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.03)\ (1/365)\ (0.9\ g/cm^3)\ (190\ cm^2)\ (6.55 \times 10^{-3}\ cm)\ (1000\ mg/g)}{(70.9\ kg)}$	0.0013	- assumes that the NP/NPEs are absorbed across the skin to the same extent as via the gastrointestinal tract; as discussed in the text, dermal absorption is likely lower, although available data are inadequate to quantitatively account for this probable difference	2.1×10^3
Spermicides	- the amount of NP9EO applied as used in contraceptive preparations ranges from 50 to 140 mg per vaginal application (Talmage, 1994) - body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)	0.71–1.97	- this is an estimated intake per event - assumes that the NP/NPEs are absorbed across the vaginal epithelium to the same extent as via the gastrointestinal tract	6

[1] Ratio of the lowest effect level identified in a study by relevant route of exposure (LOEL of 12 mg/kg-bw per day, the lowest average dose of NP for male rats exposed in the diet across three generations in a reproductive study, at which renal histopathological effects were observed in each generation) (NTP, 1997; Chapin *et al.*, 1999) to the estimated intake.

full 48 hours, Nonoxynol-2, Nonyoxynol-4 and Nonoxynol-9 were present in the receptor fluid at 0.57 ± 0.07%, 0.66 ± 0.14% and 0.49 ± 0.27% of the applied dose. Limitations of this study included lack of use of viable skin, lack of monitoring of NP or NPEs in the skin or metabolites in the skin and receptor fluid (the "skin depot" can dominate dermal absorption for lipophilic substances such as these) and lack of information on temporal changes in flux across the skin. In light of these limitations, bounding estimates of dermal exposure for consumer products were made by assuming that NP/NPEs were absorbed across the skin to the same extent as via the gastrointestinal tract — i.e., the intakes for both oral and dermal routes were compared with the critical effect level, without adjustment for differential absorption. (Available data, while indicating that dermal absorption is likely lower than gastrointestinal absorption [Talmage, 1994; Clairol Inc., 1995; U.K. Health and Safety Executive, 1999], are inadequate to quantitatively account for any difference that may exist.)[3] No estimates were made of the dermal intake of NP/NPEs from consumer products that are rinsed off (such as hair dyes, shampoos or conditioners), since the limitations of the available data on dermal absorption also preclude the development of reliable estimates for such products; however, intakes from these products would likely be relatively low, as a consequence of the brief and/or infrequent duration of contact.

The highest estimated worst-case intakes of NP/NPEs for consumer products were for "leave on" cosmetic products, specifically skin moisturizer (22.6 mg/kg-bw per day), fragrance (1.6 mg/kg-bw per day) and deodorant (0.28 mg/kg-bw per day), which were developed from product use scenarios (ECETOC, 1990, 1994; U.S. EPA, 1997b), assuming that NP/NPEs were absorbed across the skin to the same extent as via the gastrointestinal tract (Table 14). Worst-case estimated intakes for the other cosmetics considered (face makeup) were much lower, reflecting the relatively low content of NPEs. Upper-bounding estimates for intake of NP/NPEs from exposure to household cleaning products and paints were developed from product use scenarios (Versar Inc., 1986). The highest estimated intake for NP/NPEs from household products other than cosmetics was for all-purpose spray cleaner (0.51 mg/kg-bw per day by the dermal route and 0.065 mg/kg-bw per day by the inhalation route) (Table 14). Reasonable worst-case estimates of daily intake for other consumer products, including liquid laundry detergent and brush and spray paints, were considerably lower. The estimated intake of NP9EO from the use of spermicides intravaginally was up to 2.0 mg/kg-bw per event (Table 14).

It should be noted that these estimates have been made for only a limited range of media and products for which at least some data were available, often from non-Canadian sources. In addition, they do not represent typical exposures, since the limitations of the available data preclude development of such estimates; most are instead maximal or near-maximal estimates of potential exposure.

3.3.2 Human health risk characterization

As indicated in Section 1.0, an interim screening approach has been adopted for the assessment of NP/NPEs, primarily to ensure that conclusions drawn on the basis of a more robust data set on effects on environmental organisms (i.e., under Paragraph 64(a) of CEPA 1999) are protective with respect to human health, at least for sources controllable under CEPA 1999. This approach has also been adopted in the interest of identifying priorities for acquisition of additional data to permit a more defensible assessment of risks from all sources of exposure of the general population. In this screening assessment, therefore, in view of the limitations of the database, identified effect

[3] It is noted that dermal absorption studies for several different EO chain lengths were being conducted for the Chemical Manufacturers Association but were not yet available at the time of completion of this screening assessment.

levels for NP/NPEs are compared with reasonable worst-case or bounding estimates of exposure to the class of substances as a whole for the general population from various pathways and products. Weight of evidence for and adversity of observed effects have generally not been considered at this initial stage. Rather, the adequacy of these rather crude margins of exposure is considered in relation to intake from various sources, including environmental media and consumer products.

Based on preliminary assessment of available data on NP and NPEs, the lowest LOEL identified was 12–18 mg/kg-bw per day, the range of average doses of NP for male rats exposed in the diet across three generations in a reproductive study, at which renal medullary tubular dilation and cyst formation were observed in each generation (NTP, 1997). Although the available effects-related data for NPEs are somewhat limited, reported NOELs and LOELs for these substances by relevant media of exposure (i.e., diet) consistently have been greater than this value (although some are not far removed). In addition, the renal tubular histopathological changes observed in the NTP study have not been reported in animals exposed to NPEs.

The LOEL from this multigeneration study is unbounded, inasmuch as a NOEL was not identified. However, it is noted that the renal tubular histopathological changes in male rats that served as the basis for this LOEL were the only clearly treatment-related effects at this dose level, which did not affect body weight, feed consumption, a wide range of reproductive and developmental parameters, or the weights or histopathology of a number of organs. The same compound-related renal lesion was not observed in a subchronic study in the same strain of rats administered the same dose levels of NP in the diet (Cunny *et al*., 1997), even though the duration of exposure in this study was similar to that for the F_0 generation in the multigeneration study in which a low to moderate incidence of renal tubular histopathological changes occurred. The renal lesions identified in the multigeneration study were described as being of minimal to mild severity, even at the higher dose levels, and were interpreted by the authors as a slight acceleration of the tubular nephropathy normally seen in this strain of rats (Chapin *et al*., 1999). There was also no effect on serum urea nitrogen or creatinine at this dose in the subchronic study (Cunny *et al*., 1997), suggesting that renal function was not affected (though urinalysis was not conducted in any study, and plasma urea concentration is not a sensitive marker of nephropathy). Based on these considerations, it seems likely that the LOEL of 12 mg/kg-bw per day is close to a No-Observed-Adverse-Effect Level (NOAEL) for effects on the kidney, and, therefore, this effect level is considered appropriate for use in determining the margin of exposure in this screening assessment.

Comparison of the effect level of 12 mg/kg-bw per day with reasonable worst-case estimates of exposure for the general population from environmental media results in a margin of exposure for intake of NP/NPEs via food of approximately 700 (Table 14). The margin of exposure for intake via other media (air, water, soil, country food consumed by subsistence populations) is larger, ranging from approximately 1000 to 1,000,000. These margins are considered adequate to address the elements of uncertainty inherent in the available data, taking into consideration the likelihood of overestimation of exposure due to extremely limited information on concentrations of NP and NPEs in environmental media and interspecies and intraspecies (interindividual) variation in susceptibility. It is further noted that, since the general population is exposed to mixtures that include NPEs of longer chain lengths (which available data indicate are less toxic than NP), the actual margin of exposure is likely to be greater than these values would suggest.

However, the margin of exposure for some consumer products is considerably less than those for environmental media. Comparison of the effect level of 12 mg/kg-bw per day for effects of NP on renal histopathology in male rats in the multigeneration study with reasonable worst-case estimates of intake of NP and NPEs results in a

margin of exposure of 0.5 for skin moisturizer, 43 for deodorant, 8 for fragrances, 21 for household cleaners and 6 for vaginal spermicides. The ratio between the effect level and estimated intakes is larger for the other consumer products considered in this assessment, including face makeup, laundry detergent, and brush and spray paints, ranging from approximately 550 to 3200 (Table 14).

It should be emphasized that due to considerable uncertainty concerning the extent of dermal absorption, the exposure estimates on which this comparison is based are worst case, assuming that the NP/NPEs contained in such "leave on" products are absorbed across the skin to the same extent as via the gastrointestinal tract — i.e., the intakes for both oral and dermal routes were compared with the critical effect level, without adjustment for differential absorption. (Available data, while indicating that dermal absorption is likely lower than gastrointestinal absorption [Talmage, 1994; Clairol Inc., 1995; U.K. Health and Safety Executive, 1999], are inadequate to quantitatively account for this probable difference.) Based on the relatively low margins of exposure for some products calculated for worst-case assumptions with respect to both exposure and effect, therefore, research into the dermal absorption of these substances, under conditions relevant to human exposure, is identified as a clear priority for further work to permit more meaningful assessment of the potential risks to human health from consumer products.[4]

The potential estrogenicity of NP and NPEs has been investigated in a number of studies (Section 2.4.3.1). NP and NP2EO activated the estrogen receptor and had some estrogenic activity *in vitro*. NP was uterotrophic or induced other effects indicative of estrogenic activity in several studies *in vivo*. However, these compounds were between 3 and 5 orders of magnitude less active in this regard than estradiol. In addition, NP was estrogenic only at relatively high dose levels; for example, other effects (on renal histopathology) were observed at 3 times lower doses of NP than those in estrogen-responsive tissues in the multigeneration study in rats (i.e., 12 vs. 50 mg/kg-bw). In addition, NPEs of longer chain lengths (4, 9 and 12) were not uterotrophic *in vivo*, and NP12EO was not estrogenic in a recombinant yeast screen assay. Hence, while it is clear that NP and some short-chain NPEs have estrogenic potential, the evidence that this is a critical effect of these substances is considered inadequate at this time. However, NP and NPEs are likely early candidates for additional investigation when more sensitive frameworks for testing and assessment of endocrine-disrupting substances are developed. Upon completion of such testing, evaluation of the potential endocrine-mediated adverse health effects of NP and NPEs should be considered a priority.

3.3.3 Uncertainties and degree of confidence in the human health risk characterization

There is a high degree of uncertainty inherent in the population estimates of the intake of NP/NPEs, due to the paucity of available data. Indeed, the limited objectives of and approach to assessment (i.e., screening only) were predicated to some extent on knowledge of the extent and magnitude of these uncertainties, based on scoping of the limited database on exposure.

- There is reasonable certainty that the likely principal medium of exposure in the general environment (i.e., that for sources controllable under CEPA 1999) for NP and NPEs is food; this is supported by the physical/chemical properties of NP and NPEs and their direct application to foods in some uses (e.g., as a

[4] It is noted that dermal absorption studies for several different EO chain lengths were being conducted for the Chemical Manufacturers Association but were not yet available at the time of completion of this screening assessment.

dispersant/emulsifier in vegetable and fruit waxes). However, the estimated amount of this intake is highly uncertain. While there are some data to serve as an adequate basis for the reasonable worst-case estimates of intake of NP and NPEs from food contact (i.e., packaging), the estimated intake from food monitoring is based on the highest level measured in a very small study in which a single food commodity (i.e., pork) was analysed for NP only. The estimates based on modelled bioaccumulation into crops and livestock from soil and the worst-case assumptions in the food contact packaging estimates suggest that actual intake in food is probably lower than the estimates derived in this screening assessment, although the estimates derived do not consider potential exposure to NP/NPEs from products that are applied to foods.

- There is, however, a fair degree of certainty that air, drinking water and soil contribute only negligible amounts to exposure to NP/NPEs, in spite of the fact that there are very few data available. The estimated intakes from outdoor air, drinking water and soil, which are based on the highest levels of NP and NPEs reported in ambient air in the United States, in Canadian surface waters and in Swiss soil immediately after the application of sewage sludge, are several orders of magnitude less than those from food and from some consumer products.
- The confidence in the estimated exposures from products that contain NP and NPEs is low to moderate. While there are extensive data on the content of these substances in cosmetic products in Canada, which were the basis for a number of the estimates of intake, only limited information on the content of NP/NPEs in other types of consumer products was identified. In addition, there is considerable uncertainty with respect to the extent of dermal absorption of NP/NPEs contained in consumer products. Due to the limitations in the single available study of dermal absorption of these substances (Clairol Inc., 1995) and the important contribution of the skin depot to the dermal absorption of other lipophilic substances, worst-case assumptions were made in estimating dermal intake. However, it is likely that actual dermal intake is substantially lower than these estimates, as only a small fraction of the applied NPEs was detected in the available (although limited) dermal absorption study.[5] There is high confidence in the conclusion that this is an important area of further research, however, due to the small magnitudes of the admittedly crude margins of exposure for consumer products in order to refine the assessment and determine the need for measures to reduce exposure to NP/NPEs from these products through the Acts under which they are regulated.
- The overall degree of confidence in the population exposure estimates is very low, therefore, owing principally to the lack of data on the levels of NP and NPEs in environmental media, particularly food, and the lack of reliable information on the extent of dermal absorption of NP and NPEs. Indeed, the uncertainties in this exposure assessment are sufficiently great that where margins were less than what might be considered adequate, conclusions in this assessment were limited to recommendations concerning priorities for further work.
- The degree of confidence in the available data regarding the effects of NP and NPEs is moderate. The epidemiological data in humans are inadequate. NP has recently been studied in well-conducted repeated-dose and reproductive/developmental toxicity studies in animals. However, while early subchronic and chronic toxicity studies in rats and dogs have been conducted on a number of NPEs of differing EO chain lengths, there are no

[5] It is noted that dermal absorption studies for several different EO chain lengths were being conducted for the Chemical Manufacturers Association but were not yet available at the time of completion of this screening assessment.

recent repeated-dose toxicity studies in animals in which a range of endpoints has been well characterized by current standards. There is also some uncertainty about the potential for endocrine-mediated adverse health effects of NP/NPEs, which are likely early candidates for additional investigation when more sensitive frameworks for testing and assessment of these endpoints are developed.

3.4 Conclusions

CEPA 1999 64(a): Based on the available data, it is concluded that nonylphenol and its ethoxylates are entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. Therefore, nonylphenol and its ethoxylates are considered to be "toxic" as defined in CEPA 1999 Paragraph 64(a).

In particular, NP and its ethoxylates from untreated or partially treated textile mills that discharge directly to the aquatic environment occur at levels that are likely to be causing harmful effects on aquatic organisms. Additionally, discharges from municipal wastewater treatment plants and pulp and paper mills contribute NP and NPEs to the environment at levels that are of concern at a limited number of sites. These results, however, are reflective of data obtained through monitoring studies at a select group of locations. Although, based on current use and treatment practices, the risk to the aquatic environment of NP/NPEs in municipal effluents is not high, the concentrations in the environment, especially near outfalls, may approach levels of concern. Treatment of NPEs results in a shift in their relative distribution in effluents, often resulting in high concentrations of metabolites such as NP1,2EC in final effluents, which may be of concern for aquatic environments because of potential disruption of developmental or reproductive processes. The sorption of NP and NP1,2EO to sediments may represent a risk to benthic organisms outside of the immediate mixing zones of outfalls. The application of municipal sludges containing NPEs, particularly NP and NP1,2EO, to agricultural fields may also represent a minor risk to these environments. The potential for adverse effects due to exposure to NP/NPEs is generally associated with industrial and municipal effluents in Canada. The increased use of NPEs or related alkylphenolics in the future could lead to more widespread concern for the effects of these chemicals. The use of NP/NPEs in Canada, therefore, should be managed to minimize their exposure and risk to Canadian ecosystems.

CEPA 1999 64(b): Based on the available data, it is concluded that nonylphenol and its ethoxylates are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends. Therefore, nonylphenol and its ethoxylates are not considered to be "toxic" as defined in CEPA 1999 Paragraph 64(b).

CEPA 1999 64(c): On the basis of consideration of the margin of exposure between effect levels and reasonable worst-case estimates of intake from environmental media, nonylphenol and its ethoxylates are not considered a priority for investigation of options to reduce public exposure through control of sources that are addressed under CEPA 1999.

However, the relatively low margin of exposure estimated for some products indicates that there is an important need for refinement of this assessment, in order to determine the need for measures to reduce public exposure to NP/NPEs in products through the Acts under which they are regulated. Of priority in this respect is research into dermal absorption of these substances from such products and evaluation of the potential endocrine-mediated adverse health effects of NP and NPEs upon completion of more sensitive testing.

Overall conclusion: Based on critical assessment of relevant information, nonylphenol and its ethoxylates are considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Since it is concluded that nonylphenol and its ethoxylates are considered to be "toxic" as defined in Section 64 of CEPA 1999, it is recommended that, as a matter of some priority, options to reduce exposure be investigated.

Nonylphenol and its ethoxylates are present at elevated levels in textile mill, pulp and paper mill and MWWTP effluents; however, routine monitoring for NP/NPEs at these sites is not performed. It has been shown that NP and NPE concentrations in the environment often approach and in some instances exceed effect levels, and, therefore, monitoring of effluents should be performed on a routine basis.

Risk management options should include a reduction in the amount of nonylphenol and its ethoxylates in the effluent from textiles and pulp and paper processing. Additionally, risk management should result in a reduction of NP/NPE concentrations in MWWTP effluents.

Caution should be taken during risk management regarding the possible replacement or substitution of NP and NPEs. Other APEs such as OP and OPEs have many of the same physical/chemical properties, which make them likely candidates as replacement or alternative products for NP and NPEs. However, they also have similar toxicological properties and greater estrogenic properties, such that a simple replacement of NP and NPEs by other APEs (OPEs) might not reduce the risk to the environment. A full range of management options needs to be considered in the management of NP and NPEs to reduce the risk to the environment.

Once improved data on dermal absorption of NP/NPEs from consumer products and potential endocrine-mediated adverse health effects become available, this assessment for these products should be refined, in order to determine the need for measures to reduce public exposure to NP/NPEs in these products through the Acts under which they are regulated.

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APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment

Data relevant to the assessment of whether nonylphenol and its ethoxylates are "toxic" to the environment under CEPA 1999 were identified from existing review documents, published reference texts and on-line searches of the following databases for the period January 1960–December 1998: Aqualine (Water Research Centre, Buckinghamshire), ARET (Accelerated Reduction/Elimination of Toxics, Environment Canada), ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts), BIODEG (Syracuse Research Corp.), BIOLOG, BIOSIS (Biosciences Information Services), Business Opportunities Sourcing System, CAB (Commonwealth Agriculture Bureaux), Canadian Research Index (Micrologic: CRI, Government Publications/Micromedia Ltd.), Catalogue of Environmental Data in Atlantic Canada (Environment Canada, Atlantic Region), CCINFO, CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources), Chemfate (Syracuse Research Corp.), ChemINFO (Canadian Centre for Occupational Health and Safety), CHRIS (Chemical Hazard Release Information System), CPI Profile (Camford Information Services), Current Contents (Institute for Scientific Information), Datalog (Syracuse Research Corp.), Desk References, Domestic Substances List (Environment Canada), ELIAS (Environmental Library Integrated Automated System, Environment Canada library), ENVIRODAT (Environment Canada), Enviroline (R.R. Bowker Publishing Co.), Environmental Abstracts, Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara), Environmental Library, Envirosource (Environment Canada), GEOREF (Geo Reference Information System, American Geological Institute), HCA (Chemical Abstracts Service), HSBD (Hazardous Substances Data Bank, U.S. National Library of Medicine), ICAR (Inventory of Canadian Agricultural Research, Canadian Agri-food Research Council), IRL (Life Sciences Collection, Cambridge Scientific Abstracts), IRPTC (International Register of Potentially Toxic Chemicals, Geneva), Life Sciences (Cambridge Scientific Abstracts), MSDS (Material Safety Data Sheets, Canadian Centre for Occupational Health and Safety), NATES (National Analysis of Trends in Emergencies System, Environment Canada), National Emission Inventory (Canadian Chemical Producers Association), National Registry of Toxic Chemical Residues (National Wildlife Research Centre, Environment Canada), Northern Info Network, NPRI (National Pollutant Release Inventory, Environment Canada), NTIS (National Technical Information Service, U.S. Department of Commerce), Pesticide Registrant Survey (Environment Canada and Agriculture Canada), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine), REPEN (*Répertoire informatisé des bases de données environnementales sur le Fleuve Saint-Laurent*, Environment Canada, Quebec Region), RRETC (River Road Environmental Technology Centre monitoring data), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute of Occupational Safety and Health), Statistics Canada Import/Export Merchandise Trade Vols. I–II, Synopsis Northern Contaminants Program, Toxline (U.S. National Library of Medicine), TRI87-94 (Toxic Chemical Release Inventory, Office of Toxic Substances, U.S. Environmental Protection Agency), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency), USEPA-ECOTOX (including AQUIRE; U.S.

Environmental Protection Agency), USEPA-National Catalog (U.S. Environmental Protection Agency) and WASTEINFO (Waste Management Information Bureau, American Energy Agency).

A survey conducted under authority of Section 16 of CEPA, for which companies were required to supply information on uses, releases, environmental concentrations, effects or other data on nonylphenol and its ethoxylates if they met the trigger quantity of 1000 kg of NP/NPEs per year, was used to collect data on industrial uses and releases in 1995 and 1996 (Environment Canada, 1997b). Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the environmental effects of nonylphenol and its ethoxylates.

Only data acquired prior to December 1998 were considered in the environmental assessment unless they were critical data received during the 60-day public review of the report (April 1 to May 31, 2000).

Health assessment

Information on the toxicological effects of nonylphenol and its ethoxylates as well as other relevant data were derived primarily from reviews, including a recent draft Environmental Health Criteria document on these substances (WHO, 1998) and a review of major surfactants by Talmage (1994); however, the original references were verified for all potentially critical effects. In addition, several on-line databases were searched between December 1997 and May 1999 to identify relevant data on exposure and toxicity of nonylphenol and its ethoxylates that were not included in the reviews. Searches were conducted on the following databases: Canadian Research Index (Canadian governmental and institutional resources), Cancerlit (National Cancer Institute's International Cancer Information Center), CCINFO (Canadian Centre for Occupational Health and Safety), CHRIS (Chemical Hazard Response Information System, U.S. Coast Guard), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara), Food Science and Technology Abstracts, HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine), IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency), Medline (U.S. National Library of Medicine), MSDS (Material Safety Data Sheets), NIOSHTIC (National Institute of Occupational Safety and Health), NTIS (National Technical Information Service, U.S. Department of Commerce), OHMTADS (Oil and Hazardous Materials/ Technical Assistance Data System, U.S. Environmental Protection Agency), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health), Toxline (U.S. National Library of Medicine), Waternet (American Water Works Association) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior). In addition to the above sources of information, numerous provincial and federal government officials and representatives of various industrial sectors were contacted between February and August 1996 for data relevant to exposure and/or effects. In view of the relatively limited database available for assessment of the toxicity and exposure of nonylphenol and its ethoxylates, additional attempts were made to acquire copies of unpublished information through contact with representatives of industry and other Canadian federal and international agencies. In response to these requests, the Chemical Manufacturers Association's Alkylphenols and Ethoxylates Panel kindly provided several unpublished and published reports, including the following: Richards, 1989; Clairol Inc., 1995; CIR, 1996; CMA, 1997; and Müller, 1997. In addition, general information on the use of NP/NPEs in pest control products in Canada was provided by the Pest Management Regulatory Agency (Moore, 1999). Non-validated studies of Industrial Bio-Test Laboratories Inc.,

which are a subset of the studies summarized in a 1969 review by Smyth and Calandra, have been cited in this report but are not used in assessing whether nonylphenol and its ethoxylates are "toxic" under CEPA 1999.

Only data acquired prior to November 1999 were considered in this draft screening assessment for human health.

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