

TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-17-0086

Number: P-17-0086

TSCA Section 5(a)(3) Determination: The chemical substances are not likely to present an unreasonable risk (5(a)(3)(C))

Chemical Name:

Generic: Cycloalkyl, bis(ethoxyalkyl)-, trans-; Cycloalkyl, bis(ethoxyalkyl)-, cis-

Conditions of Use (intended, known, or reasonably foreseen)¹:

Intended conditions of use (generic): Import for use as a fragrance, 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 has identified processing of the new chemical substances resulting in greater environmental releases and human exposure as reasonably foreseen based on amendments to the PMN.

Summary: The chemical substances are 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 and the terms of the proposed Significant New Use Rule (SNUR) signed by EPA.² Although EPA

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.

² Reasonably foreseen conditions of use subject to a proposed SNUR are not likely to present an unreasonable risk of injury to health or the environment. Based on EPA’s experience, it is the Agency’s judgment that a new use would not commence during the pendency of a proposed SNUR because web posting of a proposed SNUR serves as the cut-off date for a significant new use. Therefore, manufacturers and processors would not commence a prohibited new use that would be legally required to cease upon the finalization of the SNUR. Once a SNUR is final and effective, no manufacturer or processor – including the PMN submitter – may undertake the conditions of use

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estimated that the new chemical substances could be very persistent, they have low potential for bioaccumulation, such that repeated exposures are not expected to cause food-chain effects via accumulation in exposed organisms. Based on test data on the new chemical substances, EPA estimates that the chemical substances have moderate environmental hazard and potential for the following human health hazards: skin irritation, specific target organ toxicity, and reproductive toxicity. The PMN describes conditions of use that mitigate the human health and environmental risks. Therefore, EPA concludes that the new chemical is not likely to present unreasonable risk to human health or the environment under the intended conditions of use.

As set forth below, the information available to EPA is sufficient to permit the Agency to conduct a reasoned evaluation of the health and environmental effects of the chemical substances under the conditions of use that are not subject to the proposed SNUR, in order to determine that the chemical substances are not likely to present an unreasonable risk under those conditions of use. As such, EPA does not need to impose testing requirements to conduct this evaluation. Whether testing is needed to evaluate the effects of the intended, known, or reasonably foreseen conditions of use of a chemical substance subject to a PMN is determined on a case-by-case basis. To the extent that testing may be necessary to conduct a reasoned evaluation of the health or environmental effects of the reasonably foreseen conditions of use that are subject to the proposed SNUR, EPA will make the appropriate determination if a Significant New Use Notice (SNUN) is submitted following finalization of the SNUR.

EPA found no known conditions of use, assessed the intended conditions of use, and addressed reasonably foreseen conditions of use by proposing a SNUR. Therefore, EPA determines the new chemical substances are not likely to present unreasonable risk to human health or the environment.

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 the new chemical substances using data submitted for the new chemical substances and EPI (Estimation Program Interface) Suite™ (<http://www.epa.gov/tsca-screening-tools/epi-suite-estimation-program-interface>). In wastewater treatment, the new chemical substances are expected to be removed with an efficiency of 50% due to sorption. Removal of the new chemical substances by biodegradation is negligible. Sorption of the new chemical substances to sludge is expected to be moderate and to soil and sediment is expected to be low to moderate. Migration of the new chemical substances to groundwater is expected to be moderate to rapid due to low to moderate sorption to soil and

identified as a significant new use of the PMN substance in the SNUR. EPA must first evaluate the new use in accordance with the requirements of TSCA Section 5 and (a) either conclude that the new use is not likely to present an unreasonable risk under the conditions of use; or (b) take appropriate action under section 5(e) or 5(f). If EPA were not to finalize the proposed SNUR, then that decision would be based on information and data provided to the Agency during the comment period demonstrating that the reasonably foreseen conditions of use subject to the proposed SNUR are not likely to present an unreasonable risk. Under either scenario, the reasonably foreseen condition of use is not likely to present an unreasonable risk.

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sediment. Due to low estimated vapor pressure and Henry's law constant, the new chemical substances are expected to undergo low volatilization to air. Overall, these estimates indicate that the new chemical substances have low potential to volatilize to air and has moderate to high potential to migrate to groundwater.

Persistence³: 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. EPA estimated degradation half-lives of the new chemical substances using data submitted for the new chemical substances. EPA estimated that the new chemical substances' aerobic biodegradation half-lives are 2 to 6 months and anaerobic biodegradation half-lives are > 6 months. These estimates indicate that the new chemical substances may be persistent in aerobic environments (e.g., surface water) and may be very persistent in anaerobic environments (e.g., sediment).

Bioaccumulation⁴: 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 substances to bioaccumulate using data submitted for the new chemical substances. EPA estimated that the new chemical substances have low bioaccumulation potential based on submitted data (bioconcentration factor = 234 [measured]). Although EPA estimated that the new chemical substances could be very persistent, the substances have low potential for bioaccumulation, such that repeated exposures are not expected to cause food-chain effects via accumulation in exposed organisms.

Human Health Hazard⁵: Human health hazard is relevant to whether a new chemical substance

³ 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 if 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)

⁴ 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 if 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)

⁵ 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

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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 these chemical substances based on estimated physical/chemical properties and available data on the new chemical substances. Absorption of the new chemical substances is expected to be moderate via all routes based on physical/chemical properties. For the new chemical substances, EPA identified systemic and developmental effects as hazards based on submitted test data for the new chemical substances. Submitted tests of the new chemical substances reported that the test substance has skin irritation potential based on in vitro testing (OECD 431, 439); is not an eye irritant in vivo or in vitro (OECD 405, 437); is not a skin sensitizer in vivo (no guideline reported); was not genotoxic (OECD 471, 476, 487); did not cause adverse effects in acute oral, inhalation, or dermal studies in rats (OECD 402, 403, 423); caused systemic toxicity in repeat-dose oral studies (non-guideline screening studies, OECD 415/416); and caused developmental toxicity in a one-generation oral study (OECD 415/416). EPA identified a NOAEL of 5 mg/kg/day based on systemic effects and a NOAEL of 15 mg/kg/day based on developmental effects, which were used to derive exposure route- and population-specific points of departure for quantitative risk assessment, described below. EPA qualitatively evaluated skin irritation effects.

Environmental Hazard⁶: Environmental hazard is relevant to whether a new chemical substance is likely to present 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 determined the environmental hazard for these new chemical substances based on acute toxicity data submitted for the new chemical substances. These substances fall within the TSCA New Chemicals Category of neutral organics.⁷ Acute toxicity values measured for fish, aquatic invertebrates, and algae are 81.5 mg/L, 73.6 mg/L, and 61.5 mg/L, respectively. Chronic toxicity values measured for fish, aquatic invertebrates, and algae are 8.15 mg/L, 7.36 mg/L, and 35.3 mg/L, respectively. These toxicity values indicate that the new chemical substances are expected to have moderate environmental hazard. Application of assessment

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](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.

⁶ 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>).

⁷ TSCA New Chemicals Program (NCP) Chemical Categories. <https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/chemical-categories-used-review-new>.

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factors of 5 and 10 to acute and chronic toxicity values, respectively, results in acute and chronic concentrations of concern of 14.72 mg/L (14,720 ppb) and 0.736 mg/L (736 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 substances 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 new chemical assessment, EPA assessed worker exposure via inhalation and dermal contact. Releases to water, air, and landfill were estimated. Exposure to the general population was assessed via drinking water and fish ingestion. Exposures to the general population via ground water ingestion (due to landfill leaching) and inhalation were not assessed because exposures from releases to landfill and air were expected to be negligible (below modeling thresholds). Exposure to consumers was assessed via inhalation and dermal contact.

Risk Characterization: EPA applies a margin of exposure approach to calculate potential human health risks of new chemicals. A benchmark (acceptable) margin of exposure (MOE) 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 1,000 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

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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 route-specific effect levels (i.e., NOAELs) described above. Risks were identified for workers for systemic and developmental effects via dermal exposure based on quantitative data on the new chemical substances ($MOE_{\text{systemic}} = 0.4$, $MOE_{\text{developmental}} = 1$; Benchmark $MOE=100$). Risks were not identified for workers for systemic or developmental effects via inhalation exposure based on quantitative data on the new chemical substances ($MOE_{\text{systemic}} = 207$, $MOE_{\text{developmental}} = 622$; Benchmark $MOE = 100$). Skin irritation hazards to workers via dermal contact were identified based on submitted test data for the new chemical substances. Risks for these endpoints were not quantified due to a lack of dose-response for these hazards. Risks will be mitigated if exposures are controlled by the use of appropriate PPE, including impervious gloves. EPA expects that employers will require and workers will use appropriate PPE (i.e., impervious gloves), consistent with the Safety Data Sheet prepared by the PMN submitter, in a manner adequate to protect them.

Risks were not identified for systemic effects for the general population via drinking water (infants only) and fish ingestion based on quantitative data on the new chemical substances ($MOE_{\text{adult}} = 2,400$, $MOE_{\text{infant}} = 572$; $MOE_{\text{fish}} = 639$; benchmark $MOE=100$). Risks were not identified for developmental effects for the general population via drinking water and fish ingestion based on quantitative data on the new chemical substances ($MOE_{\text{adult}} = 7,200$, $MOE_{\text{infant}} = 1,717$; $MOE_{\text{fish}} = 1,918$; benchmark $MOE=100$). Skin irritation hazards to the general population are not expected via exposure to drinking water due to dilution of the chemical substances in the media.

Risks were not identified for systemic or developmental effects for consumers via dermal or inhalation exposure based on quantitative data on the new chemical substances ($MOE > 1,900$; benchmark $MOE=100$). Potential for skin irritation hazards to consumers via dermal contact was identified as a hazard based on submitted test data for the new chemical substances but is not expected as long as the concentration in the mixture is maintained below 3%, as described in the PMN (i.e., [claimed CBI]% by weight).

Risks to the environment were evaluated by comparing estimated surface water concentrations with the acute and chronic concentrations of concern. Risks from acute and chronic exposures to the environment were not identified due to releases to water that did not exceed the acute or chronic COC.

It is reasonably foreseen, based on the history of submissions for these new chemical substances, that the primary processing step (fragrance compounding) for the new chemical substances could occur in a manner resulting in greater environmental releases and human exposure and that greater consumer exposures may occur. The SNUR that has been proposed for these chemical substances defines certain conditions of use as significant new uses. The proposed significant new uses include manufacturing and processing resulting in surface water concentrations greater than 330 ppb and uses in consumer products at formulations greater than 1.5%. Processors receiving the new chemical substances from primary processors (the fragrance compounding processors) at concentrations below 10% by weight are exempt from the release to water

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restrictions in the SNUR. Conditions of use that fall under the restrictions of the proposed SNUR are not likely to present unreasonable risk of injury to health or the environment because (1) those conditions of use are not likely to be commenced during the pendency of the proposed SNUR, and (2) upon finalization of the SNUR, those conditions of use would be prohibited unless and until EPA makes an affirmative determination that the significant new use is not likely to present an unreasonable risk or takes appropriate action under section 5(e) or 5(f).

4/29/2020
Date:

/s/
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