United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/petitioned-substances

Document Type:

☐ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☒ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Iodine

Livestock

Identification of Petitioned Substance

Chemical Names:
Iodine (molecular)

Other Names:
Diiodine; Iodine crystals; Iodine sublimed; Iodophor; Molecular iodine; Tincture iodine.

CAS Numbers:
7553-56-2 (molecular iodine)

Other Codes:
EINECES, Iodine: 231-442-4

Chemical Names:
2-(4-Nonylphenoxy)ethanol – iodine (1:1) ($C_{17}H_{28}I_2O_2$)

Other Names:
Losan; Nonoxinol and molecular iodine; Nonyl-phenoxy-poly-ethoxyethanol-iodine complex.

Trade Names:
Clean™ sanitizer; Dairyland Brand Cow Udder Wash; Dyne-o-might disinfectant; Udder-san Sanitizer and Udderwash.

CAS Numbers:
35860-86-7 [2-(4-Nonylphenoxy)ethanol – iodine (1:1)];
104-35-8 [2-(4-nonylphenoxy)ethanol]

Other Codes:
EC 500-024-6
NP's EINECS codes are 284-325-5 (branched) and 246-672-0 (linear)
NP's CAS codes are 84852-15-3 (branched) and 25154-52-3(linear)

NOTE: Nonylphenol ethoxylates (NPEs) are the most commonly marketed alkylphenol polyethoxylates (APEs) CAS number is 26027-38-3

Summary of Petitioned Use

This limited scope technical report provides updated technical information to the National Organic Standards Board (NOSB), for the support of the sunset review of iodine, listed at 7 CFR 205.603(a)(16) and (b)(4). Iodine is allowed for use as a disinfectant, sanitizer, and medical treatment on livestock operations under § 205.603(a)(16), and as a topical treatment, external parasiticide, or local anesthetic under § 205.603(b)(4).

Iodine was originally recommended by the NOSB for use in organic livestock production in 1995 (NOSB, 2009). It was included on the National List of Allowed and Prohibited Substances (hereafter referred to as the "National List") with the first publication of the National Organic Program (NOP) Final Rule (65 FR 80548). The NOSB has continued to recommend its renewal in 2005, 2010, 2015, and 2019 (NOSB, 2005, 2010, 2015, 2019a). During the 2019 NOSB fall meeting, the NOSB received comments that indicated iodine products without nonylphenol ethoxylates (NPEs) may be available to organic livestock producers (NOSB, 2019b). Public commenters requested that an annotation be added to iodine, prohibiting iodophors containing alkylphenols or alkylphenol ethoxylates (types of nonylphenols and nonylphenol ethoxylates).

This technical report focuses on the availability of iodine products for livestock production without NPEs in the formulation. Furthermore, we report on the potential for NPEs in such products to have detrimental effects on agroecosystems, the environment, and human health.

Focus Questions Requested by the NOSB

1. How frequently are nonylphenol ethoxylates (NPEs) used in iodine product formulations, used in livestock production?

Background

At the Fall 2019 NOSB meeting, the NOSB discussed iodine products for use with livestock healthcare [7 CFR 205.603(a)(16) and (b)(4)], in particular as teat dips, during sunset review (NOSB, 2019b). The motion to remove iodine from the list of approved healthcare products did not pass. When discussing the motion to remove iodine, one NOSB member indicated that "iodine-based teat dips are the most commonly used in organic livestock production." While farmers have indicated that iodine is an essential part of preventive healthcare in milk quality, consumer groups want the iodine to be free of nonylphenol ethoxylates (NPEs). In the oral comments, one dairy farmer indicated that "…. we have not run into any issue with finding iodine [teat dipping products] without NPEs and I think it's definitely become more of an industry standard for that to be the case" (NOSB, 2019b).

The 2015 technical report *Nonylphenol Ethoxylates* (crops) details the manufacturing process for NPEs as well as the persistence of NPEs and nonylphenols (NPs) in the environment (NOP, 2015a). The technical report authors indicate that there was limited information available at the time on the toxicity of NPEs and NPs to terrestrial animals other than rats. There was also limited information on toxicity to invertebrates and plants. The technical report authors did indicate, however, that concerns have been expressed regarding acute and chronic toxicity of NPE and NP to aquatic organisms (NOP, 2015a).

Large commercial dairy herd operations typically use iodine-based treatments pre-milking (66% of herds) and post-milking (84% of herds) (Lopez-Benavides et al., 2016). However, NPE use in the American dairy industry is a market barrier to exporting dairy products, especially to the European Union and China. As a result, there has been a movement to phase out the use of NPEs in the US dairy industry (Sullivan, 2017).

Frequency/use of NPs and NPEs in iodine products

Iodine products are available on the market that do not contain NPs or NPEs as surfactants. While most products that we considered in this section of the report do not formulate with NPEs, several may. Of the 251 teat dips considered in one data set, 19 are formulated with NPEs. Around 45% of the teat dips in this data set contain iodine. It is unclear what percentage of these products contained both iodine and NPEs.

The following information comes from an organization that certifies a large number of organic dairy operations (personal communication, November 13, 2023).

- They currently have 251 teat/udder care products in use by their clients.
- Of these, 163 are teat dips and 88 are udder care products.
- Of the 251 products, 115 contain iodine as an ingredient.
- Of the 251 products, 19 formulate with NPEs.
- Of the products that are formulated with NPEs, 16 are teat dips and 3 are udder washes.

Iodine is commonly used as an active ingredient in teat dips. We assume that many of the teat dips reported above by the certification organization include iodine.

The Organic Materials Review Institute (OMRI) has 14 products listed in the teat dip category (OMRI, 2023). Eleven of those products contain iodine. None of the teat dip products are formulated with NPEs. There are also two products listed in the udder care category and neither of these products is formulated with NPEs (or iodine).

The following sanitizing and udder wash products were listed in the 2015 technical report, *Iodine* (livestock) and contained NPEs (NOP, 2015b):

- FS-102 Sanitizer and Udderwash
- Udder-san Sanitizer and Udderwash.

These products contain iodine, but the iodine is included in the products as NPE-iodine complexes. According to a notice in the Federal Register, the EPA registration for FS-102 Sanitizer and Udderwash (EPA Registration Number 8405-3) was cancelled for non-payment of the 2017 EPA maintenance fee (83 FR 16087). Of the brand name products identified in the 2015 *Iodine* technical report, only Udder-san Sanitizer and Udderwash is currently available (NOP, 2015b). Two additional brand name products are also now available, including Dairyland Brand Cow Udder Wash and Clean™ sanitizer (see *Identification of Petitioned Substance*, above).

Dyne-o-might, manufactured by Preserve International, is another iodine animal disinfectant product currently available on the market. It is also sold under the brand name Sanacide LF acid sanitizer. According to the product label, the primary use of this disinfectant is in poultry houses to control gangrenous dermatitis caused by *Clostridium perfringens* (US EPA, 2016). It is also used in footbaths placed at the entrance to poultry houses. The manufacturer recommends its use as "a course spray for the floors of poultry houses, cattle barns, swine facilities, ratite facilities, zoos, and other animal-raising facilities which require disinfecting in the presence of high levels of organic matter found in such areas including soil, dirt, litter, blood and feces." The label indicates that the iodine in this product is not complexed with NPEs, but instead is in the form of a polyoxyethylene-polyoxypropylene block polymer iodine complex (US EPA, 2016).

The main reason to use complexing agents in iodine complexes is to keep the iodine in suspension (International Products Corporation, 2022). NPs and NPEs are also non-ionic surfactants. Surfactants are important for removing dirt from the surface. Surfactants have a hydrophobic (water-fearing) tail and a hydrophilic (water-loving) head. Since hydrophobic compounds avoid water, the tails of each surfactant surround the dirt. The water loving head is surrounded by water. The surfactant molecules combine to form micelles with the heads toward the water and the tails grouped together. The micelles work to remove the dirt. The hydrophilic head is electrically charged, and the surfactant is classified depending on the type of charge the head has. Non-ionic surfactants such as NP and NPE, have a neutral charge. They are good at emulsifying oils and removing organic soils (International Products Corporation, 2022).

Other sources of NPEs

Udder washes and teat dips are not the only sources of NPEs on a dairy farm (Sullivan, 2017). Simply switching to NPE-free teat dips may not be enough to lower bulk tank NPE levels to below detectable limits. Household laundry detergent has been NPE-free for many years, but some commercial laundry detergent manufacturers may still be using NPEs. NPEs can persist in cloth for a long time. In addition, some textiles contain NPEs, so new towels may contain NPEs. Towels have been a major factor on farms trying to reduce NPE levels in the bulk tanks (Sullivan, 2017).

There are other sources of NPEs on a dairy farm as well (Sullivan, 2017). If NPE-containing products have been previously used with equipment on the farm, these NPEs can leach back out of the rubber or plastic parts. These include parts used in teat-dip drums and totes, sprayer lines, and equipment. Gaskets, inflations, hoses, and anything rubber or plastic that could contact milk may retain NPE. Surveys of municipal drinking water supplies have shown trace levels of NPEs, and dairies with well water may also see high NPE levels (Sullivan, 2017).

In a guidance document on the use of NPEs, Pennsylvania Certified Organic (PCO) lists several products that could include NPEs (Pennsylvania Certified Organic, 2020). In addition to teat dips and udder washes, they include footbath solutions, laundry detergent, surface cleaners, dish detergents, pesticides, and fertilizers. These products should be considered when trying to remove NPEs from a farm. The document does stress, however, that iodine teat dips are the main sources of NPE on dairy farms, and PCO recommends 23 alternatives to iodine teat dips (Pennsylvania Certified Organic, 2020).

2. What is the potential for nonylphenol ethoxylates (NPEs), used in iodine product formulations, to have detrimental effects on agroecosystems and the environment? If there is potential, describe it.

Background

In April 2023, the FDA finalized the new criteria to be used for approval of teat antiseptic products (US FDA, 2023). In the revised guidelines, the manufacturers must address the potential environmental impact of a requested product. This involves:

- Estimating the mobility of the emitted chemicals in air, soil, and water.
- Researching the chemical degradation, biological transformation, or subsequent accumulation of the product or by-products.
- Determining the ecotoxicological effects resulting from exposure to those emitted chemicals.
- Predicting any potential effects on natural resources, endangered species, or historical places.

The primary use of nonylphenols (NPs) is as an intermediate in the production of NPEs (US EPA, 2010). Given their polar and non-volatile nature, NPs are shown to be persistent in the aquatic environment. They are moderately bioaccumulative and extremely toxic to aquatic organisms. NPEs are less toxic than NPs, but still highly toxic to aquatic organisms. In the environment, NPEs degrade to the more environmentally persistent NPs. NPEs can come in different chain sizes. In general, shorter chains have increased toxicity (US EPA, 2010).

The degradation products of nonylphenol polyethoxylates include the simplest forms of NPEs and nonylphenol carboxylic acids (Domene et al., 2009).[1] These are the most toxic end-products and have a higher environmental persistence. NPs have the highest toxicity in both plant and soil invertebrate bioassays. Although the apparent ecotoxicological risk is limited, the risks should not be disregarded since elevated levels can be found in some runoff events. Organic farms typically have runoff mitigation plans in place as part of their organic plan, reducing this concern (Domene et al., 2009).

The 2015 *Nonylphenol Ethoxylates* technical report (crops) included a discussion of environmental effects (NOP, 2015a). In crop production, adjuvants, such as NPEs are used to break water surface tension, allowing active ingredients to be more evenly dispersed on a surface and able to reach their targets (Czarnota & Thomas, 2023). In answer to evaluation question 4, "Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment," the *Nonylphenol Ethoxylates* technical report describes the environmental fate and persistence of NPEs and their ultimate breakdown products, which are NPs (NOP, 2015a).

Regulation

Due to the deleterious effects of NPs in the environment, the use and production of NPEs have been banned in European Union countries and is strictly monitored in many other countries, including Canada and Japan (Soares et al., 2008). NPs and NPEs are on the REACH annex XVII list of restricted substances in the European Union where their use has been almost eliminated (ChemSafety Pro, 2016).

In 2014, the United States Environmental Protection Agency (EPA) proposed a Significant New Use Rule (SNUR) requiring the agency to review the use of fifteen NP and NPEs. In addition, NP and NPEs have been added to the list of chemicals included in the Toxic Substances Control Act since they "present or may present an unreasonable risk of injury to health or the environment." They have also been added to the Toxics Release Inventory list. NP and NPEs have been found in environmental samples collected from freshwater, saltwater, and groundwater, and in sediment, soil, and aquatic biota (US EPA, 2023).

In November of 2016, the EPA proposed adding a NPEs category to the list of toxic chemicals subject to reporting under section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA), and section 6607 of the Pollution Prevention Act (PPA) (81 FR 80624). The EPA determined that short-chain NPEs are highly toxic to aquatic organisms (US EPA, 2010). While long chain NPEs are not as toxic as

[1] The term polyethoxylate is defined as a polymer of monomer ethoxylates. It indicates that there is a chain of ethoxylates. Monoethoxylate is a single ethoxylate. Diethoxylate has two. Polyethoxylate indicates a long chain of ethoxylates.

short-chain NPEs, they can break down in the environment to short-chain NPEs and NP, both of which are highly toxic to aquatic organisms. These changes were finalized in 2018 (83 FR 27291).

Effects on vertebrates

The estrogenic nature of NPs may cause adverse effects on animals (Soares et al., 2008). Due to their structural similarity, NPs can mimic the natural hormone 17ß-oestradiol, competing for the estrogen receptor binding sites. The adverse effects of NPs in the aquatic environment include feminization of aquatic organisms, a decrease in male fertility, and decreased survival of juveniles (Soares et al., 2008).

Early research showed that NP, nonylphenol monoethoxylate, and nonylphenol diethoxylate were found in tissues of freshwater organisms in Switzerland (Ahel et al., 1993). Higher concentrations were found in macrolytic algae, such as *Cladophora glomerta*, with the bioconcentration factors reaching up to 10,000x. Lower levels of NPs were found in some other algae species. The levels in fish and wild duck were lower, suggesting that biomagnification did not take place in these species (Ahel et al., 1993).

Uptake of NPs and NPEs in aquatic organisms occurs through two possible pathways – through the gills when breathing, and through the digestive tract when eating (Chokwe et al., 2017). Higher concentrations of NPs and NPEs are reported in those organisms with higher exposure to sediments. This suggests that water may not always be the main source of NPs and NPEs. In some species, however, uptake can occur via both pathways. Since NPs are the breakdown product of NPEs, they are the toxic substance of most concern. Among marine organisms, gastropods and bivalves are the most sensitive to the effects of NPs, followed by fish, other vertebrates, and algae (Chokwe et al., 2017; Oliveira-Filho et al., 2009).

An evaluation of the effects of NP and NPEs on adiposity, growth, and development of zebrafish (*Danio rerio*) demonstrated that NPEs promoted weight gain and increased fat deposition (Kassotis et al., 2022). In addition, evaluation of NP and NPEs on human mesenchymal stem cells demonstrated their ability to promote fat deposition (Kassotis et al., 2022).

NPs are common by-products of NPE biodegradation and known to be environmentally persistent and elicit an estrogenic response in both mammals and fish (Bin-Dohaish, 2008). In a bioassay study, tilapia (*Oreochromus spilurs*) were exposed to different concentrations of 4-NP for a month, and plasma samples were collected for hormonal determination. In addition, the researchers removed the gonads of the fish for histological examination. Exposure of tilapia to 4-NP significantly affected plasma estradiol-17ß and testosterone concentrations in both males and females. Estradial-17ß levels were significantly increased in both males and females, while testosterone levels were decreased in the males. Male tilapia experienced testicular regression due to vitellogenin induction (an egg-yolk protein), a process that normally depends on endogenous estrogens. There was reduction in seminiferous lobules, disruption of cyst formation, decrease in spermatids and spermatozoa, and increase in interstitial fibrous connective tissue. There was also Leydige cell damage and the appearance of testis-ova. In the ovaries of the females there was malformation of the previtellogenic oocytes and degeneration of mature ova. The bioassay demonstrated the harmful estrogenic effects of environmentally-persistent NP on the reproduction of tilapia (Bin-Dohaish, 2008).

Effects on invertebrates

Researchers conducted bioassays with NPs and NPEs, focusing on the survival and reproduction of two plants and three animals (Domene et al., 2009):

- perennial ryegrass (*Lolium perenne*)
- field mustard (*Brassica rapa*)
- earthworm (*Eisenia andrei*)
- potworm (*Enchytraeus crypticus*)[2]
- springtail (*Folsomia candida*)[3]

The researchers assessed the effect of different concentrations of the NPs and NPEs in three different soils on lethal and sublethal endpoints for the organisms (Domene et al., 2009). The researchers found contrasting toxicities between the plants and invertebrates, with clearly different toxicities in different soils.

- NPs were more toxic than NPEs, which is consistent with previously published studies.
- Plants were affected less by NPs and NPEs, compared with invertebrates. The effects on plants in the study were difficult to detect.
- For the soil invertebrates, reproduction was the most affected endpoint compared to growth or survival.
- Toxicity was the lowest in the OECD artificial soil (Organization of Economic Co-operation and Development) compared to the natural soils. The OECD soils have the highest organic matter content.

The bioassays used high levels of contamination, which the researchers indicated might be higher than expected in soils contaminated with sewage runoff as the source of the NPs (Domene et al., 2009).

Effects on microorganisms

There is limited research on the effect of NPs and NPEs on the microbial communities in soil. When soils are exposed to high levels of NP concentrations, which could represent worse case scenarios with accidental spills, the plants, fauna, and microorganisms have been negatively impacted (Mattana et al., 2019). The highest concentrations (270 mg NP/kg) negatively impacted both bacterial and fungal community structures (i.e. species richness and evenness). Fungal communities were negatively affected at all concentrations, with the impact increasing with concentrations. Bacterial communities, however, were resistant to lower concentrations (≤ 90 mg NP/kg) (Mattana et al., 2019).

Effects on plants

Plants grown on contaminated soil can also take up and bioaccumulate NPs. For example, broad beans were able to take up NPs from soils treated with NP-contaminated sewage sludge. The NP concentrations were highest in the roots, compared to shoots and seeds. This may be relevant to dietary intake of root food crops (Sjöström et al., 2008).

Fruits and vegetables may contain NPs at levels twenty times higher than the 'no observable effect level' (NOEL) set for freshwater algae (de Bruin et al., 2019). NPs can burden the plant's natural defense system, which can lead to several possible growth disorders, depending on the plant involved. The result is growth reduction, changes in organelle structure, and oxidative damage to the cells (de Bruin et al., 2019).

Internationally, the production of algae is a valuable resource for feeding poultry with local ingredients. It is also used for human consumption, for example species in the genus *Chlorella*. *Chlorella vulgaris* can bioaccumulate NPs, making it potentially toxic to both poultry and humans (Sun et al., 2014).

NP and NPEs can be very toxic to some plants, such as wheat seedlings (Zhang et al., 2016). In one study, the level of toxicity was dependent on the NPE chain length, with longer chains resulting in less toxic

[2] Enchytraeid species thrive in moist containers filled with peaty, acidic soil, giving them the nickname "potworms" (Fountain & Hopkin, 2005). They are beneficial garden worms, similar to a smaller earthworm.

[3] Collembola species are colloquially referred to as "springtails" (Fountain & Hopkin, 2005). Specifically, *F. candida* is a common and widespread arthropod found in soils throughout the world. It has been used as a standard test organism for more than 40 years to estimate the effects of pesticides and environmental pollutants on nontarget soil arthropods.

effects. NPs caused 50% root and shoot growth inhibition at the lowest concentration studied (0.2 mg/L). The wheat seeds were soaked in beakers that contained the different concentrations of Hoagland's nutrient solutions, consisting of NP, NP4EO, and NP10EO (note: 4EO and 10EO refer to the average NPE chain length of the nonylphenol polyethoxylates). While NP10EO had limited effect on wheat seed germination, there was significant germination reduction with increasing concentrations of NP4EO and NP. The inhibition effect was highest for NP (Zhang et al., 2016).

3. What is the potential for nonylphenol ethoxylates (NPEs), used in iodine product formulations, to have detrimental effects on human health? If there is potential, describe it.

As early as 1984, it was known that degradation of NPEs in the environment leads to high concentrations of NPs in sewage sludge (Giger et al., 1984). NPs have been shown to exhibit estrogenic properties in both *in vitro* and *in vivo* assays (US EPA, 2023). NPs are also associated with reproductive and developmental effects in rodents (Gu et al., 2018). NPs have been detected in human breast milk, blood, and urine (US EPA, 2023). NPs have also been shown to adversely affect human pregnancy (Bechi et al., 2010).

The review by Acir and Guenther (2018) provides a detailed discussion of the environmental occurrences and toxicity of alkylphenol ethoxylates (including nonylphenol ethoxylates). They discuss the estrogenic potential of the compounds, as well as the effects on the nervous system and cognitive function, and the effects on the immune system. NPs are an alkylphenol of particular concern (Acir & Guenther, 2018).[4]

The authors of the *Nonylphenol Ethoxylates* (crops) technical report also looked at the effects of NPEs and NPs on human health and the report includes references to many early research reports (NOP, 2015a). Human exposure to NPs, the final degradation production of NPEs, can occur through contaminated water and food products. NP has a lipophilic nature, so it can accumulate in animal tissues.

There are a number of reported adverse effects of NPs on humans. It may have estrogenic properties that can affect the development of female reproductive tissues such as breasts, uteruses, and ovaries, leading to increased tumor development (Noorimotlagh et al., 2020). NPs can also affect male reproduction (Kang et al., 2003). It also has the ability to downregulate insulin signaling in the liver of rats, which can lead to insulin-resistance (Jubendradass et al., 2012). There are, however, no reports on the effect of NPs on diabetics.

Exposure to branched NP (4-nonylphenol) may adversely affect the intestinal lining of humans (Lepretti et al., 2015). Researchers have found NPs to be cytotoxic to cells, as indicated by a reduction in the number of cells and a decrement of mitochondrial functionality after 24 hours. It also had negative effects on cell survival. It was concluded that prolonged gastrointestinal exposure to 4-NP may result in damage to the lining of the digestive tract, impairing its normal functions (Lepretti et al., 2015).

Studies of a human breast adenocarcinoma cell line clearly demonstrated that short-chain NPEs are potent tumor-initiators and promoters (Toyooka et al., 2012). Short-chain NPEs were shown to phosphorylate histone (ɣ-H2AX), which is regarded as a sensitive marker for DNA damage. Low doses of NPs may promote growth of colon cancer cells in mice (Xie et al., 2019).

[4] Alkylphenol is defined as a phenol having one or more alkyl groups attached to the carbon ring. Alkylphenols are organic industrial chemicals used in the production of lubricating oil additives, laundry and dish detergents, emulsifiers, and solubilizers. They are also used personal care products, especially hair products, as an active component of many spermicides, various laboratory detergents, and some pesticide formulations.

Report Authorship

The following individuals were involved in research, data collection, writing, editing, and/or final approval of this report:

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All individuals are in compliance with Federal Acquisition Regulations (FAR) Subpart 3.11—Preventing Personal Conflicts of Interest for Contractor Employees Performing Acquisition Functions.

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