

Nonylphenol Ethoxylates

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Identification of Petitioned Substance

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| Chemical Names: | CAS Numbers: |
| Nonylphenol Ethoxylates (NPEs) | 26027-38-3 |
| | 9036-19-5 |
| Other Names: | 9014-92-0 |
| p-Nonylphenol, ethoxylated | 9016-45-9 |
| Polyoxyethylene (1,1,3,3-tetramethylbutyl)-phenol ether | |
| Polyoxyethylene dodecylphenol | Other Codes: |
| Polyoxyethylene nonylphenol | 500-024-6 (EINECS No for CAS# 9016-45-9) |
| Trade Names: | |
| Tergitol™, Triton™ | |

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Summary of Petitioned Use

The National Organic Program (NOP) final rule currently allows synthetic inert ingredients designated as EPA List 4 – Inerts of Minimal Concern – and EPA List 3 – Inerts of unknown toxicity – for use with “nonsynthetic substances or synthetic substances listed in this section and used as an active pesticide ingredient in accordance with any limitations on the use of such substances” in organic crop production (7 CFR §205.601(m)). EPA List 3 inert ingredients are permitted for use only in passive pheromone dispensers. In addition, EPA List 4 inert ingredients may be used with nonsynthetic substances or allowed synthetic substances in organic livestock production (7 CFR §205.603(e)). The National Organic Standards Board (NOSB) has requested technical information for nonylphenol ethoxylates on EPA List 4B, including ethoxylated p-nonylphenol (CAS# 26027-38-3), polyethylene (1,1,3,3-tetramethylbutyl)phenyl ether (CAS# 9036-19-5), polyoxyethylene dodecylphenol (CAS# 9014-92-0) and polyoxyethylene nonylphenol (CAS# 9016-45-9). This report provides targeted technical information in support of the NOSB’s sunset review of these substances currently allowed for use as inert ingredient in organic crop production.

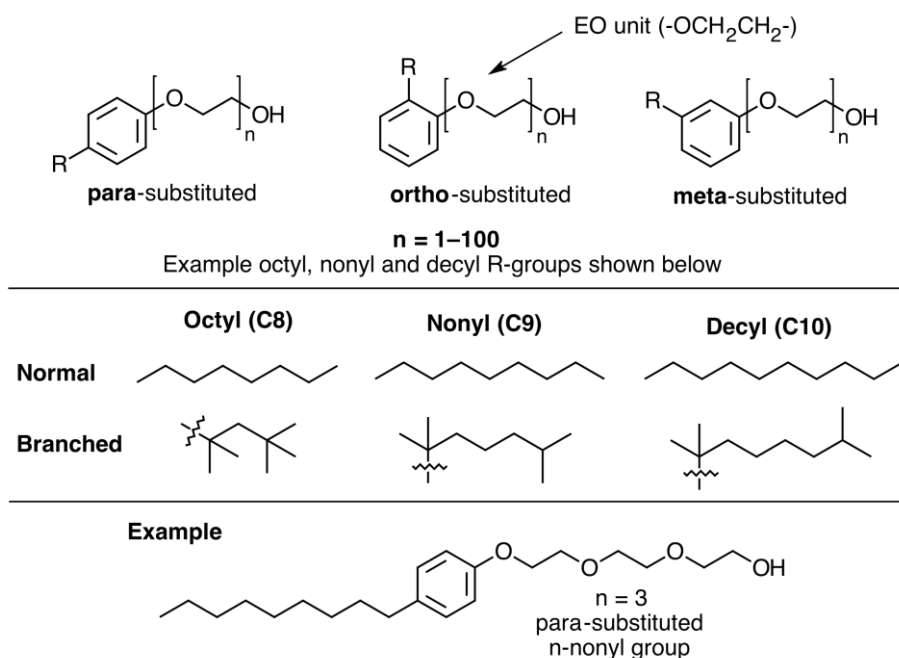
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Characterization of Petitioned Substance

Composition of the Substance:

Nonylphenol ethoxylates (NPEs) belong to the larger class of surfactant (i.e., surface active) compounds known as alkylphenol ethoxylates (APEs). This broad chemical class encompasses individual compounds with a wide range of molecular weights – from oligomers containing only a few monomeric units to polymers with tens or even one hundred monomers comprising a single molecule (Dow, 2010). In the case of APEs, the monomeric repeating unit is an ethoxy (EO) group. The number of EO groups varies between one and 100 depending on the number of ethylene oxide molecules that reacted with a particular nonylphenol (NP) molecule during the production process. APEs also vary based on the structure of the alkyl substitution on the phenol ring (US EPA, 2010). For example, APEs may have alkyl substituents with carbon atom counts of eight (octylphenol ethoxylates, or OPEs), nine (nonylphenol ethoxylates, or NPEs), ten (decylphenol ethoxylates, or DPEs), as well as larger alkyl substituents. Molecular complexity in APEs also arises from the configuration of these alkyl groups (US EPA, 2010). Within a single APE mixture, the alkyl groups on individual molecules may be linear or have extensive branching along the carbon chain. The alkyl chain may bind to the phenol ring immediately adjacent (“ortho”) to the phenol hydroxyl group or one to two carbons (“meta” and “para”) removed from the hydroxyl substitution (US EPA, 2010).

47 There are scores, if not hundreds, of individual NPE isomers (nonyl chain) and congeners (EO units) in an
 48 industrial NPE product. Each NPE is conventionally described by its average EO chain length, which
 49 varies between 1 and 100 for different formulations. The molecular weight of a particular NPE molecule is
 50 exclusively dictated by the degree of ethoxylation (i.e., number of EO groups). In addition, NPEs may
 51 contain small amounts of branched C8 (octyl) and C10 (decyl) alkyl groups depending on the level of
 52 contamination in the NP feedstock material. Alkyl substitution on the phenol ring occurs primarily ($\geq 90\%$)
 53 at the "para" position due to a thermodynamic preference, with smaller amounts of the "ortho" and
 54 "meta" substitution products observed in mixtures of NPEs and NPs. Most of the nonyl substituents on the
 55 phenol rings of NPEs are highly branched, while a significantly smaller fraction of these nonyl groups are
 56 linear chains. Figure 1 below provides a pictorial representation of the structural variations commonly
 57 observed in NPE mixtures.



58
 59 **Figure 1. The constituents of NPE formulations differ based on the degree of ethoxylation, substitution**
 60 **pattern along the phenol ring and structure of the alkyl substituent (linear vs. branched).**

61 Source or Origin of the Substance:

62 NPEs are produced through the reaction of nonylphenol (NP) and ethylene oxide with potassium
 63 hydroxide (KOH) as a catalyst (Dow, 2010). In addition to other reaction parameters, the ratio of ethylene
 64 oxide to NP generally determines the number of ethoxy (EO) units (i.e., length of the polymeric chain) and
 65 therefore the molecular weight of the molecules within the produced NPE mixture. Water may be added
 66 during formulation to simplify product handling (Dow, 2010). See the response to Evaluation Question #2
 67 for additional details regarding the predominant manufacturing process, as well as a discussion of
 68 variations of this method potentially used in the industrial production of NPEs.

69 Properties of the Substance:

70 Commercially available NPE surfactants can be either solids or liquids depending on the molecular
 71 weights of the NPE constituents and the use temperature. Solid formulations are generally white to yellow
 72 or light orange in color, and the liquids are clear to slightly cloudy (Dow, 2010). NPE mixtures consisting
 73 primarily of lower molecular weight NPEs (i.e., shorter EO chains) tend to be liquids, while technical
 74 mixtures with higher molecular weight NPE products are generally solids. The latter group is commonly
 75 diluted with water during product formulation, thus providing an aqueous solution of NPEs (Dow, 2010).

76 Because the constituents of different formulations vary in molecular complexity and composition, the
 77 product mixtures may have varying solubility in water and other industrial solvents. NPEs with four and
 78 six EO units (NP-4EO and NP-6EO) are less polar molecules, and can therefore solubilize petroleum

79 products such as kerosene and aliphatic hydrocarbons (Dow, 2010). Intermediate chain length NPE
 80 surfactants (i.e., NP-7EO through NP-15EO) are miscible with chlorinated and aromatic solvents and
 81 exhibit some solubility in water. The higher molecular weight, highly ethoxylated NPEs (NP-30EO through
 82 NP-70EO) have a higher proportion of polar functionality in their molecular structures, and are highly
 83 soluble in water (Dow, 2010).

84 A selection of chemical and physical properties for NPE and the parent/break down product NP are
 85 provided below in Table 1 for comparison. See the response to Evaluation Question #4 for a discussion of
 86 the persistence and biodegradability of NPEs and their primary by-product NP.

87 **Table 1. Chemical and Physical Properties for NPEs.**

| Property | Description |
|--|--|
| Physical state | Solid or oily liquid |
| Appearance/color | White to yellow/light orange (solids) Clear to slightly cloudy (liquids) |
| Molecular formula | Varies (mixture) C ₁₅ H ₂₄ O[C ₂ H ₄ O] ₉ (NP-9EO) C ₁₅ H ₂₄ O[C ₂ H ₄ O] ₄ (NP-4EO) |
| Molecular weight (g/mol) | Varies (mixture) 617.6 (NP-9EO) 396.2 (NP-4EO) |
| Melting point (°C) | 2.8 (NP-9EO) -40 (NP-4EO) |
| Density (g/mL) | 1.06 at 20 °C (NP-9EO) 1.02-1.03 at 25 °C (NP-4EO) |
| Water solubility (mg/L) | 42.5 (NP-12EO) 9.48 (NP-5EO) |
| Other solubilities | Kerosene and aliphatic hydrocarbons (low molecular weight NPEs), chlorinated and aromatic solvents (intermediate NPEs) |
| Octanol-water partition coefficient (log K _{ow}) | 3.59 (NP-9EO) 4.24 (NP-4EO) |
| NPE Biodegradation | Readily biodegrade to shorter-chain NPEs and NP |
| NP Biodegradation | 150 days in surface water 30 days (primary biodegradation in soil) 300 days (mineralization to CO ₂ in soil) |
| Photodegradation | Possible for NPEs and NPs in water |
| Vapor pressure | Moderately volatile (low molecular weight NPEs) Nonvolatile (high molecular weight NPEs) |

88 *Data Sources:* Dow, 2010; US EPA, 2010; Environment Canada, 2002; Health Canada, 2001.

89 **Specific Uses of the Substance:**

90 NPEs are characterized as nonionic surfactants, and are used in a variety of industrial cleaning products,
 91 processes, agricultural formulations and paints (US EPA, 2010). Specifically, market applications for NPE
 92 products fall into one or more of the following basic categories: (1) Industrial, including agriculture, leather
 93 processing, metal working, oil field, pulp and paper, textile processing and water treatment; (2) Emulsions
 94 and coatings, including paints and coatings, emulsion polymerization and adhesives; (3) Industrial and
 95 institutional cleaning, including hard-surface cleaners, circuit board cleaners, industrial laundry/dry-
 96 cleaning detergents, metal cleaning, food and dairy; and (4) Household cleaning, including detergents,
 97 laundry prewash, hard-surface cleaners and air fresheners (Dow, 2010). In addition to being used as
 98 surfactants in industrial cleaners and adjuvants in pesticide formulations, the nine mole ethoxylate (NP-
 99 9EO) serves as the active ingredient in some spermicide contraceptives (US EPA, 2006).

100 In agriculture, NPEs are used as adjuvants and co-formulated with pesticides and biocides (DEPA, 2006). A
 101 primary example is the use of NPE as an emulsifier in iodine-based teat dips, which are applied to the teats

102 of milk producing animals as antimicrobial medical treatments in both conventional and organic livestock
103 production (US EPA, 2006). Generally referred to as “iodophors,” these complexes consist of up to 20% I₂
104 by weight in loose association with NPEs and other nonionic surfactants (Lauterbach & Uber, 2011). NPE
105 surfactants are also used as adjuvants in herbicides and various other pesticide products applied to crops.
106 Surfactants can be defined as adjuvants that “facilitate and accentuate the emulsifying, dispersing,
107 spreading, wetting, or other surface modifying properties of liquids” (Czarnota & Thomas, 2013) or more
108 broadly as “any nonpesticidal material added to a pesticide product or pesticide spray mixture to enhance
109 the pesticide’s performance and/or the physical properties of the spray mixture” (Hock, 2015). As
110 adjuvants, NPE surfactants are widely used to enhance the absorption and efficacy of active ingredients in
111 pesticides. Modern pesticide active ingredients are formulated to dissolve in water; however, the waxy
112 surfaces of many insects, fungi and plants make it difficult for water-based spray solutions to penetrate the
113 target organisms. Adjuvants have been used to overcome this barrier, thereby allowing greater penetration
114 of the active pesticidal substances into its target (Czarnota & Thomas, 2013).

115 **Approved Legal Uses of the Substance:**

116 According to US EPA, NPE products are used or allowed for use in a wide variety of applications. These
117 include use as detergents, cleaners, degreasers, dry cleaning aids, petroleum dispersants, emulsifiers,
118 wetting agents, adhesives, agrochemical (including indoor pesticides), cosmetics paper and textile
119 processing formulations, prewash spotters, metalworking fluids, oilfield chemicals, paints and coatings,
120 and dust control agents (US EPA). US EPA only regulates the uses of NPEs associated with pesticide
121 products (i.e., herbicides, insecticides, fungicides, rodenticides and antimicrobials). When used as
122 surfactants and adjuvants (i.e., inert ingredients) in pesticides, residues of NPEs applied to crops during
123 and after the growing season and to animals are exempt from the requirement of a tolerance (40 CFR
124 180.910 and 180.930). US EPA has also approved tolerance exemptions for NPEs as active and inert
125 ingredients used in antimicrobial food-contact surface sanitizing solutions (40 CFR 180.940). In crop
126 production (40 CFR 180.910), US EPA provides tolerance exemptions for NPE, described as follows:

127 *α-(p-Nonylphenol)-ω-hydroxypoly(oxyethylene) produced by the condensation of 1 mole of nonylphenol*
128 *(nonyl group is a propylene trimer isomer) with an average of 4–14 or 30–90 moles of ethylene oxide; if a*
129 *blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that*
130 *is a component of the blend shall be in the range of 4–14 or 30–90.*

131 Although NPEs were once commonly used in household laundry detergents, US EPA and the detergent
132 manufacturers have cooperated to eliminate their use in this context. Based on toxicity concerns and the
133 persistence of NP in the environment, US EPA began working with manufacturers in 2010 to initiate a
134 voluntary phase-out of NPEs in industrial laundry detergents by 2013 for liquid detergents and 2014 for
135 powdered detergents (US EPA, 2010). The Agency also intends to encourage the manufacturers of all NPE-
136 containing direct-release products, such as firefighting gels and foams, dust-control agents and deicers, to
137 transition to NPE-free formulations. Lastly, US EPA intends to encourage the elimination of NPE use in
138 other industries that discharge NPEs to water, primarily in the pulp and paper processing and textile
139 processing sectors (US EPA, 2010). In comparison, EU member states and industry agreed to phase out
140 NPEs in all detergent applications in the respective countries by the year 2000 (WHO, 2004).

141 The US Food and Drug Administration (FDA) regulates a number of legal uses for various NPE
142 formulations as indirect food additives. According to 21 CFR 175.105, NPE “produced by the condensation
143 of 1 mole of p-nonylphenol (nonyl group is a propylene trimer isomer) with an average of 1–40 moles of
144 ethylene oxide” is an approved component of adhesives intended for use in packaging, transporting or
145 holding food. The “nonylphenol reaction product with 9 to 12 molecules of ethylene oxide” may be used as
146 an adjuvant substance in antimicrobial slimicides formulations used to control slime in the manufacture of
147 paper and paperboard (21 CFR 176.300). NPEs with an ethoxylate content of 11 or 15–18 moles may be
148 used as adjuvants in sanitizing solutions with antimicrobial quaternary ammonium compounds [(n-alkyl
149 (C12–C18) benzyl dimethyl ammonium chloride and n-alkyl (C12–C14) dimethyl ethylbenzyl ammonium
150 chloride (having average molecular weights of 377 to 384)] for use on food-processing equipment and
151 utensils prior to contact with food (21 CFR 178.1010). Lastly, 21 CFR 178.3400 describes the use of NPEs
152 (average ethoxylate content of 4–14 or 30–50 moles) as emulsifiers and/or surface-active agents (i.e.,

153 surfactants) in the manufacture of products intended for use in producing, manufacturing, packing,
154 processing, preparing, treating, packaging, transporting or holding food.

155 **Action of the Substance:**

156 NPEs are amphipathic, meaning they have hydrophilic (“water-attracting”) groups at one end of the
157 molecule and hydrophobic (“water-avoiding”) groups at the opposite end. The hydrophilic “head” attracts
158 water and the hydrophobic “tail” attracts poorly water-soluble substances, such as oils and greases (US
159 EPA, 2010). The ability of NPEs and other surfactants to simultaneously attract water and hydrophobic
160 substances makes these materials useful in agricultural, industrial and residential applications.
161 Surfactant/detergent uses therefore account for nearly 80% of NPE consumption (US EPA, 2010).

162 In crop production, adjuvants such as NPE are used to break water surface tension, allowing the pesticide
163 active ingredient to be more even dispersed on a surface and to reach its target (Czarnota & Thomas, 2013).
164 Water molecules are considered bipolar because they have regions of partial positive and negative charge.
165 Water molecules within the bulk liquid experience attractions to neighboring molecules in all directions
166 due to strong intermolecular forces known as hydrogen bonds (Lower, 2014). Water molecules at the
167 surface, however, experience these forces only sideways and downward, thus creating the “stretched
168 membrane” effect. The difference between forces experienced by water molecules within and at the surface
169 of the bulk liquid gives rise to the liquid’s surface tension (Lower, 2014). Aqueous solutions of some
170 pesticides will bead, run off and fail to provide adequate cover when applied to hydrophobic surface (e.g.,
171 waxy or hairy plant leaves) due to the surface tension of water (Czarnota & Thomas, 2013; UAP Canada,
172 2012). Surfactants such as NPE reduce the surface tension of water in the spray solution to that of an oil or
173 solvent, which spreads more readily on plant surfaces (UAP Canada, 2012).

174 **Combinations of the Substance:**

175 Adjuvants such as NPEs may be added to the pesticide solution at the time of formulation or to the spray
176 mix just prior to treatment (UAP Canada, 2012). Products consisting solely of adjuvants are not generally
177 registered with US EPA, while marketed pesticide products formulated as a mixture of active ingredient(s)
178 and adjuvant(s) must be EPA-registered and included in the US EPA Pesticide Product Information System
179 (US EPA, 2015). CMR Can-Hance is an activator product (i.e., adjuvant) containing a blend of
180 “nonylphenoxy poly (ethylene oxy) ethanol” and “silicone-polyether copolymer” used to maximize the
181 performance of post-emergence herbicides (Brandt, undated). NPEs are also used as adjuvants in
182 insecticide products containing the pyrethroid deltamethrin (K-Othrine® SC Insecticide) and disodium
183 octaborate tetrahydrate (Bora-Care) active ingredients (Bayer CropScience, 2011; Nisus Corporation, 2014).
184 The latter product is also labeled for use as a fungicide and algacide on wood. Alternatively, the Real Pine
185 Cleaner Disinfectant Deodorizer uses NPE as an adjuvant for the active antimicrobial agent, pine oil (White
186 Cap Inc, 2012). NPEs are typically mixed with herbicides, insecticides, fungicides and defoliant prior to
187 application based on the small number of commercially available co-formulated products. In organic
188 agriculture, NPEs may only be used as adjuvants in combination with natural substances (i.e., essential oils
189 and natural products) or synthetic materials approved for specific purposes on the National List.

190 **Status**

191
192 **Historic Use:**

193 NPEs are high-volume chemicals that have been used for more than 50 years as detergents, emulsifiers,
194 wetting agents and dispersing agents (Health Canada, 2001). The available literature does not indicate
195 when NPEs were first used as adjuvants with agricultural pest control products. In addition, no
196 information was identified concerning the historic or present use of NPEs in organic agriculture. Although
197 the use pattern in organic agriculture should be similar to conventional practices, the number of approved
198 active ingredients with which the substance can be mixed is markedly reduced in organic crop production.

199 **Organic Foods Production Act, USDA Final Rule:**

200 Synthetically produced adjuvants are eligible for use in organic production according to the requirements
201 of Section 2118 of the Organic Foods Production Act of 1990 (OFPA). Specifically, the OFPA states that the
202 National List may allow the use of substances that would otherwise be prohibited under organic

203 regulations (i.e., synthetics) if the substance contains “synthetic inert ingredients that are not classified by
204 the Administrator of the Environmental Protection Agency as inert ingredients of toxicological concern” (OFPA
205 2118(c)(B)(ii)). NPE is not listed on the US EPA List 1 – Inert Ingredients of Toxicological Concern.

206 The NOP final rule currently allows synthetic inert ingredients designated as EPA List 4 – Inerts of
207 Minimal Concern – and EPA List 3 – Inerts of unknown toxicity – for use with “nonsynthetic substances or
208 synthetic substances listed in this section and used as an active pesticide ingredient in accordance with any
209 limitation on the use of such substances” in organic crop production (7 CFR 205.601(m)). EPA List 3 inert
210 ingredients are permitted for use only in passive pheromone dispensers. In addition, EPA List 4 inert
211 ingredients may be used with nonsynthetic substances or allowed synthetic substances in organic livestock
212 production (7 CFR 205.603(e)). The following nonylphenol ethoxylate formulations are included on EPA
213 List 4B and approved for use as inert ingredients in organic crop and livestock production: ethoxylated p-
214 nonylphenol (CAS# 26027-38-3), polyethylene (1,1,3,3-tetramethylbutyl)phenyl ether (CAS# 9036-19-5),
215 polyoxyethylene dodecylphenol (CAS# 9014-92-0) and polyoxyethylene nonylphenol (CAS# 9016-45-9).

216 **International**

217 A review of the organic regulations and standards from selected international organizations—including the
218 Canadian General Standards Board (CAN, 2011), Codex Alimentarius Commission (Codex, 2013),
219 European Union (EC, 2008), Japanese Ministry of Agriculture, Forestry and Fisheries (JMAFF, 2012) and
220 International Federation of Organic Agriculture Movements (IFOAM, 2014) – revealed that only Canadian
221 regulations explicitly address the use of NPE adjuvants in organic crop production. Canadian organic
222 regulations permit the use of NPEs consisted with the rationale developed by the USDA National Organic
223 Program. According to the Canadian Organic Production Systems Permitted Substances Lists, “only
224 formulants that are classified by the Pest Management Regulatory Agency (PMRA) in Regulatory Note
225 REG2007-04 as List 4A or 4B or are non-synthetic may be used with substances in par. 4.3 that are applied
226 directly to crops” (CAN, 2011). The PMRA List of Formulants includes p-nonylphenol ethoxylated
227 (CAS#26027-38-3) and polyoxyethylene nonylphenol (CAS#9016-45-9) as List 4B, thereby allowing use of
228 these materials in combination with approved active substances (PMRA, 2010).

229 **Evaluation Questions for Substances to be used in Organic Crop or Livestock Production**

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231 **Evaluation Question #1: Indicate which category in OFPA that the substance falls under: (A) Does the**
232 **substance contain an active ingredient in any of the following categories: copper and sulfur**
233 **compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated**
234 **seed, vitamins and minerals; livestock parasiticides and medicines and production aids including**
235 **netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is**
236 **the substance a synthetic inert ingredient that is not classified by the EPA as inert ingredients of toxicological**
237 **concern (i.e., EPA List 4 inert ingredients) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert**
238 **ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part**
239 **180?**

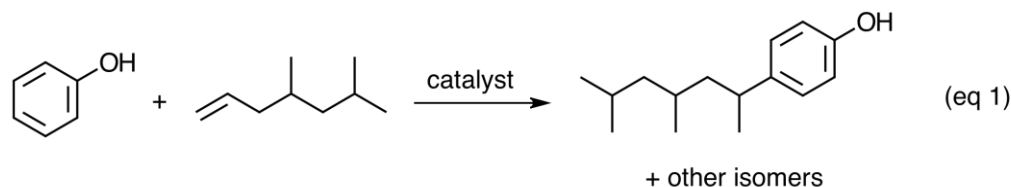
240 (A) Nonylphenol ethoxylates (NPEs) are used as inert ingredients, and do not contain any of the active
241 substances listed in the Organic Foods Production Act (OFPA 2118(c)(B)(i)).

242 (B) NPE is not listed on the US EPA List 1 – Inert Ingredients of Toxicological Concern (US EPA, 2004b).
243 Rather, several forms of the substances are included in EPA List 4B – Other ingredients for which EPA has
244 sufficient information to reasonably conclude that the current use pattern in pesticide products will not
245 adversely affect public health or the environment (US EPA, 2004a).

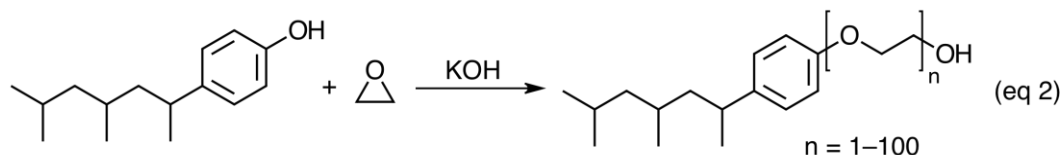
246 **Evaluation Question #2: Describe the most prevalent processes used to manufacture or formulate the**
247 **petitioned substance. Further, describe any chemical change that may occur during manufacture or**
248 **formulation of the petitioned substance when this substance is extracted from naturally occurring plant,**
249 **animal, or mineral sources (7 U.S.C. § 6502 (21)).**

250 The synthesis of NPE is a two-step procedure, first involving production of NP from phenol and alkenes
251 via Friedel Crafts alkylation, followed by one or several iterations of the NP ethoxylation reaction using
252 excess ethylene oxide and catalytic amounts of potassium hydroxide. Details regarding these individual
253 synthetic steps are provided in the following paragraphs.

254 NP is produced on an industrial scale through alkylation of phenol under acid catalysis. According to one
 255 production process, a mixture of NP and propylene trimer (a mixture of nonene isomers) undergoes two
 256 successive alkylation reactions mediated by a macroporous, anhydrous (water-free) ion-exchange resin
 257 catalyst at elevated temperatures of 100–120 °C (equation 1). The product mixture of the second reaction
 258 step is distilled to afford purified NP, and the phenol and propylene trimer recycled for use in subsequent
 259 reactions (Fiege, 2000). Due to skeletal rearrangements that occur during the oligomerization of propylene
 260 to form nonene, commercial grade nonene generally exists as a complex mixture of alkenes, mostly tri- and
 261 tetrasubstituted mono-alkenes (Lorenc, 2003). Nonene is fractionally distilled to produce technical nonene
 262 consisting of approximately 90% C9 (nonene) alkenes and 10% C8 (octenes) and C10 (decenes) alkenes. The
 263 two commercial purity grades of para-NP are technical grade, which is primarily composed of para-NP
 264 (85–90%) with 10–12% ortho-NP and up to 5% 2,4-dinonylphenol, and high purity para-NP containing a
 265 minimum of 95% para-NP and only a trace of 2,4-dinonylphenol (Lorenc, 2003). A generic reaction between
 266 phenol and one component of the propylene trimer mixture is shown in equation one. Other methods of
 267 NP synthesis – including Friedel-Crafts alkylations using AlCl₃ or FeCl₃ catalysts – have been used for
 268 small scale syntheses, but not likely for industrial production of nonylphenol (Boehme, 2010).



269
 270 According to US EPA, the primary use of NP is as an intermediate in the manufacture of NPEs. The
 271 industrial production of NPE involves reaction of NP with ethylene oxide in the presence of an alkaline
 272 catalyst, mostly in the form of potassium hydroxide (KOH) (US EPA, 2010; Dow, 2010). The ratio of
 273 ethylene oxide to NP determines the length of the ethoxylate (EO) chain and thus the molecular weight of
 274 the NPE molecules produced (Dow, 2010). These ethoxylation reactions are considered semibatch processes
 275 in which the starting NP and base (potassium hydroxide) are charged to the reaction vessel and the system
 276 is heated to greater than 100 °C as water is removed to shift the equilibrium from potassium hydroxide
 277 base to the potassium phenoxide base (McDaniel & Reese, 2009). Air is cleared from the reactor and
 278 replaced with inert nitrogen (N₂) gas before ethylene oxide is incrementally added to the system. The rate
 279 of ethylene oxide addition is controlled by the ability to dissipate the heat of reaction and maintain
 280 ethylene oxide in a safe operating range (McDaniel & Reese, 2009). The process continues until ethylene
 281 oxide is completely consumed, at which point the catalyst is neutralized with an organic acid. To increase
 282 the degree of ethoxylation, shorter-chain NPEs produced in one step may be subjected to subsequent base-
 283 catalyzed reactions with ethylene oxide until the desired EO count is achieved (McDaniel & Reese, 2009).



284
 285 **Evaluation Question #3: Discuss whether the petitioned substance is formulated or manufactured by a**
 286 **chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).**

287 According to USDA organic regulations, the NOP defines synthetic as “a substance that is formulated or
 288 manufactured by a chemical process or by a process that chemically changes a substance extracted from
 289 naturally occurring plant, animal, or mineral sources” (7 CFR 205.2). NPEs are not naturally occurring
 290 chemicals and are not directly generated from naturally occurring materials. Instead, NPEs and NP
 291 precursors must be obtained through chemical synthesis to allow the production of commercially available
 292 NPE surfactants and adjuvants. The primary industrial method for NP preparation involves the
 293 combination of phenol and mixtures of nonenes, both of which are derived from petroleum products and
 294 therefore considered synthetic materials. NPs are then subjected to high pressures of ethylene oxide under
 295 alkaline conditions to afford the desired NPEs used in combination with pesticides in conventional and
 296 organic crop production. It therefore follows that NPEs of varying composition are synthetic substances

297 based on NOP definitions, as well as the use of chemical reagents and solvents during production,
298 processing and product formulation. This assessment is consistent with the NOSB's classification of US
299 EPA List 4B Inerts – which includes several NPEs and related chemicals – as synthetic materials approved
300 for use as inert ingredients with naturally occurring or approved synthetic active ingredients.

301 **Evaluation Question #4: Describe the persistence or concentration of the petitioned substance and/or its**
302 **by-products in the environment (7 U.S.C. § 6518 (m) (2)).**

303 Use of NPEs as surfactants and dispersing agents in pesticides will result in releases to the environment
304 through various waste streams. This section provides a summary of available information regarding the
305 environmental fate and persistence of NPEs and their ultimate breakdown product, NP.

306 **Nonylphenol Ethoxylates.** NPEs readily cycle between environmental compartments¹, and are chemically
307 broken down according to a variety of degradation processes. If released to the atmosphere, small
308 oligomers (0–2 ethoxylate units) may exist in both the vapor and particulate phases, while larger oligomers
309 are expected to exist solely in the particulate phase (HSDB, 2012). Particulate-phase NPEs may be removed
310 from air through both wet and dry deposition. NPEs do not contain chromophores (substituents with
311 photochemical activity) that absorb at wavelength greater than 290 nanometers, and are thus unlikely to be
312 susceptible to direct photolysis in sunlight (HSDB, 2012). NPEs released to waterways are likely to adsorb
313 to suspended solids and sediment. Volatilization from water surfaces and moist soil is not expected to be
314 an important fate process based on the measured Henry's Law constants for NP6EO (4.1×10^{-12}
315 $\text{atm} \cdot \text{m}^3/\text{mole}$) and NP (2.45×10^{-9} $\text{atm} \cdot \text{m}^3/\text{mole}$). The estimated bioconcentration factor (BCF) of less than
316 1.4 suggests that bioaccumulation in aquatic organisms such as fish and aquatic invertebrates should be
317 low for NPEs (HSDB, 2012). The constituents of NPE mixtures are expected to have moderate mobility in
318 soils. NP and small oligomers (NP1EO and NP2EO) released to soils are likely to adsorb suspended solids
319 and sediments, while higher molecular weight NPEs with greater water solubility should not adsorb to
320 sediment (HSDB, 2012). In addition, NPEs are not expected to volatilize from dry soil surfaces based on the
321 available vapor pressure data (HSDB, 2012).

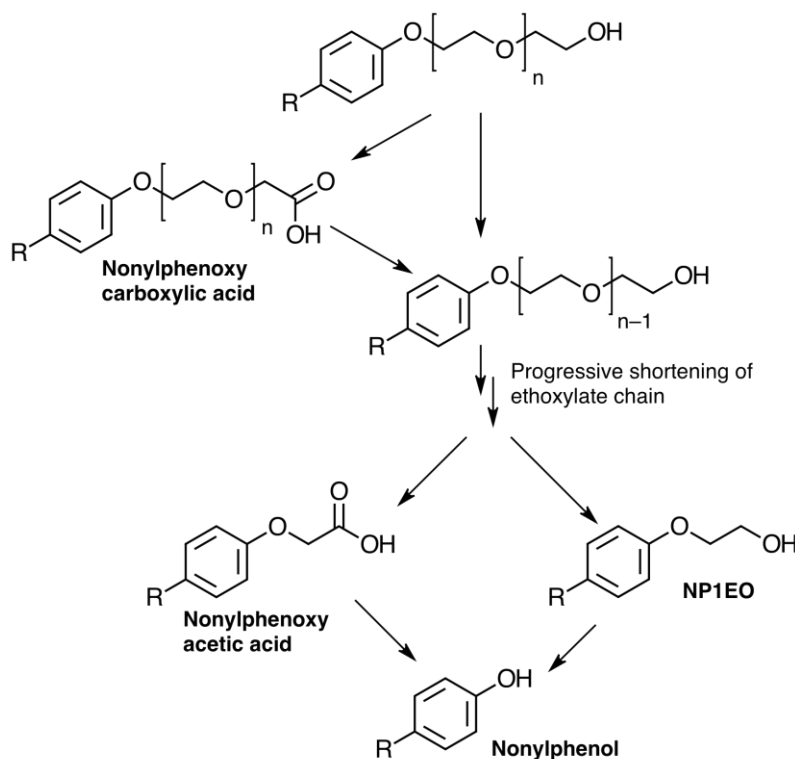
322 Microbial biodegradation is the primary breakdown process for NPEs released to soils and waterways.
323 NPEs are released most often to sewage treatment plants, where they are degraded to NPEs with shorter
324 ethoxylate chains (UE EPA, 2010). Aerobic biodegradation of NPE mixtures in moist soil provides
325 nonylphenol diethoxylate (NP2EO) and nonylphenol ethoxylate (NP1EO) with 68–91% degradation of the
326 parent NPEs within 8–21 days (HSDB, 2012). These shorter-chain NPEs are then further degraded to NP
327 (US EPA, 2005). Microbial degradation of NPEs in sewage sludge, soils and waterways occurs through a
328 mechanism of stepwise loss of ethoxylate groups to form lower ethoxylated congeners, carboxylated
329 products and ultimately NP (Scheme 1). The intermediate and final products of microbial metabolism are
330 more persistent than the parent long-chain NPEs; however, soil and water microbes are expected to
331 ultimately metabolize these intermediates and mineralize NP to carbon dioxide (Health Canada, 2001).
332 Temperature strongly influences the rate of NPE biodegradation, with breakdown of these compounds at
333 22.5 °C occurring at rates 2–10 times the corresponding rate at 13 °C (Soares, 2008). Primary biodegradation
334 of longer-chain NPEs is readily achievable, but ultimate biodegradation of NP1EO, NP2EO, carboxylate
335 derivatives and NP is considerably slower. Indeed, more than 60% of the higher-chain NPEs that enter
336 wastewater treatment plants exit the facility as stable metabolites such as short-chain NPEs and NP in the
337 effluents or sludges (Health Canada, 2001).

338 **Nonylphenol.** NP is a clear to pale yellow viscous liquid at room temperature with moderate water
339 solubility and vapor pressure, indicating the potential for mobility between environmental compartments.
340 Indeed, research has indicated that there may be water-to-air volatilization that results in significant
341 atmospheric concentrations of NP (Health Canada, 2001). NP is unlikely to be persistent in air due to
342 atmospheric hydroxyl radical-mediated degradation pathways (half-life = 0.3 days). In sewage treatment
343 plants, NP partitions preferentially adsorbs to sludge biomass; however, the substance is likely to partition
344 between water and sediment when released to aquatic environments (US EPA, 2005; Health Canada, 2001).
345 In contrast to ethoxylated NP, the phenol core of NP is photosensitive, making NP susceptible to photolysis

¹ The term "environmental compartments" refers to different areas of the environment (e.g., air, water, sediments, and biota) where chemical contaminants may be transported, sequestered and decomposed.

346 when present on the surface of water (photolysis half-life = 10–15 hours) (Health Canada, 2001). NP
 347 undergoes microbial biodegradation in surface waters with an estimated half-life of approximately 150
 348 days in the absence of light (Health Canada, 2001).

349 Studies have found that NP residues are more persistence in landfills under anaerobic conditions when
 350 compared to aerobic conditions, suggesting similar decomposition behavior for NP in soils. A variety of
 351 chemical and environmental factors influence biodegradation of NP; as such, half-lives for NP aerobic
 352 (with oxygen) degradation in sewage sludge and sediment ranged range from 1.1 to 99 days (Mao, 2012).
 353 The U.K. Environment Agency estimated that primary biodegradation of NP in soils occurs with a half-life
 354 of about 30 days, while ultimate mineralization of NP to carbon dioxide has an estimated half-life of 300
 355 days (Health Canada, 2001). Biodegradation experiments using laboratory soil microcosms (small
 356 replicated soil environments) supplemented with NP-contaminated sewage sludge demonstrated that
 357 microorganisms capable of mineralizing NP are naturally occurring in cultivated agricultural soils, as well
 358 as non-cultivated and pristine arctic soils (Topp & Starratt, 2000). A related study demonstrated rapid
 359 disappearance of initial NP soil concentrations of 5.5 mg/kg soil, and reported that NP was undetectable in
 360 these soils after 90 days (Health Canada, 2001). The work of Topp & Starratt (2000) indicates that soil
 361 contaminated with high concentrations of NP under conditions of low temperature and soil oxygen levels
 362 will exhibit slower rates of NP mineralization and thus greater persistence of this substance.



363

364 **Scheme 1. Microbial metabolism of NPEs likely involves the progressive removal of ethoxylate groups**
 365 **through either ether cleavage or terminal alcohol oxidation followed by cleavage of the resulting**
 366 **carboxylic acid. Adapted from Warhurst, 1995.**

367 **Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its**
 368 **breakdown products and any contaminants. Describe the persistence and areas of concentration in the**
 369 **environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).**

370 Although NPEs can be irritating to the skin and eyes, NPEs with greater than three EO groups are
 371 classified as slightly toxic to practically non-toxic on an acute exposure basis (Bakke, 2003). NP9EO is
 372 considered minimally to severely irritating to rabbit skin, and moderately to severely irritating to rabbit
 373 eyes. Acute doses of NP9EO lethal to 50% of the experimental population (LD₅₀) are somewhat variable
 374 among experimental animals, with LD₅₀ ranges of 1,410–5,600 mg/kg in rats and 620–4,400 mg/kg in
 375 rabbits, mice and guinea pigs (Bakke, 2003; Health Canada, 2001). The corresponding acute LD₅₀ values for

376 the shorter-chain NP4EO in rats vary between 4,290 and 7,400 mg/kg (Health Canada, 2001). Based on the
377 low level of toxicity observed in acute exposure studies for NP9EO and NP4EO, NPEs would be placed in
378 US EPA Toxicity Categories III or IV as slightly toxic to practically non-toxic substances (Bakke, 2003). The
379 toxicity of NP is somewhat higher than that observed for NP4-9EO; however, the LD₅₀ values for NP (580-
380 1,620 mg/kg) indicate that NP is slightly toxic (Toxicity Category III) to mammals (Health Canada, 2001;
381 Bakke, 2003).

382 Subchronic and chronic testing of NPE and NP in rats and beagles indicates that the liver and kidney are
383 the organs most likely affected by exposure to these substances (Bakke, 2003). In a 90-day subchronic
384 feeding study, rats were fed NP9EO in the diet at doses of 10, 50, 250 and 1,250 mg/kg-day. There was a
385 slight decrease in kidney weight and liver polysaccharide content at the 50 mg/kg-day and higher dose
386 levels, leading to determination of a No Observed Adverse Effect Level (NOAEL) of 10 mg/kg-day. The
387 main adverse effect observed in a related rat feeding study was retardation of weight gain at dietary
388 NP9EO intakes exceeding 65 mg/kg-day (Bakke, 2003). It is unclear based on the available information
389 whether the reduction in body weight gain is a result of decreased consumption of NPE contaminated
390 food. In a third study, increased liver weight was observed in both male and female rats exposed to
391 moderate NP9EO doses of 66-75 mg/kg-day in rat feed (Bakke, 2003). Compared to rats, beagles are
392 significantly less sensitive to NPE dietary exposure on a subchronic (90-day feeding) basis. Only a decrease
393 in body weight gain – related to a voluntary decrease in contaminated food consumption – was observed in
394 beagles at the highest doses of NP9EO tested (approximately 170 and 1,200 mg/kg-day). The NOAEL for
395 this beagle study is approximately 11-15 mg/kg-day. In other dietary beagle studies using NP4EO,
396 vomiting occurred during the first three weeks of dietary exposure at high doses (200 mg/kg-day);
397 however, changes in liver weight were not consistently observed even at high doses (Bakke, 2003).

398 Chronic exposure to NPE and NP has also been evaluated in laboratory animals. Few adverse effects have
399 been reported as a result of daily dietary exposure of rats and beagles to NP9EO and NP4EO over the
400 course of two years. Indeed, only reduced weight gain was observed in rats provided high dietary doses
401 (200 and 1,000 mg/kg-day) due to poor palatability of the diet. The only effect attributable to treatment in
402 beagles was an increase in relative liver weight at the highest dose tested (88 mg/kg-day) (Bakke, 2003). No
403 evidence of carcinogenicity was reported in 2-year chronic oral toxicity studies of NP9EO with rats and
404 dogs. NPEs do not appear to be immunotoxic or neurotoxic at doses considered protective of kidney or
405 liver effects. No evidence of carcinogenicity was reported in any of the two-year chronic toxicity studies of
406 NP9EO with rats and dogs. Further, intravaginal dosages of NP9EO in rats of up to 20 times the rates
407 recommended for use in humans as a spermicide administered over the course of two years provide no
408 evidence of carcinogenicity related to NPE exposure. The available chronic exposure studies also provide
409 no evidence of carcinogenesis for NP (Bakke, 2003).

410 It should also be noted that ethylene oxide has been found in NP9EO at low levels (i.e., up to 12.2 mg/L) in
411 unreacted form as a residual substance from the manufacturing process (Bakke, 2003). Ethylene oxide has
412 been described as a probable human carcinogen with sufficient evidence in experimental animals to
413 support a finding as a carcinogen (IARC, 2014; OEHHA, 2014). The substance also exhibits mutagenic
414 activity in laboratory testing (Bakke, 2003). Based on the available information, it is uncertain whether
415 manufacturing processes have been improved to reduce the concentration of ethylene oxide in finished
416 NPE formulations.

417 NP and NPE exhibit estrogenic activity based on the results of both *in vitro* and *in vivo* tests involving
418 terrestrial and aquatic organisms (Bakke, 2003). Endocrine disruptors are substances that can disturb the
419 hormonal system by mimicking the occurrence of naturally occurring hormones (e.g., estrogen), blocking
420 their production, and/or inhibiting or stimulating the endocrine system. NP and, to a lesser extent, short-
421 chain NPEs have been found to mimic the natural hormone 17- β -estradiol by competing for the binding
422 site of the estrogenic receptor due to their structural similarities of these species (Soares, 2008). The
423 available data suggests that, in comparison to natural estrogen 17- β -estradiol, NP is approximately 1,000 to
424 100,000 times weaker in eliciting estrogenic responses (Bakke, 2003). NPE has been found to be weakly
425 estrogenic using *in vitro* tests, but is less potent than NP by one to three orders of magnitude (i.e., 10X to
426 1,000X). One study found that NP, NP1EO and NP2EO stimulated cell proliferation in MCF-7 human
427 breast cancer cells, which indicated estrogenic activity. In contrast, results of a recombinant estrogen yeast

428 screen assay showed that NP12EO exhibited no estrogenic effects (Bakke, 2003). A three-generation feeding
429 study found reproductive effects – including decreased epididymal sperm density and testicular spermatid
430 head counts (males), as well as increased estrus cycle length and decreased ovarian weights (females) –
431 only in experimental rats exposed to the highest levels of NP (650 and 2,000 mg/kg) in the diet (NTP, 1997).
432 Based on the body of available data, it has been concluded that NPEs with greater than three EO groups
433 have little, if any, estrogenic effect, and the estrogenic activity of these substances appears to decrease with
434 increasing EO number. As described in Soares *et al.* (2008), the endocrine disrupting potential of NP is
435 complicated:

436 *The capacity of nonylphenol to disrupt the endocrine system, measured as the no-observed-effect*
437 *concentration (NOEC), is frequently found to be far higher than the concentrations of nonylphenol found in*
438 *the environment. However, this does not mean that nonylphenol is not implicated, but rather in the*
439 *environment there exists more than one stress factor or contaminant that might adversely affect the*
440 *organism. In the case of xenoestrogens, it has been demonstrated in several investigations that the effect of*
441 *two or more compounds with endocrine disruption capacity, even at low concentrations, can be additive or*
442 *synergistic.*

443 A limited amount of information is available regarding the toxicity of NPE and NP to other terrestrial
444 organisms, including birds, invertebrates and plants. In one study, bobwhite quail chicks exposed to
445 NP9EO in the diet for five days at concentrations ranging from 0 to 5,000 parts per million (ppm) exhibited
446 no adverse behavioral effects, and no mortality was observed in this study (Bakke, 2003). Toxicity to
447 terrestrial invertebrates is commonly assessed using the honey bee. One such study involved the
448 application of excessively high spray volumes of aqueous surfactant solutions to anesthetized bees placed
449 in a petri dish. For the alkylphenol ethoxylate (APE) surfactant, concentrations up to 0.1% in water at a rate
450 equivalent to 205–250 gallons per acre were applied to test bees. It was found that concentrations above
451 0.031% resulted in increased mortality over controls; however, the authors speculated that the observed
452 lethal effects are due to drowning rather than the toxicity of the surfactant (Bakke, 2003).

453 Concerns have been expressed regarding acute and chronic toxicity of NPE and NP to aquatic organisms
454 (Bakke, 2003; US EPA, 2010). Ninety-six hour 50% lethal concentrations (LC₅₀) for exposure of fathead
455 minnow, rainbow trout and Japanese medaka to NP9EO in standard toxicity tests range from 4–14 ppm,
456 indicating NPEs are slightly to moderately toxic to aquatic organisms (Bakke, 2003). In addition,
457 subchronic NOECs for NPEs typically range from 1–23 ppb based on laboratory studies using various fish
458 species. Acute and chronic toxicity values for NP9EO are one to three orders of magnitude lower than the
459 corresponding values for NP, with the toxicity values of NPEs tending to decrease with increasing
460 ethoxylation (EO groups). However, the results of one study in *Moina macrocopa* (a type of water flea)
461 indicated that the toxic effects of NP10EO and NP mixtures are more severe than those related to the
462 individual chemicals for this aquatic invertebrate species (Hu, 2014). The available acute and chronic
463 toxicity data of NP to aquatic organisms indicates that NP is highly toxic to fish, aquatic invertebrates and
464 aquatic plants. Indeed, most 96-hour LC₅₀ values for exposure of tested fish species to NP range from 0.1–
465 0.46 ppm (Bakke, 2003).

466 Similar to the result for mammals, experimental studies have indicated that the direct toxicity of NP may
467 be of greater concern than estrogenic effects (Schwaiger, 2000). The relative toxicity (based on LC₅₀) of
468 NPEs and NP can be expressed as follows: NP > NP1–3EO > NP1–3EC > NP4–9EO, where EO refers to
469 ethoxylates and EC refers to carboxylate breakdown intermediates (Health Canada, 2001). Likewise, the
470 relative estrogenic potency of these species can be represented as NP > NP1–2EO > NP1–2EC > NP9EO
471 (Health Canada, 2001). Multiple studies have demonstrated the ability of NP and the short chain congeners
472 NP1EO and NP2EO to increase vitellogenin levels in the isolated hepatocytes of rainbow trout as well as
473 the serum of adult male and female fish species (Bakke, 2003). Vitellogenin is a protein that naturally
474 occurs in the serum of adult female non-mammalian species during egg production; its presence in the
475 blood of male fish can thus serve as an indicator of exposure to endocrine active substances (Bakke, 2003).
476 In a year-long exposure study, NP induced vitellogenin production at concentrations as low as 1–10 µg/L,
477 equivalent to one part per billion in some of the exposed rainbow trout (Ackermann, 2002). It was further
478 determined that these field-realistic NP concentrations that cause increased vitellogenin product had no
479 effect on rainbow trout hatching rate, body weight, sex ratios of offspring, or the development of testis/ova
480 in males. The induction of vitellogenin may thus be the most sensitive endpoint for exposure to NP, but

481 does not necessarily correspond to reproductive harm to male fish at low concentrations (Ackermann,
482 2002).

483 Based on the available aquatic toxicity data, non-reproductive toxicity is likely to be more critical to
484 experimental animals than toxicity associated with the estrogenic activity of NP. Reproductive effects
485 potentially associated with the endocrine activity of NP, such as programmed cell death in spermatocytes
486 and other testicular cells of exposed Japanese rice fish, only occurs at relatively high concentrations (e.g.,
487 100 µg/L) (Bakke, 2003). Further, the 90-day NOEC for NP in rainbow trout based on growth effects is
488 6 µg/L, while the minimum concentration required for vitellogenin induction in the same species is
489 20 µg/L (Bakke, 2003). The monitored concentrations of NP in United States lakes and rivers, which
490 typically ranges from 0.01 to 1.0 µg/L, suggests that vitellogenin induction and any related reproductive
491 effects are unlikely to result from NP exposure in US waters not directly adjacent to an NP application or
492 spill site (US EPA, 2010).

493 **Evaluation Question #6: Describe any environmental contamination that could result from the**
494 **petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).**

495 There is general agreement among experts in the scientific community that widespread, low-concentration
496 environmental contamination with NPEs and NP exists (Porter & Hayden, 2002). The most common route
497 of NPE and NP entry into the environment is through wastewater, although large-scale use of NPEs as
498 dispersing agents with pesticides will also result in releases to soil, groundwater and nearby surface
499 waters. Landfilling of sludge, or the application of sewage sludge or pulp and paper mill sludge to
500 agricultural soils also represent common pathways for these substances to the terrestrial and even aquatic
501 environments (Careghini, 2014). NPEs used in domestic laundry detergents, industrial soaps and cleansers,
502 cosmetics and paints are discharged to the sewer system and travel to wastewater treatment plants. Under
503 the anaerobic conditions found in sewers, sediments and most treatment operations, NPEs are biodegraded
504 to the more persistent contaminant NP according to the stepwise loss of ethoxylate groups described in
505 Evaluation Question #4. It seems clear that contamination of the terrestrial or aquatic environment
506 associated with use of NPEs will occur in the form of more highly toxic and persist NP.

507 The high degree of hydrophobicity indicates that NP should preferentially adsorb to biosolids, sediments
508 and soils. High concentrations of NP (i.e., 1.45–2.43 mg/kg dry weight) were measured in soils treated with
509 sewage sludge, with detectable residues levels persisting for up to eight years after amendment with sludge
510 had ceased. In contrast, the reported NP concentrations in unamended soils, soils fertilized with manure or
511 with limited amounts of sewage sludge were between 0.01 and 0.98 µg/kg dry weight (Careghini, 2014).
512 Variability of up to four orders of magnitude were observed in the dataset for NP residues in sediment,
513 with reported concentrations ranging from 3.6 µg/kg to 72 mg/kg dry weight. The higher concentrations
514 observed in sediments were generally associated with specific point sources, such as industrial plants or
515 large volumes of domestic wastewater entering a river as it flows through urban areas. Careghini *et al.*
516 (2014) remark specifically “the presence of NP in freshwater sediments was primarily ascribed to domestic
517 and industrial wastes and to a lesser extent by agricultural activities (pesticide applications, sludge
518 amendment, and irrigation with wastewater).” However, the use of NPEs in organic agriculture is
519 ultimately tied to the environmental contamination resulting from the industrial production of NPE
520 adjuvants and associated waste streams from these processes.

521 In addition to soils and sediments, NP has also been detected in groundwater and various surface waters.
522 Recent monitoring of groundwater resulted in measured NP concentrations ranging from below the limit
523 of detection to 3.85 µg/L (Careghini, 2014). According to Luo *et al.* (2014), the observed NP contamination
524 of groundwater is likely associated with the percolation of landfill leachate, water drainage from
525 agricultural land and/or seepage from septic tanks and sewer systems. Measured NP concentrations in
526 surface waters range from 0.0003 to 37.3 µg/L (Careghini, 2014). When working in a single location,
527 researchers often observe higher concentrations in surface sediments than in surface waters due to the high
528 hydrophobicity and propensity of NP to adsorb to suspended solids and eventually accumulate in
529 sediments. NP is spatially distributed similarly in surface waters and sediments, with the highest levels
530 closely related to the influx of industrial or domestic wastewater discharges as well as wastewater
531 treatment plant effluents (Careghini, 2014). NP concentrations are generally lower in the surface waters of
532 rural and agricultural areas when compared to levels in urbanized and industrialized sections of a

533 particular river (Careghini, 2014; Luo, 2014). Despite the general assumption that agricultural lands are
534 minor point sources of NP, an Italian study reported NP concentrations in water samples collected from an
535 agricultural segment of the Tiber River in excess of 0.3 µg/L (Patrolecco, 2006). These NP concentrations
536 are thus comparable to levels detected in effluents from wastewater treatment plants (Careghini, 2014).

537 Certain food items may also contain significant NP residues due to direct application in pesticide sprays
538 and/or contamination of waters, sediments and agricultural land with NPE and NP. Monitoring studies by
539 Dodder *et al.* (2014) reported maximum NP residues levels exceeding 50 µg/kg and detection frequencies
540 of greater than 50% in the tissues of mussels collected along the California coast. The data supports a
541 general trend of increasing NP residue levels in mussel tissue with increasing urbanization of the sampling
542 site. High NP concentrations have also been reported in related studies of edible marine species from Asia
543 and Europe (Careghini, 2014). Likewise, measured NP residue concentrations in commercially available
544 vegetables and fruits varied between five and 50 µg/kg food weight (Careghini, 2014). For example, Lu *et*
545 *al.* (2013) detected residues of both branched and linear NP in the tissues of pumpkin, carrot, citrus and
546 apple samples purchased in Florida, with the highest concentration of 18.5 µg/kg being reported for citrus.
547 Experiments investigating the accumulation of NP in various parts of lettuce and collard plants indicate
548 minimal translocation of NP from the roots to upper leaves when plants are grown soils contaminated with
549 NP. Indeed, Dodgen *et al.* (2013) reported NP concentrations of 1.18–4.31 µg/kg (lettuce) and 3.79–
550 6.95 µg/kg (collards) in the stems and leaves versus 926.9 and 339.2 µg/kg in the roots of lettuce and
551 collards, respectively.

552 NPEs do not exhibit the high levels of toxicity, estrogenic activity or environmental persistence associated
553 with NP. However, release of NPEs to the environment from agricultural and consumer products
554 ultimately leads to the introduction of more highly toxic and persistent NP residues. A lifecycle analysis of
555 NPEs therefore highlights a conflict between use of these substances and the principles of organic
556 agriculture, which seeks to avoid contamination of the environment with toxic and persistent substances.

557 **Evaluation Question #7: Describe any known chemical interactions between the petitioned substance**
558 **and other substances used in organic crop or livestock production or handling. Describe any**
559 **environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).**

560 According to the Materials Safety Data Sheet (MSDS) for Tergitol® NP-9, NPEs are not chemically
561 compatible with acids, strong bases and strong oxidizing agents (Sigma Aldrich, 2014). Further, any other
562 materials that may react with hydroxyl groups should not be combined with or brought into proximity of
563 NPE solutions to avoid potentially violent chemical reactions (Dow, 2010). The MSDS recommends that
564 manufacturers and users of NPE products keep containers of these materials tightly closed in dry and well-
565 ventilated locations for safe storage and to avoid reactions with incompatible substances. Opened
566 containers of NPEs should be carefully resealed and kept upright to prevent leakage to the surroundings.
567 The available literature also indicates that NPE-based surfactants are unlikely to interact, either
568 synergistically or antagonistically, with the herbicides commonly applied in forestry with regard to human
569 health impacts (Bakke, 2003). Rather, adjuvants such as NPEs used with herbicide and other pesticide
570 sprays break water surface tension to allow more even distribution of the pesticide active ingredient on the
571 target surface (Czarnota & Thomas, 2013).

572 **Evaluation Question #8: Describe any effects of the petitioned substance on biological or chemical**
573 **interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt**
574 **index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).**

575 Domene *et al.* (2009) conducted a series of experiments evaluating the acute toxicity and sublethal effects
576 associated with exposure of plants, earthworms and other soil invertebrates to soil mixtures containing
577 NP8EO or NP. In comparison mammalian and aquatic toxicity tests, the chemicals tested showed
578 contrasting toxicity, with NP being significantly more toxic than NP8EO. The authors also reported
579 substantial differences in sensitivity among of the tested species to these chemicals. Only relatively high
580 NP8EO concentrations in excess of 10 g/kg soil would be required to suppress germination by 50% relative
581 to controls (EC₅₀) in *Brassica rapa* (a dicot plant) and *Lolium perenne* (a monocot plant), suggesting NPEs are
582 not acutely toxic to plants (Domene, 2009). The test plants were more sensitive to NP exposure, but only
583 moderate toxicity was observed since EC₅₀ values were consistently above 1 g/kg soil (i.e., the threshold
584 concentration of concern). NP8EO and NP were also tested in three soil invertebrate species, including

585 *Eisenia andrei* (earthworm), *Enchytraeus crypticus* (annelid worms) and *Folsomia candida* (soil arthropod) –
586 were less sensitive to NP8EO compared to NP. Concerning the effects on survival of these invertebrates,
587 NP8EO exhibited a lower acute toxicity ($LC_{50} = 747$ to greater than 3,000 mg/kg) compared to the effects
588 observed for NP ($LC_{50} = 69$ to 615 mg/kg). Reproduction of these invertebrates was effected at somewhat
589 lower concentrations for NP8EO ($EC_{50} = 356$ to 1,876 mg/kg) and NP (64 to 226 mg/kg). Effects on
590 earthworm total biomass occurred at higher concentrations of both substances in soils (Domene, 2009). The
591 authors conclude there is a low ecological risk of NPEs for plants and soil invertebrates since the normal
592 soil concentrations (i.e., below 2.6 mg/kg) are significantly lower than any of the concentrations associated
593 with toxicity in this study.

594 Naturally occurring soil microbes are capable of utilizing NPE and NP with little or no lag phase, at
595 applied concentrations of NP in the soil ranging from one to 250 mg/kg. These observations suggest a
596 general lack of toxicity of both NPE and NP to most soil microorganisms at concentrations typically
597 observed in soils (Bakke, 2003). Few studies have demonstrated effects of NPEs on bacteria, which
598 generally appear to be more tolerant of NPEs than other organisms (Health Canada, 2001). Toxicity studies
599 using *Photobacterium phosphoreum* and other bacterial strains revealed a decrease in toxicity with NPEs of
600 increasing EO chain length, growth inhibition only at high concentrations, and growth stimulation at low,
601 environmentally relevant concentrations (Health Canada, 2001). Mineralization of the more persistent
602 metabolite (NP) has been observed in a variety of soil types – including agricultural soils with various
603 textures, non-cultivated temperate soils and soils from the Canadian tundra – through the metabolic
604 actions of presumably diverse microbial populations (Topp & Starratt, 2000). Although NP undergoes
605 aerobic degradation in water, sediment and soil systems, high concentrations of the substance can be toxic
606 to microorganisms (Careghini, 2014).

607 Little information is available regarding the potential or actual impacts of the substance on endangered
608 species and populations or the potential for measurable reductions in genetic, species or eco-system
609 biodiversity. NP has exhibited estrogenic activity in numerous laboratory studies; however, the doses of
610 NP required to elicit estrogenic responses are generally higher than the endpoints for non-reproductive
611 toxicity. In studies of terrestrial invertebrates, reproductive effects associated with NPE and NP exposure
612 occur at concentrations significantly higher than environmentally relevant levels in soil. Higher
613 concentrations of NPEs and NP in soils resulting from large-volume spills could impact the reproductive
614 health and survival of beneficial soil invertebrates, such as earthworms. Likewise, higher concentrations of
615 these substances could impact biodiversity in the affected area since tolerant species can more easily adapt
616 to these environmental stressors.

617 **Evaluation Question #9: Discuss and summarize findings on whether the use of the petitioned**
618 **substance may be harmful to the environment (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A)**
619 **(i)).**

620 Pesticide mixtures containing NPE surfactants are applied in agricultural settings to control weeds, insects
621 and plant pathogens. NPEs will necessarily be released to the environment according to this use pattern
622 in conventional and organic crop production.

623 The constituents of NPE mixtures are expected to have moderate mobility in soils, with variation in this
624 parameter based on the degree of ethoxylation (HSDB, 2012). Only the metabolite NP and smaller
625 oligomers (NP1EO and NP2EO) expected to adsorb suspended solids and sediments. Microbial
626 degradation is the primary break down process, and occurs rapidly for NPEs with greater than three EO
627 groups. Under aerobic conditions, higher molecular weight NPEs biodegrade to NP1EO and NP2EO with
628 68–91% conversion over the course of 8–21 days (HSDB, 2012). The short chain oligomers are more slowly
629 transformed to NP, which is itself persistent in the environment. According to Health Canada (2001), more
630 than 60% of the higher-chain NPEs that enter wastewater treatment plants exit the facility as stable
631 metabolites such as short-chain NPEs and NP in the effluents and sludges. The ultimate metabolite, NP, is
632 persistent in soil and water with respective half-lives of 30 and 150 days (Health Canada, 2001).

633 NPEs are generally considered low to moderate toxicity surfactants based on studies in terrestrial and
634 aquatic organisms. In mammals, NP and the small oligomers NP1EO and NP2EO have exhibited weak
635 estrogenic activity in cell culture assays and live animal studies. The available data suggests that, in
636 comparison to the natural estrogen substrate 17- β -oestradiol, NP is approximately 1,000 to 100,000 times

637 weaker in eliciting estrogenic responses in mammalian species (Bakke, 2003). Acute and chronic toxicity
638 doses for NP9EO are one to three orders of magnitude higher (i.e., lower toxicity) than the corresponding
639 values for the persistent NP metabolite, with decreasing toxicity observed in NPEs with higher degrees of
640 ethoxylation. In contrast to the toxicity level in mammals, the NP metabolite is highly toxic to aquatic
641 organisms (i.e., fish and aquatic invertebrates) based on lethal concentrations and non-reproductive
642 endpoints determined in acute toxicity studies (Bakke, 2003). Low-level exposure to NP has consistently
643 resulted in vitellogenin induction in both male and female fish; however, reproductive effects associated
644 with NP have not been observed at environmentally relevant concentrations. Therefore, the high acute
645 toxicity and non-reproductive effects are considered more sensitive endpoints compared to the potential
646 for endocrine disruption in fish.

647 Virtually every environmental compartment can be contaminated through the use of NPEs. These
648 substances generally enter the environment through wastewater, although large-scale applications of NPE
649 dispersing agents in pesticide mixtures will also result in releases to soil, groundwater and neighboring
650 surface waters. In the long term, contamination associated with NPE use occurs in the form of the more
651 toxic and persistent metabolite, NP. Indeed, low to moderate concentrations of NP have been detected in
652 soils, groundwater and surface water, as well as organisms that live and grow in these media, such as fish,
653 shellfish and various crops (Careghini, 2014). NP concentrations ranging from a few to several hundred
654 parts per billion are commonly found in the tissues of shellfish (e.g., mussels) and raw agricultural
655 commodities, including pumpkin, carrots, citrus and apples (Dodder, 2014; Lu, 2013). The ecological effects
656 associated with chronic exposure to low concentrations of these chemicals remains uncertain.

657 **Evaluation Question #10: Describe and summarize any reported effects upon human health from use of**
658 **the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i) and 7 U.S.C. § 6518**
659 **(m) (4)).**

660 Few adverse effects have resulted from NPE exposure in laboratory animals and human volunteers. NPEs
661 containing four to nine ethoxylate groups are classified as slightly toxic to practically non-toxic to
662 mammals and are thus assigned to US EPA Toxicity Category III or IV (Bakke, 2003). Contact dermatitis
663 and contact photosensitivity have been reported in humans following exposure to NPE mixtures in
664 consumer products (Bakke, 2003). Studies have specifically investigated the effects of human exposure to
665 mixtures primarily consisting of NP6EO, NP10EO and NP12EO. In one experiment, application of NP4EO
666 to the skin on the back resulted in faint to moderate erythema in approximately 32% (i.e., 36 of 111) of
667 human volunteers. Only three of these cases were classified as allergic contact dermatitis (Health Canada,
668 2001). The acute toxicity of the primary metabolite NP is somewhat higher than that observed for NP4-9EO
669 in laboratory mammals; however, the LD₅₀ values for NP (580-1,620 mg/kg) indicate that NP is classified
670 as slightly toxic (Toxicity Category III) to mammalian species (Health Canada, 2001; Bakke, 2003).

671 Many of the studies investigating human exposure to NPEs involve vaginal applications of nonoxynol-9
672 (NP9EO) due to its use in contraceptives as a spermicide. Several studies in which women were exposed
673 intravaginally to NP9EO at doses ranging from 1.5 to 12 mg/kg-day for 14 days indicated no treatment
674 related differences in blood chemistry and liver function (Bakke, 2003). In a related study, female
675 volunteers were exposed to 150 mg NP9EO four times per day for 14 days, which corresponds to a daily
676 dose of 9 mg/kg-day (assuming a 64 kg body weight). Some subjects in this trial experienced vaginal
677 irritation, disruption and redness of the epithelium and bleeding. More severe reactions, including swelling
678 of the application site with bleeding of the cervix, were observed in one of the 14 subjects (Bakke, 2003).
679 This NPE formulation has caused adverse effects when administered at higher doses in rats. For example, a
680 single intravaginal dose of 50 mg/kg NP9EO caused inflammation and necrosis of mucosal cells in the
681 vagina (Bakke, 2003). Although sensitivity to the substance has been observed, the bulk of the available
682 data suggest that NPEs pose a low risk of adverse effects in humans undergoing repeated dermal exposure
683 to these substances.

684 The estrogenic activity associated with exposure to NP has only been observed in whole organisms (i.e., *in*
685 *vivo*) studies in the context of laboratory animals. Decreased sperm density, reduced ovarian weights and
686 other reproductive effects associated with the demonstrated estrogen response generally occur at the
687 highest NP concentrations tested (NTP, 1997). Therefore, it is uncertain whether humans and terrestrial
688 wildlife are at risk of reproductive effects from exposure to NP at the relatively low environmental

689 concentrations that exist. All of the studies suggesting the potential for estrogenic effects in humans
690 associated with NPE and NP exposure were performed using human cell cultures. For example, one study
691 found that NP, NP1EO and NP2EO stimulated cell proliferation in MCF-7 human breast cancer cells, which
692 may serve as an indicator of estrogenic activity in humans (Bakke, 2003). A recent study further
693 demonstrated that NP and 17- β -estradiol induce similar gene expression responses in the MCF-7 cell line,
694 although the response is significantly weaker for NP (Amaro, 2014). It is also known that NP is transferred
695 from the mother to embryo, and the results of cell culture experiments by Bechi *et al.* (2006) using a
696 placental cancer cell line suggest that the human trophoblast (cells that provide nutrients to the embryo)
697 may be highly responsive to NP. In the absence of epidemiological evidence, it is difficult to determine
698 whether the estrogenic activity of NP in cell culture studies is indicative of reproductive and
699 developmental effects in humans.

700 Occupational exposure of agricultural workers to the metabolic breakdown products of NPEs, primarily
701 consisting of NP, is unlikely considering the use pattern in conventional and organic crop production. In
702 agricultural production, workers involved in combining the pesticide and adjuvant solution in a tank mix
703 may be exposed to NPEs through the dermal route. Rain and irrigation water may wash residues of
704 applied NPEs from the surfaces of treated plants to the surrounding soil before workers are involved in
705 intensive crop maintenance activities (e.g., weeding and pruning). Residues of NPEs and metabolites from
706 these treatments are, however, available for uptake from the soil, and post-harvest applications of pesticide
707 sprays containing NPEs may result in the contamination of food for human consumption with NP. Based
708 on the concentration of NP in food (see Evaluation Question #6 for details) and the predicted consumption
709 rates, the average daily intake of NP varies between 0.067 and 0.370 mg/kg-day for adults weighing
710 approximately 60 kilograms (Careghini, 2014). In a survey of Italian women, Ademollo *et al.* (2008)
711 revealed a positive correlation between fish consumption levels and the concentration of NP detected in
712 breast milk. The authors calculated a maximum daily intake of 3.94 μ g/kg-day, which is close to the
713 tolerable daily intake (5 μ g/kg-day) proposed by the Danish Institute of Safety and Toxicology. Based on
714 the available information, diet may represent a major exposure route for segments of the human
715 population not directly involved in the industrial production and use of NPEs and NP.

716 **Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be**
717 **used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed**
718 **substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).**

719 Although naturally occurring surfactants exist, the available literature does not indicate whether these
720 substances are commonly used as adjuvants in pesticide sprays. Many plants produce significant quantities
721 of saponins (steroid or triterpenoid glycosides), which naturally have surfactant properties (Hargreaves,
722 2003). For example, the soapwort plant *Saponaria officianalis* produces a glycoside capable of wetting,
723 foaming and grease dispersion. These natural glycosides are still in use today for specialized processes
724 such as the washing of delicate fabrics (Hargreaves, 2003). Another natural surfactant substance known as
725 lecithin is a fat-based material belonging to the phospholipid class of biomolecules. Phospholipids contain
726 both hydrophobic (fat attractive) and hydrophilic (water attractive) functionality, making lecithin-based
727 materials work well with both oil-soluble and water-soluble pesticides (UAP, 2012). Although lecithin
728 would be considered a natural substance, lecithin derivatives formulated in some surfactant products are
729 obtained from the hydrogenation/hydroxylation of natural soy lecithin and would likely be classified as
730 synthetic materials (UAP, 2012). Depending on the economics of substitution, saponins and lecithin are
731 attractive alternatives due to their natural, plant-based status and minimal likelihood of adversely affecting
732 the growth and productivity of treated plants.

733 A variety of synthetic substances are available as alternatives to NPE-based surfactants. Most nonionic
734 surfactants, such as NPEs, rely on polyethoxylation to provide the hydrophilic moiety (US EPA, 2010).
735 Other surfactants are based on glycerol (glycerin), glucosides, or other sugars existing as either
736 monosaccharides (e.g., sorbitol) or disaccharides (e.g., sucrose). The simplest alternatives to NPEs and
737 other alkylphenol ethoxylates (APEs) include alcohol ethoxylates (AEs) derived from aliphatic
738 (hydrocarbon-based) alcohols instead of nonylphenol or other alkyl phenols. Glucose-based carbohydrate
739 derivatives such as alkylpolyglucoside, glucamides and glucamine oxides may also be viable alternatives
740 in pesticide sprays. Many of these alternatives are less persistent and biodegrade to breakdown products
741 and metabolites with lower degrees of aquatic toxicity than NP (US EPA, 2010).

742 US EPA's Design for the Environment (DfE) program recently completed an alternatives assessment for
743 synthetic surfactants to assist in the voluntary phase-out of NPEs used in industrial detergents (US EPA,
744 2012). The DfE assessment for NPEs reviewed several alternatives to NPE surfactants – including
745 ethoxylated surfactants and glucosides – that are comparable in cost, readily available, and rapidly
746 biodegrade to non-polluting, lower hazard compounds in aquatic environments. The alternatives with
747 greatest molecular similarity to APEs are the alcohol ethoxylates (AEs), which are produced through the
748 reaction of linear or branched fatty alcohols with ethylene oxide. Although AEs are highly toxic to aquatic
749 organisms on an acute basis, these materials are rapidly transformed to lower toxicity degradates in the
750 environment (US EPA, 2012). In addition, ethoxylated and propoxylated [-CH₂CH(CH₃)O-] products of
751 linear or branched alcohols are included on US EPA's List 4B, indicating that these materials could easily
752 serve as alternatives to NPEs in organic crop production (US EPA, 2004). Alkyl polyglucose (APG) is
753 another common alternative prepared through the reaction of fatty alcohols (synthetic derivatives of
754 natural fats and oils) and the natural sugar, glucose. Similar products may also be obtained from other
755 sugars such as sucrose. APG and related sugar-based surfactants have very lower persistence, moderate
756 toxicity to aquatic organisms and rapidly form low toxicity breakdown products (US EPA, 2012).

757 In addition to commonly used AE and glucoside surfactants, sulfonates, sulfate esters and ether sulfates
758 are also potential alternatives to NPEs. Linear alkylbenzene sulfonates (LAS) are produced through a two-
759 step processing involving the acid-catalyzed alkylation of benzene followed by sulfonation of the alkyl
760 benzene intermediate. LASs are highly toxic to aquatic organisms on an acute basis, but produce no known
761 degradates of concern and are rapidly degraded (US EPA, 2012). Like LASs, alkyl sulfate esters are formed
762 through sulfonation (in this case, sulfonation of fatty alcohols), and are low impact alternatives to toxic
763 surfactants. Sodium lauryl sulfate (CAS# 151-21-3) is a common example of the AS chemical class, and is
764 listed on US EPA's 4B List of Inerts (US EPA, 2004). Caution should be exercised in using sodium lauryl
765 sulfate on crops, however, since the substance is also listed as an active ingredient in herbicides, such as
766 the BurnOut Weed & Grass Killer product (Patton & Weisenberger, 2011). Sulfonation of an alcohol
767 ethoxylate (AE) surfactant provides alkyl ether sulfonates (AESs), which US EPA DfE also recommends as
768 an alternative to NPEs based on a low persistence rating and absence of toxic metabolites (US EPA, 2012).

769 The final category of alternative surfactants recommended in the US EPA DfE report is the sorbitan esters.
770 These synthetic surfactants are produced through the reaction of sorbitan (derived from natural sorbitol)
771 and fatty acid methyl esters in the presence of an alkaline catalyst (US EPA, 2012). According to US EPA,
772 the sorbitan fatty acids esters are inert ingredients used as surfactants, related adjuvants of surfactants,
773 emulsifiers, buffering agents and corrosion inhibitors in a variety of pesticide products (US EPA, 2005).
774 Based on the low hazard profile and long history of use, US EPA renewed tolerance exemptions for
775 residues of sorbitan esters used as inert ingredients on crops during the growing season and following
776 harvest (40 CFR 180.910 and 180.920).

777 **Evaluation Question #12: Describe any alternative practices that would make the use of the petitioned**
778 **substance unnecessary (7 U.S.C. § 6518 (m) (6)).**

779 Cultural practices will not replace the intended function of surfactants/adjuvants in organic crop
780 production for enhancing the spread and leaf penetrability of aqueous pesticide solutions. For pesticide
781 applications to be most effective, a high degree of coverage and spread of the spray droplets on the leaf
782 surface is necessary (Zhu, 2012). The utility of surfactants and other adjuvants is most pronounced for
783 hairy or waxy leaf surfaces. Nonionic surfactants are commonly recommended for use in formulations and
784 tank mixtures of foliar-applied spray treatments because they effectively break the surface tension and
785 allow pesticide solution droplets to spread evenly and adhere longer on leaf surfaces (Zhu, 2012). Using
786 botanical pesticides and essential oils that naturally spread over the leaf surface may preclude the use of
787 adjuvants in combination with aqueous pesticide solutions. Preventative pest management practices will,
788 by definition, reduce the necessity of pesticide applications and associated use of synthetic adjuvants.

789 Organic farmers are generally dependent upon preventative cultural practices and physical controls for
790 suppressing pest insects, weeds and soil-borne pathogens. The "Crop pest, weed, and disease management
791 practice standard" in the NOP rule states that producers must use the following management practices to
792 prevent crop pests, weeds and diseases (7 CFR 205.206(a)):

- 793
- Crop rotation and soil and crop nutrient management practices;

- 794 • Sanitation measures to remove disease vectors, weed seeds and habitat for pest organisms;
795 • Cultural practices that enhance crop health, including selection of plant species and varieties with
796 regard to suitability to site-specific conditions and resistance to prevalent pests, weeds and
797 diseases.
- 798 Pest problems may be controlled through mechanical or physical methods (7 CFR 205.206(b)):
- 799 • Augmentation or introduction of predators or parasites of the pest species;
800 • Development of habitat for natural enemies of pests;
801 • Nonsynthetic controls such as lures, traps and repellents.
- 802 Organic producers may control weed problems using the following activities (7 CFR 205.206(c)):
- 803 • Mulching with fully biodegradable materials;
804 • Mowing;
805 • Livestock grazing;
806 • Hand weeding and mechanical cultivation;
807 • Flame, heat or electrical means;
808 • Plastic or other synthetic mulches: *Provided* that, they are removed from the field at the end of the
809 growing or harvest season.
- 810 Lastly, the standard allows for the following activities to control plant disease problems (7 CFR 205.206(d)):
- 811 • Management practices which suppress the spread of disease organisms;
812 • Application of nonsynthetic biological, botanical or mineral inputs.

References

- 814 Ackermann GE, Schwaiger J, Negele RD, Fent K. 2002. Effects of long-term nonylphenol exposure on
815 gonadal development and biomarkers of estrogenicity in juvenile rainbow trout (*Oncorhynchus mykiss*).
816 *Aquatic Toxicology* 60(3-4): 203-221.
- 817 Ademollo N, Ferrara F, Delise M, Fabietti F, Funari E. 2008. Nonylphenol and octylphenol in human breast
818 milk. *Environment International* 34(7): 984-987; doi:10.1016/j.envint.2008.03.001.
- 819 Amaro AA, Esposito AI, Mirisola V, Mehilli A, Rosano C, Noonan DM, Albin A, Pfeiffer U, Angelini G.
820 2014. Endocrine disruptor agent nonyl phenol exerts an estrogen-like transcriptional activity on estrogen
821 receptor positive breast cancer cells. *Curr Med Chem* 21(5): 630-640.
- 822 Bakke D. 2003. Human and Ecological Risk Assessment of Nonylphenol Polyethoxylate-based (NPE)
823 Surfactants in Forest Service Herbicide Applications. Pacific Southwest Region (Region 5). USDA Forest
824 Service. Retrieved January 7, 2015 from
825 http://www.fs.usda.gov/Internet/FSE_DOCUMENTS/stelprdb5346866.pdf.
- 826 Bayer CropScience. 2011. Label: K-Othrine® SC Insecticide. Bayer Environmental Science. Bayer
827 CropScience LP. Retrieved January 9, 2015 from
828 http://iaspub.epa.gov/apex/pesticides/f?p=PPLS:102:::NO::P102_REG_NUM:432-763.
- 829 Bechi N, Ietta F, Romagnoli R, Focardi S, Corsi I, Buffi C, Paulesu L. 2006. Estrogen-like response to p-
830 nonylphenol in human first trimester placenta and BeWo choriocarcinoma cells. *Toxicol Sci* 93(1): 75-81.
- 831 Boehme RM, Andries T, Dötz KH, Thiele B, Guenther K. 2010. Synthesis of defined endocrine-disrupting
832 nonylphenol isomers for biological and environmental studies. *Chemosphere* 80: 813-821;
833 doi:10.1016/j.chemosphere.2010.03.064.
- 834 Brandt. Undated. Specimen Label: CMR Can-Hance Modified Vegetable Oil Concentrate. Creative
835 Marketing & Research Inc. Retrieved January 9, 2015 from
836 <http://adjuvants.brandt.co/ProductListing/CMRCANHANCE.aspx>.

- 837 CAN. 2011. Organic Production Systems Permitted Substances Lists: CAN/CGSB-32.311-2006. Canadian
838 General Standards Board. Retrieved January 9, 2015 from <http://www.tpsgc-pwgsc.gc.ca/ongc-cgsb/programme-program/normes-standards/internet/bio-org/documents/032-0311-2008-eng.pdf>.
- 839
- 840 Careghini A, Mastorgio AF, Saponaro S, Sezenna E. 2014. Bisphenol A, nonylphenols, benzophenones, and
841 benzotriazoles in soils, groundwater, surface water, sediments, and food: a review. *Environmental Science
842 and Pollution Research* 1–31.
- 843 Codex. 2013. Guidelines for the Production, Processing, Labeling and Marketing of Organically Produced
844 Foods (CAC/GL 32-1999). Codex Alimentarius Commission. Retrieved January 9, 2015 from
845 http://www.codexalimentarius.org/standards/list-of-standards/en/?no_cache=1.
- 846 Czarnota M, Thomas P. 2013. Using Surfactants, Wetting Agents, and Adjuvants in the Greenhouse (B
847 1319). University of Georgia Extension. Retrieved January 7, 2015 from
848 <http://extension.uga.edu/publications/detail.cfm?number=B1319>.
- 849 DEPA. 2006. Fact Sheet: Nonylphenol and nonylphenol ethoxylates. Danish Environmental Protection
850 Agency. Retrieved January 7, 2015 from <http://eng.mst.dk/topics/chemicals/legislation-on-chemicals/fact-sheets/fact-sheet-nonylphenol-and-nonylphenol-ethoxylates/>.
- 851
- 852 Dodder NG, Maruya KA, Lee Ferguson P, Grace R, Klosterhaus S, La Guardia MJ, et al. 2014. Occurrence of
853 contaminants of emerging concern in mussels (*Mytilus* spp.) along the California coast and the influence of
854 land use, storm water discharge, and treated wastewater effluent. *Marine Pollution Bulletin* 81: 340–346;
855 doi:10.1016/j.marpolbul.2013.06.041.
- 856 Dodgen LK, Li J, Parker D, Gan JJ. 2013. Uptake and accumulation of four PPCP/EDCs in two leafy
857 vegetables. *Environ Pollut* 182: 150–156; doi:10.1016/j.envpol.2013.06.038.
- 858 Domene X, Ramírez W, Solà L, Alcañiz JM, Andrés P. 2009. Soil pollution by nonylphenol and nonylphenol
859 ethoxylates and their effects to plants and invertebrates. *Journal of Soils and Sediments* 9: 555–567;
860 doi:10.1007/s11368-009-0117-6.
- 861 Dow. 2010. Product Safety Assessment: Dow™ Nonylphenol Ethoxylate Surfactants. The Dow Chemical
862 Company. Revised: October 11, 2010. Retrieved January 7, 2015 from
863 <http://www.dow.com/productsafety/finder>.
- 864 EC. 2008. Commission Regulation (EC) No 889/2008 of 5 September 2008: Laying down detailed rules for
865 the implementation of Council Regulation (EC) No 834/2007 on organic production and labeling of organic
866 products with regard to organic production, labeling and control. European Commission. Retrieved
867 January 9, 2015 from <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:250:0001:0084:EN:PDF>.
- 868
- 869 Environment Canada. 2002. Canadian Sediment Quality Guidelines for the Protection of Aquatic Life:
870 Nonylphenol and its Ethoxylates. Canadian Council of Ministers of the Environment. Retrieved January 7,
871 2015 from <http://ceqg-rcqe.ccme.ca/download/en/242>.
- 872 Fiege H, Voges H-W, Hamamoto T, Umemura S, Iwata T, Miki H, et al. 2000. Phenol Derivatives. In
873 *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA.
- 874 HSDB. 2012. National Library of Medicine, TOXNET. *Polyethylene Glycol Nonylphenol Ether*. Hazardous
875 Substances Data Bank. Retrieved January 12, 2015 from <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>.
- 876
- 877 Hargreaves T. 2003. Surfactants: The ubiquitous amphiphiles. Royal Society of Chemistry. Retrieved
878 January 15, 2015 from <http://www.rsc.org/chemistryworld/Issues/2003/July/amphiphiles.asp>.
- 879 Health Canada. 2001. Priority Substances List Assessment Report: Nonylphenol and its Ethoxylates. April
880 2001. Retrieved January 7, 2015 from <http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/nonylphenol/index-eng.php>.
- 881

- 882 Hock WH, Richards KH, Gripp SI. 2015. Spray Adjuvants. Penn State Extension. Retrieved January 9, 2015
883 from [http://extension.psu.edu/pests/pesticide-education/applicators/fact-sheets/pesticide-
safety/spray-adjuvants](http://extension.psu.edu/pests/pesticide-education/applicators/fact-sheets/pesticide-
884 safety/spray-adjuvants).
- 885 Hu X, Sun Z, Wang J, An M, Duan S. 2014. Sublethal Toxic Effects of Nonylphenol Ethoxylate and
886 Nonylphenol to *Moina macrocopa*. *Bull Environ Contam Toxicol* 93: 204–208; doi:10.1007/s00128-014-1310-
887 x.
- 888 IARC. 2014. Agents Classified by the *IARC Monographs*, Volumes 1–111. Last update: 23 October 2014.
889 International Agency for Research on Cancer. Retrieved January 13, 2015 from
890 <http://monographs.iarc.fr/ENG/Classification/>.
- 891 IFOAM. 2014. The IFOAM Norms for Organic Production and Processing. International Federation of
892 Organic Agriculture Movements. Dated: August 2014. Retrieved January 9, 2015 from
893 <http://www.ifoam.org/en/ifoam-norms>.
- 894 JMAFF. 2012. Japanese Agricultural Standard for Organic Plants (Notification No 1605). Japanese Ministry
895 of Agriculture, Forestry and Fisheries. Retrieved January 9, 2015 from
896 http://www.maff.go.jp/e/jas/specific/pdf/833_2012-3.pdf.
- 897 Lauterbach A, Uber G. 2011. Iodine and Iodine Compounds. *Kirk-Othmer Encyclopedia of Chemical
898 Technology*. John Wiley & Sons, Inc. Pages 1-28.
- 899 Lorenc JF, Lambeth G, Scheffer W. 2003. Alkylphenols. In *Kirk-Othmer Encyclopedia of Chemical Technology*,
900 John Wiley & Sons, Inc.
- 901 Lower S. 2014. Hydrogen-Bonding and Water. UC Davis ChemWiki. University of California at Davis.
902 Retrieved January 9, 2015 from
903 [http://chemwiki.ucdavis.edu/Wikitexts/Simon_Fraser_Chem1%3A_Lower/06_States_of_Matter/Hydro
gen-Bonding_and_Water](http://chemwiki.ucdavis.edu/Wikitexts/Simon_Fraser_Chem1%3A_Lower/06_States_of_Matter/Hydro
904 gen-Bonding_and_Water).
- 905 Lu J, Wu J, Stoffella PJ, Wilson PC. 2012. Analysis of Bisphenol A, Nonylphenol, and Natural Estrogens in
906 Vegetables and Fruits Using Gas Chromatography–Tandem Mass Spectrometry. *J. Agric. Food Chem.* 61:
907 84–89; doi:10.1021/jf304971k.
- 908 Luo Y, Guo W, Ngo HH, Nghiem LD, Hai FI, Zhang J, Liang S, Wang XC. 2014. A review on the occurrence
909 of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. *Sci
910 Total Environ* 473–474: 619–641.
- 911 Mao Z, Zheng X-F, Zhang Y-Q, Tao X-X, Li Y, Wang W. 2012. Occurrence and Biodegradation of
912 Nonylphenol in the Environment. *Int J Mol Sci* 13: 491–505; doi:10.3390/ijms13010491.
- 913 McDaniel KG, Reese JR. 2009. High Productivity Process for Alkylphenol Ethoxylates. US Patent #
914 7,473,677 B2. Retrieved January 7, 2015 from <http://www.google.com/patents/US7473677>.
- 915 NTP. 1997. Nonylphenol: Multigenerational Reproductive Effects in Sprague-Dawley Rats when Exposed
916 to Nonylphenol (CASRN: 84852-15-3) in the Diet. National Toxicology Program. Retrieved January 14, 2015
917 from <http://ntp.niehs.nih.gov/testing/types/repro/abstracts/racb/index-101.html>.
- 918 Nisus Corporation. 2014. Label: BoraCare® Termiticide, Insecticide and Fungicide Concentrate. Retrieved
919 January 9, 2015 from [http://iaspub.epa.gov/apex/pesticides/f?p=PPLS:102:::NO::P102_REG_NUM:64405-
1](http://iaspub.epa.gov/apex/pesticides/f?p=PPLS:102:::NO::P102_REG_NUM:64405-
920 1).
- 921 OEHHA. 2014. Chemicals Known to the State of California to Cause Cancer or Reproductive Toxicity.
922 Dated: December 26, 2014. California Environmental Protection Agency – Office of Environmental Health
923 Hazard Assessment. Retrieved January 13, 2015 from
924 http://oehha.ca.gov/prop65/prop65_list/files/p65single122614.pdf.

- 925 PMRA. 2010. PMRA List of Formulants. Dated: 31 August 2010. Pesticide Management Regulatory Agency.
926 Retrieved January 9, 2015 from [http://publications.gc.ca/collections/collection_2010/arla-pmra/H114-22-](http://publications.gc.ca/collections/collection_2010/arla-pmra/H114-22-2010-eng.pdf)
927 [2010-eng.pdf](http://publications.gc.ca/collections/collection_2010/arla-pmra/H114-22-2010-eng.pdf).
- 928 Patrolecco L, Capri S, De Agnelis S, Pagnotta R, Polesello S, Valsecchi S. 2006. Partition of nonylphenol and
929 related compounds among different aquatic compartments in Tiber River (Central Italy). *Water Air Soil*
930 *Poll* 172: 151–166.
- 931 Patton A, Weisenberger D. 2011. Efficacy of Current Organic Postemergent Weed Control Options in
932 Turfgrass Systems. Purdue University Turfgrass Science. Retrieved January 15, 2015 from
933 http://www.agry.purdue.edu/turf/report/2011/PDF/06_AGRY_Patton_organic%20weed%20control.pdf
- 934 Porter AJ, Hayden NJ. 2002. Nonylphenol in the Environment: A Critical Review. College of Engineering
935 and Mathematical Sciences (CEMS). University of Vermont. Retrieved January 14, 2015 from
936 www.emba.uvm.edu/~nhayden/npreview.pdf.
- 937 Schwaiger J, Spieser OH, Bauer C, Ferling H, Mallow U, Kalbfus W, Negele RD. 2000. Chronic toxicity of
938 nonylphenol and ethinylestradiol: Haematological and histopathological effects in juvenile Common carp
939 (*Cyprinus carpio*). *Aquat Toxicol*. 51(1): 69–78.
- 940 Sigma Aldrich. 2014. Material Safety Data Sheet: Tergitol® NP-9. Version 5.6. Revision Date: 11/25/2014.
941 Retrieved January 14, 2015 from <http://www.sigmaaldrich.com/united-states.html>.
- 942 Soares A, Guieysse B, Jefferson B, Cartmell E, Lester JN. 2008. Nonylphenol in the environment: A critical
943 review on occurrence, fate, toxicity and treatment in wastewaters. *Environment International* 34: 1033–
944 1049; doi:10.1016/j.envint.2008.01.004.
- 945 Topp E, Starratt A. 2000. Rapid Mineralization of the Endocrine-Disrupting Chemical 4-Nonylphenol in
946 Soil. *Environmental Toxicology and Chemistry* 19(2): 313–318.
- 947 US EPA. 2015. Pesticide Product Information System (PPIS). Last updated on 1/6/2015. US Environmental
948 Protection Agency. Retrieved January 9, 2015 from <http://www.epa.gov/pesticides/PPISdata/>.
- 949 US EPA. 2010. Nonylphenol (NP) and Nonylphenol Ethoxylates (NPEs) Action Plan [RIN 2070-ZA09]. US
950 Environmental Protection Agency, August 2010. Retrieved January 7, 2015 from
951 [http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/RIN2070-ZA09_NP-](http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/RIN2070-ZA09_NP-NPEs%20Action%20Plan_Final_2010-08-09.pdf)
952 [NPEs%20Action%20Plan_Final_2010-08-09.pdf](http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/RIN2070-ZA09_NP-NPEs%20Action%20Plan_Final_2010-08-09.pdf).
- 953 US EPA. 2006. Registration Eligibility Decision for Iodine and Iodophor Complexes. US Environmental
954 Protection Agency, July 2006. Retrieved January 8, 2015 from
955 <http://www.epa.gov/oppsrrd1/reregistration/REDs/iodine-red.pdf>.
- 956 US EPA. 2005a. Aquatic Life Ambient Water Quality Criteria – Nonylphenol. FINAL. US Environmental
957 Protection Agency. Retrieved January 7, 2015 from
958 [http://water.epa.gov/scitech/swguidance/standards/criteria/aqlife/nonylphenol/upload/2006_5_18_cr-](http://water.epa.gov/scitech/swguidance/standards/criteria/aqlife/nonylphenol/upload/2006_5_18_criteria_nonylphenol_final-doc.pdf)
959 [iteria_nonylphenol_final-doc.pdf](http://water.epa.gov/scitech/swguidance/standards/criteria/aqlife/nonylphenol/upload/2006_5_18_criteria_nonylphenol_final-doc.pdf).
- 960 US EPA. 2005b. Inert Reassessment – Members of the Sorbitan Fatty Acid Esters and the Polysorbates. US
961 Environmental Protection Agency. Retrieved January 16, 2015 from
- 962 US EPA. 2004a. List 4B – Other ingredients for which EPA has sufficient information to reasonably
963 conclude that the current use pattern in pesticide products will not adversely affect public health or the
964 environment. Updated August 2004. US Environmental Protection Agency. Retrieved January 7, 2015 from
965 http://www.epa.gov/opprd001/inerts/inerts_list4Bname.pdf.
- 966 US EPA. 2004b. List 1 – Inert Ingredients of Toxicological Concern. Updated August 2004. US
967 Environmental Protection Agency. Retrieved January 9, 2015 from
968 http://www.epa.gov/opprd001/inerts/list1_chemname.pdf.

- 969 UAP Canada. 2012. Improving Pesticide Performance with Surfactant Technology: The LI 700® Way. A
970 White Paper for Crop Producers, Retailers, Custom Applicators and Crop Consultants. United Agri
971 Products Canada Inc. Retrieved January 9, 2015 from
972 http://www.uap.ca/products/documents/UAP_LI700_WhitePaper_Final_LoRez.pdf.
- 973 WHO. 2004. Integrated Risk Assessment: Nonylphenol Case Study. International Programme on Chemical
974 Safety. World Health Organization. Retrieved January 15, 2015 from
975 www.who.int/ipcs/methods/Nonylphenol.pdf.
- 976 Warhurst M. 1995. An Environmental Assessment of Alkylphenol Ethoxylates and Alkylphenols. Friends
977 of the Earth-UK. Retrieved January 7, 2015 from
978 http://www.foe.co.uk/sites/default/files/downloads/ethoxylates_alkylphenols.pdf.
- 979 White Cap Inc. 2012. Label: Real Pine Cleaner Disinfectant Deodorizer. Retrieved January 9, 2015 from
980 http://iaspub.epa.gov/apex/pesticides/f?p=PPLS:102:::NO::P102_REG_NUM:72138-1.
- 981 Zhu H. 2012. Evaporation and spread of surfactant-amended droplets on leaves. Updated 4/23/2012.
982 USDA Agricultural Research Service. Retrieved January 16, 2015 from
983 <http://www.ars.usda.gov/Research/docs.htm?docid=19299>.