TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-16-0470

Number: P-16-0470
TSCA Section 5(a)(3) Determination: The chemical substance is not likely to present an unreasonable risk (5(a)(3)(C))

Chemical Name:
Specific: 2,7-Nonadien-4-ol, 4,8-dimethyl-; CASRN: 103983-77-3

Conditions of Use (intended, known, or reasonably foreseen)[1]:
Intended conditions of use (generic): Import for use as part of a fragrance formula, consistent with the manufacturing, processing, use, distribution, and disposal information described in the PMN.
Known conditions of use: Applying such factors as described in footnote 1, EPA evaluated whether there are known conditions of use and found none.
Reasonably foreseen conditions of use: Applying such factors as described in footnote 1, EPA evaluated whether there are reasonably foreseen conditions of use and found none.

Summary: The chemical substance is not likely to present an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant by the Administrator under the conditions of use, based on the risk assessment presented below. EPA estimated that the new chemical substance will not be persistent and has low potential for bioaccumulation, such that repeated exposures are not expected to be cumulative. EPA estimates that the chemical substance has moderate environmental hazard and potential for the following human health hazards: Skin irritation, eye irritation, and liver and thyroid toxicity. EPA concludes that the new chemical substance is not likely to present an unreasonable risk under the conditions of use.

[1] Under TSCA § 3(4), the term "conditions of use" means "the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." In general, EPA considers the intended conditions of use of a new chemical substance to be those identified in the section 5(a) notification. Known conditions of use include activities within the United States that result from manufacture that is exempt from PMN submission requirements. Reasonably foreseen conditions of use are future circumstances, distinct from known or intended conditions of use, under which the Administrator expects the chemical substance to be manufactured, processed, distributed, used, or disposed of. The identification of "reasonably foreseen" conditions of use will necessarily be a case-by-case determination and will be highly fact-specific. Reasonably foreseen conditions of use will not be based on hypotheticals or conjecture. EPA's identification of conditions of use includes the expectation of compliance with federal and state laws, such as worker protection standards or disposal restrictions, unless case-specific facts indicate otherwise. Accordingly, EPA will apply its professional judgment, experience, and discretion when considering such factors as evidence of current use of the new chemical substance outside the United States, evidence that the PMN substance is sufficiently likely to be used for the same purposes as existing chemical substances that are structurally analogous to the new chemical substance, and conditions of use identified in an initial PMN submission that the submitter omits in a revised PMN. The sources EPA uses to identify reasonably foreseen conditions of use include searches of internal confidential EPA PMN databases (containing use information on analogue chemicals), other U.S. government public sources, the National Library of Medicine's Hazardous Substances Data Bank (HSDB), the Chemical Abstract Service STN Platform, REACH Dossiers, technical encyclopedias (e.g., Kirk-Othmer and Ullmann), and Internet searches.

Fate: Environmental fate is the determination of which environmental compartment(s) a chemical moves to, the expected residence time in the environmental compartment(s) and removal and degradation processes. Environmental fate is an important factor in determining exposure and thus in determining whether a chemical may present an unreasonable risk. EPA estimated physical/chemical and fate properties of this new chemical substance using measured data for the chemical substance and EPI (Estimation Program Interface) Suite™ (http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface). The chemical substance is estimated to be removed during wastewater treatment with an efficiency of 0-50% via sorption and stripping. For the new chemical substance removal by biodegradation is negligible based on data for the new chemical substance. Sorption to sludge is estimated to be moderate, and sorption to soil and sediment is estimated to be low to moderate, resulting in moderate migration to groundwater for the new chemical substance. Volatilization to air is estimated to be moderate due to moderate estimated vapor pressure and Henry's Law constant. Overall, these estimates are indicative of moderate potential for this chemical substance to volatilize into the air and a moderate potential for this chemical substance to migrate into groundwater.

Persistence[2]: Persistence is relevant to whether a new chemical substance is likely to present an unreasonable risk because chemicals that are not degraded in the environment at rates that prevent substantial buildup in the environment, and thus increase potential for exposure, may present a risk if the substance presents a hazard to human health or the environment. Based on data for the new chemical substance and EPI Suite™, EPA estimated the biodegradation half-lives of the new chemical substance to be less than two months. These estimates indicate that the new chemical substance will not be persistent in aerobic environments (e.g., surface water) or anaerobic environments (e.g., sediment).

Bioaccumulation[3]: Bioaccumulation is relevant to whether a new chemical substance is likely to present an unreasonable risk because substances that bioaccumulate in aquatic and/or terrestrial species pose the potential for elevated exposures to humans and other organisms via food chains. EPA estimated the potential for the new chemical substance to bioaccumulate using EPI Suite™. These estimates indicate that the chemical substance has low bioaccumulation potential (bioconcentration factor = 149; bioaccumulation factor = 343). Because EPA estimated that the new chemical substance will not be persistent and has low potential for bioaccumulation, repeated exposures are not expected to cause food chain effects via accumulation in exposed organisms.

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[2] Persistence: A chemical substance is considered to have limited persistence if it has a half-life in water, soil or sediment of less than 2 months or there are equivalent or analogous data. A chemical substance is considered to be persistent if it has a half-life in water, soil or sediments of greater than 2 months but less than or equal to 6 months or if there are equivalent or analogous data. A chemical substance is considered to be very persistent if it has a half-life in water, soil or sediments of greater than 6 months or there are equivalent or analogous data. (64 FR 60194; November 4, 1999)

[3] Bioaccumulation: A chemical substance is considered to have a low potential for bioaccumulation if there are bioconcentration factors (BCF) or bioaccumulation factors (BAF) of less than 1,000 or there are equivalent or analogous data. A chemical substance is considered to be bioaccumulative if there are BCFs or BAFs of 1,000 or greater and less than or equal to 5,000 or there are equivalent or analogous data. A chemical substance is considered to be very bioaccumulative if there are BCFs or BAFs of 5,000 or greater or there are equivalent or analogous data. (64 FR 60194; November 4 1999)

Human Health Hazard[4]: Human health hazard is relevant to whether a new chemical substance is likely to present an unreasonable risk because the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and the extent of exposure to the substance. EPA estimated the human health hazard of this chemical substance based on its estimated physical/chemical properties and available data on the new chemical substance. Absorption of the new chemical substance is expected to be good via all routes based on physical/chemical properties. For the new chemical substance, EPA identified irritation to the skin and eyes as hazards based on positive results in an OECD 439 in vitro skin irritation test and an OECD 405 acute eye irritation test on the new chemical substance. Liver and thyroid toxicity were identified as hazards based on an OECD 407 28-day repeated dose study on the new chemical substance. Solvent neurotoxicity was initially identified as a hazard based on structural alert, however no neurotoxicity was observed in the OECD 407 test thus these effects were not considered in the risk assessment. EPA qualitatively evaluated irritation effects. EPA quantitatively assessed the new chemical substance using test data on the new chemical substance and identified a NOAEL of 300 mg/kg-day based on liver effects, which was used to derive exposure route- and population-specific points of departure for quantitative risk assessment, described below. A benchmark MOE of 100 was used.

Environmental Hazard[5]: Environmental hazard is relevant to whether a new chemical substance is likely to present unreasonable risks because the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and the extent of exposure to the

[4] A chemical substance is considered to have low human health hazard if effects are observed in animal studies with a No Observed Adverse Effect Level (NOAEL) equal to or greater than 1,000 mg/kg/day or if there are equivalent data on analogous chemical substances; a chemical substance is considered to have moderate human health hazard if effects are observed in animal studies with a NOAEL less than 1,000 mg/kg/day or if there are equivalent data on analogous chemical substances; a chemical substance is considered to have high human health hazard if there is evidence of adverse effects in humans or conclusive evidence of severe effects in animal studies with a NOAEL of less than or equal to 10 mg/kg/day or if there are equivalent data on analogous chemical substances. EPA may also use Benchmark Dose Levels (BMDL) derived from benchmark dose (BMD) modeling as points of departure for toxic effects. See https://www.epa.gov/bmds/what-benchmark-dose-software-bmds. Using this approach, a BMDL is associated with a benchmark response, for example a 5 or 10 % incidence of effect. The aforementioned characterizations of hazard (low, medium, high) would also apply to BMDLs. In the absence of animal data on a chemical or analogous chemical substance, EPA may use other data or information such as from in vitro assays, chemical categories (e.g., Organization for Economic Co-operation and Development, 2014 Guidance on Grouping of Chemicals, Second Edition. ENV/JM/MONO(2014)4. Series on Testing & Assessment No. 194. Environment Directorate, Organization for Economic Co-operation and Development, Paris, France. (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en)), structure-activity relationships, and/or structural alerts to support characterizing human health hazards.

[5] A chemical substance is considered to have low ecotoxicity hazard if the Fish, Daphnid and Algae LC50 values are greater than 100 mg/L, or if the Fish and Daphnid chronic values (ChVs) are greater than 10.0 mg/L, or there are not effects at saturation (occurs when water solubility of a chemical substance is lower than an effect concentration), or the log Kow value exceeds QSAR cut-offs. A chemical substance is considered to have moderate ecotoxicity hazard if the lowest of the Fish, Daphnid or Algae LC50s is greater than 1 mg/L and less than 100 mg/L, or where the Fish or Daphnid ChVs are greater than 0.1 mg/L and less than 10.0 mg/L. A chemical substance is considered to have high ecotoxicity hazard, or if either the Fish, Daphnid or Algae LC50s are less than 1 mg/L, or any Fish or Daphnid ChVs is less than 0.1 mg/L (Sustainable Futures https://www.epa.gov/sustainable-futures/sustainable-futures-p2-framework-manual).

substance. EPA determined the environmental hazard for this new chemical substance based on acute and chronic toxicity data submitted with the PMN. Acute toxicity values measured for fish, aquatic invertebrates, and algae are 11.3 mg/L, 21 mg/L, and 17 mg/L, respectively. Chronic toxicity values measured for fish, aquatic invertebrates, and algae are 1.13 mg/L, 2.1 mg/L (Acute-to-Chronic Ratio (ACR) of 10), and 7.2 mg/L (ACR of 10), respectively. These toxicity values indicate that the new chemical substance is expected to have moderate environmental hazard. Application of assessment factors of 5 and 10 to acute and chronic toxicity values, respectively, results in acute and chronic concentrations of concern of 2.26 mg/L (2,260 ppb) and 0.113 mg/L (113 ppb), respectively.

Exposure: The exposure to a new chemical substance is potentially relevant to whether a new chemical substance is likely to present unreasonable risks because the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and the extent of exposure to the substance.

EPA estimates occupational exposure and environmental release of the new chemical substance under the intended conditions of use described in the PMN using ChemSTEER (Chemical Screening Tool for Exposures and Environmental Releases https://www.epa.gov/tsca-screening-tools/chemsteer-chemical-screening-tool-exposures-and-environmental-releases). EPA uses EFAST (the Exposure and Fate Assessment Screening Tool; https://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014) to estimate general population, consumer, and environmental exposures.

EPA considers workers to be a potentially exposed or susceptible subpopulation (PESS) on the basis of greater exposure potential compared to the general population. EPA also considers PESS in conducting general population drinking water exposures by evaluating risks associated with water intake rates for multiple age groups, ranging from infants to adults. EPA considers consumers of specific products to be a potentially exposed or susceptible subpopulation on the basis of greater exposure potential compared to the general population who do not use specific products.

For this assessment, EPA assessed worker exposure via dermal and inhalation exposure and general population via drinking water and fish ingestion but not inhalation since releases to air are expected to be negligible. Consumers were assessed via dermal and inhalation exposures.

Risk Characterization: EPA applies a margin of exposure approach to calculate potential human health risks of new chemicals. A benchmark (acceptable) margin of exposure is derived by applying uncertainty factors for the following types of extrapolations: intra-species extrapolation (UF_H = 10 to account for variation in sensitivity among the human population), inter-species extrapolation (UF_A = 10 to account for extrapolating from experimental animals to humans) and LOAEL-to-NOAEL extrapolation (UF_L = 10 to account for using a LOAEL when a NOAEL is not available). Hence, in the New Chemicals Program, a benchmark MOE is typically 100 and 1000 when NOAELs and LOAELs, respectively, are used to identify hazard. When allometric scaling or pharmacokinetic modeling is used to derive an effect level, the UF_H may be reduced to 3, for a benchmark MOE of 30. The benchmark MOE is used to compare to the MOE calculated by comparing the toxicity NOAEL or LOAEL to the estimated exposure concentrations. When the calculated MOE is equal to or exceeds the benchmark MOE, the new

chemical substance is not likely to present an unreasonable risk. EPA assesses risks to workers considering engineering controls described in the PMN but in the absence of personal protective equipment (PPE) such as gloves and respirators. If risks are preliminarily identified, EPA then considers whether the risks would be mitigated by the use of PPE (e.g., impervious gloves, respirator).

Risks to human health for the new chemical substances were evaluated using the points of departure (i.e., NOAEL) described above. Irritation hazards to workers via inhalation and dermal contact were identified based on positive dermal irritation data on the new chemical substance. Risks for these endpoints were not quantified due to a lack of dose-response for these hazards. However, exposures can be mitigated by the use of appropriate personal protective equipment (PPE), including (impervious gloves, eye protection, and respiratory protection). EPA expects that employers will require and that workers will use appropriate PPE consistent with the Safety Data Sheet prepared by the new chemical submitter, in a manner adequate to protect them. Risks were not identified for workers for liver and thyroid effects via inhalation or dermal exposures based on quantitative hazard data for the new chemical ($MOE_{Inhalation}$ = 1,846; MOE_{Dermal} = 109; benchmark MOE = 100).

Risks were not identified for the general population for liver and thyroid effects via oral ingestion (drinking water and fish) based on quantitative hazard data for the new chemical (MOE_{Infant} =26,700; MOE_{Adult}=112,000; MOE_{Fish}= 10,608; benchmark MOE = 100). Risks were not identified for the general population for irritation via drinking water since these concerns are expected to be mitigated by dilution in the media. Risks were not evaluated for the general population via inhalation exposure because exposures were estimated to be negligible (below modeling thresholds).

Irritation hazard was identified for the new chemical substance. Risks for this endpoint were not quantified due to a lack of dose-response for this hazard. However, no dermal irritation was observed in acute dermal tests of the new chemical substance using a concentration of 98%; therefore, a 4% concentration in consumer formulations is unlikely to cause irritation.

Risks were not identified for consumers for liver and thyroid effects via inhalation or dermal exposures based on quantitative hazard data for the new chemical ($MOE_{Inhalation}$ = 1,020; MOE_{Dermal} = 2,180; benchmark MOE = 100).

Risks to the environment were evaluated by comparing estimated surface water concentrations with the acute and chronic concentrations of concern. Risks to the environment were not identified because the estimated surface water concentrations did not exceed the acute or chronic COCs.

Because worker exposures can be controlled by PPE, and no unreasonable risks to the general population, consumers or the environment were identified, EPA has determined that the new chemical substance is not likely to present unreasonable risk to human health or the environment under the conditions of use.

5/17/2019
Date:

/s/
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