UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 31, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessments: Four Exemptions from the Requirement of a Tolerance for Nonylphenol Ethoxylates

FROM: Pauline Wagner, Chief Pauline Wagner 7/31/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

TO: Lois A. Rossi, Director
Registration Division (7505P)

I. FQPA REASSESSMENT ACTION

Action: Reassessment of four inert ingredient exemptions from the requirement of a tolerance. Current exemptions are to be maintained.

Chemical: See Table 1

Table 1. Tolerance Exemption Expression

40 CFR	Inert Ingredients	Limits	Uses (Pesticidal)	CAS Reg. No. and Names
180.910	α-(*p*-Nonylphenyl)-ω-hydroxypoly(oxyethylene) produced by the condensation of 1mole of nonylphenol (nonyl group is a propylene trimer isomer) with an average of 4-14 or 30-90 moles of ethylene oxide; if a blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that is a component of the blend shall be in the range of 4-14 or 30-90	None	Surfactants; related adjuvants, of surfactants	127087-87-0 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-, branched) 26027-38-3 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-) 68412-54-4 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)-ω-hydroxy-, branched) 125279-66-5 (Poly(oxy-1,2-ethanediyl), α-(tripropylenephenyl)-ω-hydroxy-) 9016-45-9 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)- ω-hydroxy-)

40 CFR	Inert Ingredients	Limits	Uses (Pesticidal)	CAS Reg. No. and Names
				37205-87-1 (Poly(oxy-1,2-ethanediyl), α-(isononylphenyl)-ω-hydroxy-)
180.910	Poly(oxy-1,2-ethandiyl), α-(carboxymethyl)-ω-(nonylphenoxy) produced by the condensationof 1 mole of nonylphenol (nonyl group is a propylene trimer isomer) with an average of 4-14 or 30-90 moles of ethylene oxide. The molecular weight (in amu) ranges are 454-894 and 1598-4238.	None	Surfactants	150678-63-0 (Poly(oxy-1,2-ethanediyl), α-(carboxymethyl)-ω-(4-nonylphenoxy)-) 28212-44-4 (Poly(oxy-1,2-ethanediyl), α-(carboxymethyl)-ω-(4-nonylphenoxy)-)- 53610-02-9 (Poly(oxy-1,2-ethanediyl), α-(carboxymethyl)-ω-(nonylphenoxy)-)
180.920	α-(*p*-Nonylphenyl)-ω-hydroxypoly(oxyethylene) produced by the condensation of 1 mole of nonylphenol (nonyl group is a propylene trimer isomer) with an average of 4-14 or 30-100 moles of ethylene oxide; if a blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that is a component of the blend shall be in the range of 4-14 or 30-100	None	Surfactant	127087-87-0 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-, branched) 26027-38-3 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-) 68412-54-4 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)-ω-hydroxy-, branched) 125279-66-5 (Poly(oxy-1,2-ethanediyl), α-(tripropylenephenyl)-ω-hydroxy-) 9016-45-9 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)- ω-hydroxy-) 37205-87-1 (Poly(oxy-1,2-ethanediyl), α-(isononylphenyl)- ω-hydroxy-)
180.930	α-(p-Nonylphenyl)-ω-hydroxypoly(oxyethylene) produced by the condensation of 1 mole of nonylphenol (nonyl group is a propylene trimer isomer) with an average of 4-15 or 30-90 moles of ethylene oxide; if a blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that is a component of the blend shall be in the range of 4-15 or 30-90	None	Surfactant, emulsier, related adjuvants of surfactants	127087-87-0 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-, branched) 26027-38-3 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-) 68412-54-4 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)-ω-hydroxy-, branched) 125279-66-5 (Poly(oxy-1,2-ethanediyl), α-(tripropylenephenyl)-ω-hydroxy-) 9016-45-9 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)- ω-hydroxy-) 37205-87-1 (Poly(oxy-1,2-ethanediyl), α-(isononylphenyl)- ω-hydroxy-)

Use Summary: Nonylphenol ethoxylates are used in a variety of consumer products including household cleaners, cosmetics and shampoos. They also have industrial uses as surfactants in the production of rubber, plastics, and lubricating oils. As inert ingredients they are used as surfactants, emulsifiers and related adjuvants of surfactants in pesticide formulations.

List Classification Determination: Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to these chemicals when used as an inert ingredients in pesticide formulations, the List Classification for nonylphenol ethoxylates (as listed in Table 1) will be List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the four exemptions from the requirement of a tolerance for the inert ingredients nonylphenol ethoxylates (as listed in Table 1), as well as the List Classification determination described above. I consider the four exemptions established in 40 CFR 180.910, 920 and 930 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois Rossi

Lois A. Rossi, Director
Registration Division

August 1, 2006

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

July 31, 2006

MEMORANDUM

SUBJECT: Reassessment of Four Exemptions from the Requirement of a Tolerance for Nonylphenol Ethoxylates

FROM: Kerry Leifer
Inert Ingredient Assessment Branch
Registration Division (7505P)

and

Pauline Wagner, Chief
Inert Ingredient Assessment Branch
Registration Division (7505P)

TO: Lois Rossi, Director
Registration Division (7505P)

BACKGROUND

Attached is the science assessment for nonylphenol ethoxylates. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of nonylphenol ethoxylates. The purpose of this document is to reassess the four exemptions from the requirement of a tolerance for residues of nonylphenol ethoxylates when used as inert ingredients in pesticide formulations as required under the Food Quality Protection Act (FQPA).

EXECUTIVE SUMMARY

This document evaluates the four inert ingredient tolerance exemptions from nonylphenol ethoxylates for use on growing crops, raw agricultural commodities after harvest and animals identified in Table 1. An inert ingredient is defined by the U.S. Environmental Protection Agency (USEPA) as any ingredient in a pesticide product that is not intended to affect a target pest.

The nonylphenol ethoxylates are nonionic surfactants that are formed by the base-catalyzed reaction of p-nonylphenol with ethylene oxide (EO). The number of units of ethylene oxide added to the nonylphenol parent determines the degree of ethoxylation with the different degrees of ethoxylation accounting for a range of detergent and emulsification properties. Nonylphenol ethoxylates are used in a wide variety of consumer products, commercial products, and in many industrial cleaning processes.

Nonylphenol ethoxylates are classified as slightly toxic or non-toxic for acute exposure with the lower ethoxylates being slightly more toxic than those with a higher degree of ethoxylation. The LD_{50} values for varying nonylphenol ethoxylates range from 1680 mg/kg to over 5000 mg/kg. In general the shorter EO chain length nonylphenol ethoxylates are corrosive to the skin, but nonylphenol ethoxylates with longer EO chain lengths appear to be non-corrosive.

Repeated dose oral toxicity studies on nonylphenol ethoxylates over a range of EO chain lengths suggest that the liver and kidney are the main target organs for the lower chain lengths with an effect level of 40 mg/kg/day for the nonylphenol ethoxylate with a chain length of 6 ethylene oxide units (NP6EO). For the higher ethoxylates, retarded growth or decreased body weight gain at relatively high doses only appear to be the main effects. Several authors have attributed these findings to the poor palatability of food containing nonylphenol ethoxylates.

In vitro Salmonella typhimurium mutagenicty studies on a nonylphenol ethoxylate (NP10EO) were negative except for strain TA98 which produced positive results with activation at the two highest doses. The highest dose also produced marked toxicity.

Nonylphenol ethoxylate (NP10EO) has been tested for carcinogenicity in female Fischer 344 rats and female B6C3F1 mice. The results of the two studies were negative for carcinogenicity.

Developmental/teratology studies were conducted on nonylphenol ethoxylates. None of the studies showed any sensitivity in developing animals. There were no maternal or fetal effects at any dose level for NP30EO up to the limit dose of 1000 mg/kg/day. For NP9EO, the lowest dose level of 50 mg/kg/day was determined to be the no-observed- effect level (NOEL) for both maternal and developmental effects. The lowest-observed-adverse-effect level (LOAEL) for NP9EO was 250 mg/kg/day for both maternal and developmental effects For NP4EO, the maternal and developmental NOAEL was 50 mg/kg/day and the maternal and developmental LOAEL was 250 mg/kg/day .

Nonylphenol and nonylphenol ethoxylates are weakly estrogenic when tested in *in vitro* and *in vivo* systems. However, nonylphenol is reported to be 1000 to 100,000 times weaker in estrogenic potential than endogenous 17-β estradiol. NP9EO is reported to be less potent than nonylphenol by one to three orders of magnitude.

Based upon an analysis of the weight fractions in pesticide products of surfactants (90th percentile concentrations <5% w/w), the use patterns of products containing nonylphenol ethoxylates, the inherent biodegradation of the nonylphenol ethoxylates, and available data on concentrations of nonylphenol ethoxylates in drinking water, the inert ingredient use of nonylphenol ethoxylates as pesticide product inert ingredients is expected to result in human exposure below any dose level that would produce an adverse effect.

Taking into consideration all available information on nonylphenol ethoxylates, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to the nonylphenol ethoxylates when used as an inert ingredient in pesticide products when considering dietary exposure and all non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the four exemptions from the requirement of a tolerance established for residues of nonylphenol ethoxylates can be considered reassessed as safe under section 408(q) of FFDCA,

The nonylphenol ethoxylates are slightly toxic to nontarget aquatic species, however biodegradation in the environment produces lower nonylphenol ethoxylate congeners, followed by the production of nonylphenol ethoxylate carboxylate and nonylphenol which have greater toxicity to nontarget aquatic species. Aquatic Life Ambient Water Quality Criteria have been established by EPA's Office of Water for nonylphenol (EPA, 2005). Based on these ambient water quality criteria for nonylphenol, application of pesticide products containing nonylphenol ethoxylates as inert ingredients may exceed the acute and chronic levels of concern (LOC) for nonylphenol for certain nontarget aquatic species.

There are no data in the published literature on the effects of nonylphenol ethoxylates to nontarget terrestrial plants and animals.

A more complete assessment of the ecological risks associated with the use of EPA-registered pesticide products containing nonylphenol ethoxylates as inert ingredients is expected to be conducted in conjunction with the Office of Pesticide Program's registration review program.

I. Introduction

This report provides a qualitative assessment for the nonylphenol ethoxylates, pesticide inert ingredients which have four exemptions from the requirement of a tolerance when used as surfactants in pesticide formulations applied to raw agricultural commodities after harvest and growing crops under 40 CFR 180.910, to growing crops only under 40 CFR 180.920 and to animals under 40 CFR180.930.

II. Use Information

A. Pesticide Uses

The tolerance exemption expressions for nonylphenol ethoxylates are provided in Table 1 below.

40 CFR	Inert Ingredient	Limits	Uses	CAS Reg. No. and 9CI Name
180.910[a]	α-(*p*-Nonylphenyl)-ω-hydroxypoly(oxyethylene) produced by the condensation of 1mole of nonylphenol (nonyl group is a propylene trimer isomer) with an average of 4-14 or 30-90 moles of ethylene oxide; if a blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that is a component of the blend shall be in the range of 4-14 or 30-90	None	Surfactants;related adjuvants, of surfactants	127087-87-0 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-, branched) 26027-38-3 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-) 68412-54-4 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)-ω-hydroxy-, branched) 125279-66-5 (Poly(oxy-1,2-ethanediyl), α-(tripropylenephenyl)-ω-hydroxy-) 9016-45-9 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)- ω-hydroxy-) 37205-87-1 (Poly(oxy-1,2-ethanediyl), α-(isononylphenyl)-ω-hydroxy-)
180.910[a]	Poly(oxy-1,2-ethandiyl), α-(carboxymethyl)-ω-(nonylphenoxy) produced by the condensationof 1 mole of nonylphenol (nonyl group is a propylene trimer isomer) with an average of 4-14 or 30-90 moles of ethylene oxide. The molecular weight (in amu) ranges are 454-894 and 1598-4238.	None	Surfactants	150678-63-0 (Poly(oxy-1,2-ethanediyl), α-(carboxymethyl)-ω-(4-nonylphenoxy)-) 28212-44-4 (Poly(oxy-1,2-ethanediyl), α-(carboxymethyl)-ω-(4-nonylphenoxy)-)- 53610-02-9 (Poly(oxy-1,2-ethanediyl), α-(carboxymethyl)-ω-(nonylphenoxy)-)

40 CFR	Inert Ingredient	Limits	Uses	CAS Reg. No. and 9CI Name
180.920[b]	α-(*p*-Nonylphenyl)-ω-hydroxypoly(oxyethylene) produced by the condensation of 1 mole of nonylphenol (nonyl group is a propylene trimer isomer) with an average of 4-14 or 30-100 moles of ethylene oxide; if a blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that is a component of the blend shall be in the range of 4-14 or 30-100	None	Surfactant	127087-87-0 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-, branched) 26027-38-3 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-) 68412-54-4 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)-ω-hydroxy-, branched) 125279-66-5 (Poly(oxy-1,2-ethanediyl), α-(tripropylenephenyl)-ω-hydroxy-) 9016-45-9 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)- ω-hydroxy-) 37205-87-1 (Poly(oxy-1,2-ethanediyl), α-(isononylphenyl)- ω-hdroxy-)

40 CFR	Inert Ingredient	Limits	Uses	CAS Reg. No. and 9CI Name
180.930[c]	α-(p-Nonylphenyl)-ω-hydroxypoly(oxyethylene) produced by the condensation of 1 mole of nonylphenol (nonyl group is a propylene trimer isomer) with an average of 4-15 or 30-90 moles of ethylene oxide; if a blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that is a component of the blend shall be in the range of 4-15 or 30-90	None	Surfactant, emulsier, related adjuvants of surfactants	127087-87-0 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-, branched) 26027-38-3 (Poly(oxy-1,2-ethanediyl), α-(4-nonylphenyl)-ω-hydroxy-) 68412-54-4 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)-ω-hydroxy-, branched) 125279-66-5 (Poly(oxy-1,2-ethanediyl), α-(tripropylenephenyl)-ω-hydroxy-) 9016-45-9 (Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)- ω-hydroxy-) 37205-87-1 (Poly(oxy-1,2-ethanediyl), α-(isononylphenyl)- ω-hdroxy-)

[a] Residues listed in 40 CFR 180.910 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or raw agricultural commodities after harvest.
[b] Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.
[c] Residues listed in 40 CFR 180.930 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.

B. Other Uses

Nonylphenol ethoxylates are used in a variety of consumer products including household cleaners, cosmetics and shampoos. They also have industrial uses as surfactants in the production of rubber, plastics, and lubricating oils (Chemical Market Reporter, 2001 as cited in USDA, 2003).

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of nonylphenol ethoxylates with average degrees of ethoxylation of four and nine units of ethylene oxide (NP4EO

and NP9EO, respectively), along with a generic structure, are found in Table 2. The properties of NP4EO and NP9EO are considered to be representative of the nonylphenol ethoxylates and are presented herein because the available data set for these two compounds is the most complete.

Structure	 n=4 (NP4EO) or 9 (NP9EO)		ChemIDplus, 2004
Physical State	white to light amber liquid	almost colorless liquid	CIR, 1993 as cited in Health Canada, 2001 WHO, 1998 as cited in Health Canada, 2001
Molecular Weight	396.2 (M)	617.6 (M)	Health Canada, 2001
Water Solubility	7.65 mg/L (M)	"soluble" (M)	Ahel and Giger, 1993a as cited in Health Canada, 2001 CIR, 1993 as cited in Health Canada, 2001
Melting Point	-40 ºC (M)	2.8 ºC (M)	Weinheimer and Varineau, 1998 as cited in Health Canada, 2001
Henry's Law Constant		2.37×10^{-9} atm-m^3/mole @ 25ºC (E)	CIR, 1983 as cited in Health Canada, 2001
Vapor Pressure	Not available	Not available	---
Octanol/Water Partition Coefficient (Log P)	4.24 (M)	3.59 (M)	Ahel and Giger, 1993b as cited in Health Canada, 2001

(E)=Estimated Value
(M)=Measured Value

IV. Hazard Assessment

A. Hazard Profile

The main sources of hazard information for this reassessment are the human health risk assessment performed as part of the Priority Substances List Assessment Report for Nonylphenol and its Ethoxylates performed by Health Canada (Health Canada, 2001), the U.S. Department of Agriculture's Human and Ecological Risk Assessment of Nonylphenol Polyethoxylate-based Surfactants (USDA, 2003), unpublished test data submitted to EPA under sections 8(d) and 8(e) of the Toxic Substances Control Act (TSCA), as well as other published peer-reviewed references for toxicity data on nonylphenol ethoxylates.

Nonylphenol ethoxylates are classified as slightly toxic or nontoxic for acute exposure with the lower ethoxylates being slightly more toxic than the ones with a higher degree of ethoxylation. The LD_{50} values range from 1680 mg/kg for a 6-unit ethylene oxide chain (NP6EO) to over 5000 mg/kg for a 150-unit ethylene oxide chain (NP150EO). In general the shorter ethylene oxide chain length nonylphenol ethoxylates are corrosive to the skin, but nonylphenol ethoxylates with longer ethylene oxide chains appear to be noncorrosive.

Repeated dose oral toxicity studies on nonylphenol ethoxylates over a range of ethoxylation suggest that the liver and kidney are the main target organs for the lower ethoxylates with an effect level of 40 mg/kg/day for the 6 unit ethylene oxide chain nonylphenol ethoxylate (NP6EO). For the higher ethylene oxide chain length nonylphenol ethoxylates, retarded growth or decreased body weight gain appear to be the main effects only at relatively high doses. Several authors have attributed these findings to poor palatability of the food (Smith and Calandra, 1969).

In vitro Salmonella typhimurium data on a nonylphenol ethoxylate (NP10EO) was negative except for strain TA98 which produced positive results with activation at the two highest doses. The highest dose also produced marked toxicity.

Nonylphenol ethoxylate (NP10EO) has been tested for carcinogenicity in female Fischer 344 rats and female B6C3F_1 mice. The results of the two studies were negative for carcinogenicity (Hiroyuki *et al* 1999a, 1999b).

Developmental/teratology studies were conducted on nonylphenol ethoxylates with ethylene oxide chain lengths of 4, 9, and 30 units of ethylene oxide (NP4EO, NP9EO, and NP30EO). None of the studies showed any sensitivity. There were no maternal or fetal effects at any dose level for NP30EO. The no-observed-effect level (NOEL) for the study was 1000 mg/kg/day. For NP9EO, there was significant decrease in maternal weight gain, statistically significant decrease in average litter size, and increase in pre-implantation loss at the two highest doses. A dose-related increase in extra ribs and rudiments of ribs occurred in fetuses at the two highest doses. The lowest dose level of 50 mg/kg/day was determined to be the NOEL for both maternal

and developmental effects. For NP4EO, there was decreased weight gain and food consumption at the two highest doses. The percentage of all fetuses with variations was statistically significant at the highest dose and there were increased incidences of skeletal variations at the two highest doses. The maternal and developmental no-observed-adverse-effect level (NOAEL) was 50 mg/kg/day.

Nonylphenol and nonylphenol ethoxylates are weakly estrogenic when tested in *in vitro* and *in vivo* systems. However, nonylphenol is reported to be 1000 to 100,000 times weaker in estrogenic potential than endogenous 17-β estradiol. Nonylphenol ethoxyate (NP9EO) is reported to be less potent than nonylphenol by one to three orders of magnitude (Sevos, 1999; Sohoni and Sumpter, 1998; USEPA 1996; White, 1994 as cited in USDA, 2003).

B. Toxicological Data

Acute Toxicity

Nonylphenols are classified as slightly toxic to non-toxic (EPA Category III or IV) with lower exthoxylated nonylphenols being slightly more toxic than the ones with a higher degree of ethoxylation. Lonza, Inc. conducted acute toxicity testing on a number of nonylphenol ethoxylates (Lonza, 1996) and submitted the data to EPA's Office of Pollution Prevention and Toxics pursuant to Section 8(d) of the Toxic Substance Control Act (TSCA). The results are displayed in Table 3, including the relevant TSCA Test Submission database (TSCATS) document number reference.

Table 3. Summary of Acute Toxicity Data on Nonylphenol Ethoxylates

Parameter	Toxicity Value	Reference
Oral LD_{50}	Carsonon N-6 [a] 1680 mg/kg	TSCATS 86970000016
Oral LD_{50}	Carsonon N-10[a] 1890 mg/kg	TSCATS 86970000018
Oral LD_{50}	Carsonon N-150[a] >5000mg/kg	TSCATS 86970000019
Dermal LD_{50}, rabbit	NA	
Inhalation LC_{50}, rat	NA	
Eye Irritation, rabbit	Carsonon N-150 practically non-irritating	TSCATS 86970000019
Skin Irritation, rabbit	Carsonon N-6[a] corrosive	TSCATS 86970000016.
Skin Irritation, rabbit	Carsonon N-10[a] corrosive	TSCATS 86970000018
Skin Irritation, rabbit	Carsonon N-150[a] Non-irritation	TSCATS 86970000019
Dermal sensitization	NA	

[a] N number = number of ethoxy units; NA = Not Available

Subchronic Toxicity

Two unpublished feeding study in rats were submitted to the Agency by Dow Chemical Company under TSCA Section 8(d). In these studies Dowfax 9N9, a nonylphenol ethoxylate with 9 units of ethylene oxide and Dowfax 9N40, a nonylphenol ethoxylate with 40 units of ethylene oxide, were fed to rats for 90 days.

Male and female rats (ten/sex/group) were fed diets treated with doses of 0, 0.03, 0.1, 0.3, 1.0, or 3.0% of Dowfax 9N40 (approximately 0, 6.3, 22, 69, 210, or 630 mg/kg/day for males and 0, 5.7, 19, 63, 220, or 600 mg/kg/day for females based on average food consumption). There were no deaths at any dose level. At sacrifice no effects were seen in either males or females at 0.3% [(69 mg/kg/day (M), 63 mg/kg/day (F)] or lower doses. At a dose of 3% in the diet microscopic examination showed "some central lobular granular degeneration and necrosis in the liver and generalized cloudy swelling" males and females. Males showed "slight central lobular granular degeneration and necrosis with petechial areas of necrosis throughout the lobules." At a dose of 1% male rats showed a "very slight central lobular granular degeneration with petechial areas of necrosis throughout the lobules." There were no adverse effects seen in the females at 1%. The NOAEL for the study was 1% for females (220 mg/kg/day) and 0.3% (69 mg/kg/day) for males (Dow, 1997).

Male and female rats (ten/sex/group) were fed diets treated with 0, 0.1(females only) 0.3 or 1% (approximately 0, 75,or 240 mg/kg/day for males and 0, 22, 66,or 200 mg/kg/day for females based on average food consumption) of Dowfax 9N9. There were no deaths at any dose level. Significant growth retardation was seen in males dosed at 1% and the absolute average liver weights were significantly increased for both sexes at 1.0 and 0.3 % dose levels. At 1% a slight increase in average kidney weight was observed in males and in females a slight increase in average spleen weight was observed also at 1%. Histopathological examination revealed liver changes characterized as "very slight central lobular granular degeneration and necrosis accompanied in females by aggregates of round cells portally." In both males and females, kidneys showed changes including slight cloudy swelling of the renal tubular epithelium. Females dosed at 0.1 % had slight, non-significant changes in the liver. The study author characterized these changes as commonly found in animals of the colony, readily reversible and therefore not significant (Dow, 1997).

In the 1960s producers of alkylphenol ethoxylates cooperated in sponsoring toxicological evaluations of that family of products. These studies were conducted in five laboratories overseen by a committee of toxicologists. The results of these studies are reported in a 1969 journal article by Smyth and Calandra. Smyth was a member of the committee. Although studies were conducted on several alkylphenol ethoxylates, this assessment will only focus on the nonylphenol ethoxylates. Some of the studies were ultimately published separately while others remain unpublished (Smyth and Calandra, 1969).

The study protocols employed for the studies were similar--the dosing was oral and the studies ran for 90 days. The experimental animals were rats and dogs.

In one series of experiments Sprague-Dawley rats, 10/sex/dose, were fed diets that contained 0, 0.04, 0.2, or 1.0 g/k/day of the following nonylphenol ethoxylates: Nonyl 4 (Igepal CO-430), Nonyl 6 (Sterox DF), Nonyl 15s (Surfonic N-150). The results of the experiments were presented in table and narrative form. Nonyl 20 (Triton X-205) and Nonyl 30s (Surfonic N-300) were also tested in a similar experiment, but different

dose levels were used. The results of this experiment are also presented in the Table 4 below.

Table 4 Results from Smith and Calandra (1969) (Data from IBT(1963-1965))

Material	Doses(g/kg)	Lowest Dose at which effects occurred		
		Retarded growth	Increased absolute liver weight	Increased liver/body wt ratio
Nonyl 4	0, 0.04, 0.2, 1.0	1.0	1.0	0.2
Nonyl 6	0, 0.04, 0.2, 1.0	1.0	0.2	0.04
Nonyl 15s	0, 0.04, 0.2, 1.0	0.2	-	-
Nonyl 20	0, 0.2, 1.0, 5.0	5	-	-
Nonyl 30s	0, 0.2, 1.0, 5.0	-	-	-

The authors attribute the retarded growth to poor palatability of the food. For the nonylphenol ethoxylates with shorter ethylene oxide chain lengths, liver weight and increased liver/body wt ratio were seen at doses of 40 mg/kg/day and above while the nonylphenol ethoxylates with 15 or more ethylene oxide units showed no liver effects. Histopathology showed no microscopic changes in the liver.

In another 90 day feeding study, Charles River rats were fed diets treated with Nonyl 9t (Tergitol TP-9) at doses of 0, 0.01, 0.05, 0.25, or 1.25 g/kg/day. No deaths were reported. Liver as a percentage of body weight was high in males at the 1.25 g/kg/day dose level and in females at the 1.25 and 0.25 g/kg/day dose levels. Liver focal hepatic cell necrosis was seen at 1.25 g/kg/day and cloudy swelling of central hepatic cords was seen at 0.25 g/kg/day. Kidney focal tubular necrosis was also seen at 1.25 g/kg/day and focal cloudy swelling of proximal convoluted tubules was seen at 0.25g/k/day. These effects were seen in both males and females. At 0.05 g/kg/day there was a slight reduction in polysaccharides (unpublished data from the Mellon Institute (1959-1965) as cited in Smyth and Calandra, 1969).

Sherman Wistar rats were fed diets treated with Nonyl 9i (Igepal CO-630) at levels of 0, 0.01, 0.04, 0.16, 0.64, 2.5, or 5.0% (approximately 0, 1.3, 5, 20, 71, 258, or 500 mg/kg/day for males and 0, 1, 4, 17, 65, 243, or 470 mg/kg/day for females, based on average food consumption) for 90 days. The histopathology showed no changes that would be indicative of toxic effects. The only statistically significant effect was retardation of weight gain which was attributed to poor palatability of the food at 0.64% (71/65 mg/kg/day M/F) and higher levels (Shelanski, 1960 as cited in Smyth and Calandra, 1969).

A series of nonylphenol ethoxylates were administered by capsule to dogs (2/sex/dose) for ninety days. The compounds tested were Nonyl 4, Nonyl 6, Nonyl 15a, Nonyl 20d and Nonyl 30s. The doses tested were 0, 0.04, 0.2, or 1 g/kg/day for Nonyl 4, Nonyl 6 and Nonyl 15s; 0, 0.04, 0.2, or 1, 5 g/kg/day for Nonyl 20d and 0, 0.2; or 1 g/kg/day for Nonyl 30s. For Nonyl 4 and Nonyl 6, the only effect reported was an increased liver to body weight ratio at 0.2 g/kg/day and 1 gm/kg/day, respectively, with no effects reported for Nonyl 15s. For Nonyl 20d, death and gross focal myocardial necrosis was reported at 1 g/kg/day and microscopic focal myocardial necrosis or

degeneration was reported at 0.04 g/kg/day. Nonyl 30s produced no effects at any dose. The focal myocardial necrosis was further investigated and was found to be reproducible; however, ethylene oxide chain lengths from 15 to 29 units are excluded from the tolerance exemption expressions for the four exemptions being reassessed in this document. The effect has been included for completeness, but will not be included in further discussions (data from Industrial BioTest (1963-1965), as cited in Smyth and Calandra, 1969).

In another 90 day feeding study Beagle dogs (2/sex/dose) were given 0, 0.04, 0.64 or 5% nonyl 9i in their feed. The only statistically significant finding was retarded weight gain at the 0.64 and 5% levels (Shelanski, 1960 as cited in Symith and Calandra,1969).

Chronic Toxicity

As part of a chronic/carcinogenicity study female rats were fed diets treated with 0, 1000, 3000 or 9000 ppm (0, 60.5, 182 or 559 mg/kg/day, respectively) of nonlyphenol ethoxylate (NP10EO) for 52 weeks. No mortality was seen until week 52 of administration. Body weight gain was suppressed in the 9000 ppm group from week 1 until the termination of the study and at 3000 ppm from week 21 to the termination of the study. Food consumption and food efficiency was depressed in the 9000 and 3000 ppm groups. The liver and adrenal weights were increased at 3000 and 9000 ppm. Increased kidney weight was reported at 1000 and 3000 ppm and increased adrenal and ovary weights at 1000 ppm. The differences were statistically significant, but were not dose-related and fell within the normal range. Relative organ weights were also higher in all groups and were statistically significant, but fell within normal ranges. Blood chemistry values were altered, but stayed within normal ranges. Slight bile duct hyperplasia of the liver was noted at 52 weeks. Histopathology did not show any abnormal findings. The NOAEL for chronic toxicity was 1000 ppm (60.5 mg/kg/day) (Inoue, 1999).

Male and female Sprague-Dawley rats were treated with 0, 0.04, 0.2 or 1 g/kg/day Nonyl 4 in feed for 2 years. There were no deaths in the two year period. At 1 and 0.2 g/kg/day females had gained less weight than the controls at twelve months, but the difference disappeared by twenty-four months. The only effect reported was a higher liver to body weight ratio in both sexes at 1 g/kg/day; however the livers appeared normal when histopathology was performed (Smyth and Calandra, 1969).

Carworth-Elias male and female rats were fed Nonyl 9t via the diet at concentrations of 0. 0.03, 0.09, or 0.27% for 2 years. No effects were seen that were attributed to the Nonyl 9t. Details on the specifics were lacking (Smyth and Calandra. 1969).

Nonyl 4 was administered by capsule to male and female Beagle dogs at doses of 0, 0.04, 0.2 or 1 g/kg/day over a two year period. At the end of the two years, there was a moderate elevation in the liver to body weight ratio and alkaline phosphatase

levels at 1gm/kg, but there were no significant microscopic changes in the liver. At 0.2 g/kg/day these effects were also seen, but to a lesser degree. The NOEL was set at 0.04 g/kg/day (Smyth and Calandra, 1969).

Nonyl 9t was also administered to male and female Beagle dogs for 2 years. The dogs were fed 0, 0.0085, 0.028, and 0.088 g/kg/day Nonyl 9t in Friskies Dog Food Meal. The only effect reported was an increased liver to body weight ratio at 0.088 g/kg/day. Histopathology revealed no abnormalities (Smyth and Calandra 1969).

Neurotoxicity

No neurotoxicity studies were identified. However,the available toxicity studies did not produce signs of neurotoxic effects at the doses tested.

Mutagenicity

Nonylphenol ethoxylate (NP10EO) was tested in *in vitro Salmonella typhimurium* with and without activation. The doses tested were 40, 200, 1000, 5000 or 25,000 µg per plate. Sterile water was the negative control; sodium azide and 2-anthramine were the positive controls. The results were negative in strains TA 1535, TA 100, TA 1537 and TA98 without activation and also negative with S9 activation in strains TA 1535, TA100 and TA 1537. Strain TA 98 produced an elevation number of revertants (30%) at the two highest doses. The highest dose produced marked toxicity (Meyer *et al*, 1988).

Carcinogenicity

Female F344 rats (70/group) were fed diets containing 0, 1000, 3000 or 9000 ppm (0, 55.2, 166, or 520 mg/kg/day for 104 weeks) nonylphenol ethoxylate (NP10EO) for 2 years. No animals died until week 52 of dosing. At 78 weeks mortality was 6, 4, 2, 2% for the 0, 1000, 3000 and 9000 ppm groups, respectively. At week 104 the mortality was 28, 26, 14, and 14% respectively. Body weight gain was suppressed in the 9000 ppm group until the termination of the study and in the 3000 ppm group from week 21 to week 88. The 1000 ppm group only showed slight body weight gain suppression during weeks 38-54 with no differences from control thereafter. Food consumption decreased in the 9000 and 3000 ppm groups, but only periodically in the 1000 ppm group. Although there were variations in hematological parameters, the variations stayed within normal ranges. Changes in organ weights at 104 weeks were similar to controls. Relative organ to body weights were higher in the 9000 and 3000 ppm groups at 104 weeks, but were all within the normal ranges. Histopathology revealed no neoplastic lesions that were attributable to the treatment. Proliferative duct of the pancreas was the single lesion that may be attributed to the treatment. Oral treatment of female F344 rats with nonylphenol ethoxylate NP10EO) for two years was negative for carcinogenicity (Inoue *et al*, 1999a).

Female B6C3F$_1$ mice (50/group) were fed diets containing 0, 500, 1500, or 4500 ppm nonylphenol ethoxylate (NP10EO) for 2 years. There were no mortalities until week 42. Mortalities at 104 weeks were 14, 12, 18, and 14% for the 0, 500, 1500, and 4500 ppm groups, respectively. Body weight gain was depressed in the 4500 ppm group from week 1 until termination. Absolute liver and kidney weights were lower than controls and relative brain, liver and kidney weights were higher than controls in the 4500 ppm groups. In the two lower dose groups, no differences were reported in the weights of the organs compared to the control group. At necropsy thymus atrophy and spleen enlargement were observed in all groups. Histopathological findings could not be unequivocally attributed to the treatment. No benign or malignant tumors could be attributed to the treatment. Oral treatment of female B6C3F$_1$ mice with nonylphenol ethoxylate (NP10EO) for two years was negative for carcinogenicity (Inoue *et al*, 1999b).

Developmental and Reproductive Toxicity

Union Carbide submitted an oral developmental study on Tergitol NP-4 (NP4EO) to the Agency under TSCA Secton 8(e). In this study female Sprague-Dawley rats were treated orally by gavage at doses of 0, 50, 250 or 500 mg/kg/day of Tergitol NP-4 on gestational days 6 to 15. Maternal weights were significantly reduced at the 250 and 500 mg/kg/day doses as was food consumption. Maternal weight gain was also reduced at these doses. Maternal absolute and relative liver weights were reduced at all dose levels, although the authors did not consider the effects at the 50 mg/kg/day dose to be toxicologically significant. Treatment-related clinical signs in the dams were seen at the two highest doses. There were no effects of treatment on pre- or post-implantation loss, the number of live fetuses per litter, sex ratio, or average fetal body weight per litter. The percentage of all fetuses with variations was statistically significant at the highest dose and there were an increased incidence of skeletal variations at the two highest doses. The maternal and developmental NOAEL was 50 mg/kg/day (Union Carbide, 1999)

Teratology studies were carried out on two nonlyphenol ethoxylates in which pregnant SPF female rats were dosed by gavage from gestation days 6 to15 with nonylphenol ethoxylate (NP9EO) at doses of 0, 50, 250, or 500 mg/kg/day and nonylphenol ethoxylate (NP30EO) at doses of 0, 50, 250, or 1000 mg/kg/day. Two additional testing regimes were conducted with the two chemicals: 500 mg/kg NP9EO was given to pregnant rats by gavage on gestation days 1-20 and 1000 mg/kg NP30EO was given to pregnant rats from gestation days 1-20. None of the NP30EO-dosed dams demonstrated any adverse effects during the gestation period. No reproductive effects were seen in any dose group of the NP30EO study or were there any effects on the fetuses. The NOEL for NP30EO is 1000 mg/kg/day for both maternal and developmental toxicity (Meyers *et al*, 1988).

Oral doses of NP9EO at 250 mg/kg on days 6-15 and 500 mg/kg on days 6-15 and 1-20 caused a significant decrease in weight gain. A small, but statistically significant decrease in average litter size was observed in the 250 and 500 mg/kg

(dosing on days 6-15) groups, as well as an increase in pre-implantation loss. A dose-related increase in extra ribs and rudiments of ribs occurred in fetuses dosed with 250 and 500 mg/kg/day of NP9EO. The NOEL for fetal and maternal effects was determined to be 50 mg/kg/day (Meyers *et al,* 1988).

Endocrine Disruption

Nonylphenol and nonylphenol ethoxylates are weakly estrogenic when tested in *in vitro* and *in vivo* systems. However, nonylphenol is reported to be 1000 to 100,000 times weaker in estrogenic potential than endogenous 17-β estradiol. Nonylphenol ethoxyate (NP9EO) is reported to be less potent than nonylphenol by one to three orders of magnitude (Sevos, 1999; Sohoni and Sumpter, 1998; USEPA, 1996; White,1994 as cited in USDA, 2003).

C. Mode of Action, Metabolism, and Pharmacokinetics

In a study of metabolism, the excretion of nonylphenol ethoxylates has been evaluated. Male rats were dosed with eight ^{14}C-labeled samples of nonylphenol ethoxylate labeled in the ethoxylate chain, 7-, 10-, 12-, and 15-mole adducts. Excretion in urine was nearly complete in 2 days. Based on an intraperitoneal injection metabolism study of nonylphenol ethoxylates, it was determined that the ethoxylate chain moiety was absorbed from the digestive tract following oral exposure and metabolized less completely as the chain length increased. The nonylphenol moiety from nonylphenol ethoxylate (NP9EO) was excreted in the same pattern as nonylphenol. The principal urinary metabolites were identified as the carboxylic acids of polyethylene glycols and glucuronic acid conjugates of nonylphenol (Knaak *et al,* 1966 as cited in Smyth and Calandar, 1969).

D. Special Considerations for Infants and Children

The database for the nonylphenol ethoxylates is sufficient for assessing the potential developmental effects of these chemicals. In developmental toxicity studies in rats and mice, there was no incidence of developmental toxicity in the absence of maternal toxicity. The NOELs for both maternal and developmental toxicity ranged from 50 mg/kg/day to 1,000 mg//kg/day. No quantitative or qualitative susceptibility was observed from the available developmental toxicity studies in rats and mice. Therefore, there is no concern at this time for increased sensitivity to infants and children from nonylphenol ethoxylates. For the same reason, a safety factor analysis has not been used to assess the risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

E. Environmental Fate Characterization and Drinking Water Considerations

Nonylphenol ethoxylates are nonvolatile substances, and partition to soils and water, where they are unlikely to undergo abiotic degradation, but are reported to be

inherently biodegradable, with the mechanism involving stepwise loss of ethoxy groups from nonylphenol ethoxylate to form lower nonylphenol ethoxylate congeners, followed by the production of nonylphenol ethoxylate carboxylate and nonylphenol, depending upon experimental conditions (Rudling and Solyom, 1974; Maki *et al,* 1994 as cited in Health Canada, 2001). These compounds are expected to be relatively non-mobile, with a K_{oc} in the 10,000 range, in terrestrial environments. The nonylphenol ethoxylates will move off site mainly with the sediment fraction when applied to fields. Reported concentrations of nonylphenol ethoxylates, nonylphenol ethoxylate carboxylates and nonylphenols in fresh water samples ranged from <0.02 µg/L to 17 µg/L (Health Canada, 2001) and in drinking water samples ranged from below the limit of detection (not specified) to 0.25 µg/L (Guardiola *et al,* 1991 as cited in Health Canada, 2001).

VI. Exposure Assessment

Dietary exposures to nonylphenol ethoxylates may occur as the result of consuming food following the application of pesticide products containing nonylphenol ethoxylates as inert ingredients or from the consumption of water containing nonylphenol ethoxylates.

Residential exposure (primarily via the dermal and inhalation routes) to nonylphenol ethoxylates may occur as a result of their use in detergents and other household cleaning products and from residential use pesticide products containing nonylphenol ethoxylates as inert ingredients.

VII. Aggregate Exposures

In examining aggregate exposure, the Federal Food, Drug, and Cosmetic Act (FFCDA) section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For nonylphenol ethoxylates, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the exposure via these pathways is orders of magnitude less than the no-observed-effect levels and no observed-adverse-effect levels seen in a number of toxicity studies in animals, including repeated dose studies, developmental toxicity studies, chronic toxicity studies and carcinogenicity studies.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to these nonylphenol ethoxylates and any other substances, and the nonylphenol ethoxylates do not appear to produce toxic metabolites produced by other substances. For the purposes of these tolerance actions, therefore, EPA has not assumed that the nonylphenol ethoxylates have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

IX. Human Health Risk Characterization

Nonylphenol ethoxylates are classified as slightly toxic or non-toxic for acute exposure with the lower ethoxylates being slightly more toxic than the ones with a higher degree of ethoxylation. The LD_{50} values range from 1680 mg/kg for a 6-unit ethylene oxide chain (NP6EO) to over 5000 mg/kg for a 150-unit ethylene oxide chain (NP150EO). In general the shorter ethylene oxide chain length nonylphenol ethoxylates are corrosive to the skin, but nonylphenol ethoxylates with longer ethylene oxide chains appear to be noncorrosive.

Repeated dose oral toxicity studies on nonylphenol ethoxylates over a range of ethoxylation suggest that the liver and kidney are the main target organs for the lower ethoxylates with an effect level of 40 mg/kg/day for the 6 unit ethylene oxide chain length nonylphenol ethoxylate (NP6EO). For the higher ethylene oxide chain length nonylphenol ethoxylates, retarded growth or decreased body weight gain appear to be the main effects only at relatively high doses. Several authors have attributed these findings to poor palatability of the food (Smith and Calandra, 1969).

In vitro Salmonella typhimurium data on a nonylphenol ethoxylate (NP10EO) was negative except for strain TA98 which produced positive results with activation at the two highest doses. The highest dose also produced marked toxicity.

Nonylphenol ethoxylate (NP10EO) has been tested for carcinogenicity in female Fischer 344 rats and female B6C3F_1 mice. The results of the two studies were negative for carcinogenicity (Hiroyuki *et al* 1999a, 1999b).

Developmental/teratology studies were conducted on nonylphenol ethoxylates with ethylene oxide chain lengths of 4, 9, and 30 units of ethylene oxide (NP4EO, NP9EO, and NP30EO). None of the studies showed any sensitivity. There were no maternal or fetal effects at any dose level for NP30EO. The no-observed-effect level (NOEL) for the study was 1000 mg/kg/day. For NP9EO, there was significant decrease in maternal weight gain, statistically significant decrease in average litter size, and increase in pre-implantation loss at the two highest doses. A dose-related increase in

extra ribs and rudiments of ribs occurred in fetuses at the two highest doses. The lowest dose level of 50 mg/kg/day was determined to be the NOEL for both maternal and developmental effects. For NP4EO, there was decreased weight gain and food consumption at the two highest doses. The percentage of all fetuses with variations was statistically significant at the highest dose and there were increased incidences of skeletal variations at the two highest doses. The maternal and developmental no-observed-adverse-effect level (NOAEL) was 50 mg/kg/day (Union Carbide, 1999; Meyers *et al*, 1988).

Nonylphenol and nonylphenol ethoxylates are weakly estrogenic when tested in *in vitro* and *in vivo* systems. However, nonylphenol is reported to be 1000 to 100,000 times weaker in estrogenic potential than endogenous 17-β estradiol. Nonylphenol ethoxyate (NP9EO) is reported to be less potent than nonylphenol by one to three orders of magnitude (Sevos, 1999; Sohoni and Sumpter, 1998; USEPA 1996; White, 1994 as cited in USDA, 2003).

Based upon an analysis of the weight fractions in pesticide products of surfactants (90th percentile concentrations <5% w/w), the use patterns of products containing nonylphenol ethoxylates, the inherent biodegradation of the nonylphenol ethoxylates, and available data on concentrations of nonylphenol ethoxylates in drinking water, the inert ingredient use of nonylphenol ethoxylates as pesticide product inert ingredients is expected to result in human exposure below any dose level that would produce any adverse effect.

Taking into consideration all available information on nonylphenol ethoxylates, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to the nonylphenol ethoxylates when used as an inert ingredient in pesticide products when considering dietary exposure and all non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the four exemptions from the requirement of a tolerance established for residues of nonylphenol ethoxylates can be considered reassessed as safe under section 408(q) of FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

The following characterization of nonylphenol ethoxylate toxicity to fish, aquatic invertebrates, algae and soil microorganisms was provided in the Health Canada assessment of nonylphenol ethoxylates (Health Canada, 2001):

> The toxicity of NPEs decreases with increasing EO chain length in a wide variety of species, including fish, invertebrates, algae and soil microorganisms. The LC50s and EC50s for NP9EO are much higher than those reported for NP in fish, invertebrates and algae. LC50 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 LC50 of NP9EO in Daphnia magna was reported as 14 000 µg/L by Dorn et al. (1993). The 48-hour LC50 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 LC50 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 EC50 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 (EC50) 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.

Nonylphenol ethoxylates undergo biodegradation in the environment to form lower nonylphenol ethoxylate congeners, followed by the production of nonylphenol ethoxylate carboxylate and nonylphenol. Aquatic Life Ambient Water Quality Criteria have been established by EPA's Office of Water for nonylphenol (EPA, 2005). Based on these ambient water quality criteria for nonylphenol, application of pesticide products containing nonylphenol ethoxylates as inert ingredients may exceed the acute and chronic levels of concern (LOC) for nonylphenol for certain nontarget aquatic species.

A search of the Agency's ECOTOX database (http://www.epa.gov/ecotox) and other sources indicate that there are no data in the published literature on the effects of nonylphenol ethoxylates to nontarget terrestrial plants and animals.

A more complete assessment of the ecological risks associated with the use of EPA-registered pesticide products containing nonylphenol ethoxylates as inert ingredients is expected to be conducted in conjunction with the Office of Pesticide Progam's registration review program

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