

TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-18-0322

Number: P-18-0322

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

Chemical Name:

Generic: Heteromonocycle, 4,6-dimethyl-2-(1-phenylethyl)-

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

Intended conditions of use (generic): Import for use as a fragrance ingredient in consumer products, 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 identified increased concentrations in formulation based on information in the original submission and domestic manufacture based on manufacture of similar chemical substances by the submitter within the United States as reasonably foreseen conditions of use.

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 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

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estimated that the new chemical substance could be very persistent, the new chemical substance has low potential for bioaccumulation, such that repeated exposures are not expected to be cumulative. Based on submitted test data on the new chemical substance, EPA estimates that the chemical substance has moderate environmental hazard and potential for the following human health hazards: skin irritation and sensitization, GI tract effects, liver and thyroid toxicity. The PMN describes conditions of use that mitigate human health and environmental risks. Therefore, EPA concludes that the new chemical substance is not likely to present an unreasonable risk 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 substance under the conditions of use that are not subject to the proposed SNUR, in order to determine that the chemical substance is not likely to present an unreasonable risk under those conditions of use. As such, EPA does not need to impose test 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 SNUR 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 substance is not likely to present an 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 substance using data received for the new chemical substance and EPI (Estimation Program Interface) Suite™ (<http://www.epa.gov/tsca-screening-tools/epi-suite-estimation-program-interface>). In wastewater treatment, the new chemical substance is expected to be removed with an efficiency of 50 - 75% via sorption and stripping. Removal of the new chemical substance by biodegradation is negligible. Sorption of the new chemical substance to sludge, soil, and

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 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 present an unreasonable risk.

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sediment is strong. Migration of the new chemical substance to groundwater is expected to be slow due to strong sorption to soil and sediment. Due to estimated vapor pressure and Henry's law constant, the new chemical substance is expected to undergo moderate - extensive volatilization to air. Overall, these estimates indicate that the new chemical substance has moderate - high potential to volatilize to air, has low potential to migrate to groundwater, and is likely to be removed in wastewater treatment.

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 substance using data received for the new chemical substance. EPA estimated that aerobic biodegradation half-life is 2 - 6 months and anaerobic biodegradation half-life is > 6 months. These estimates indicate that the new chemical substance will be persistent in aerobic environments (e.g., surface water) and will 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 substance to bioaccumulate using EPI Suite™. EPA estimated that the new chemical substance has low bioaccumulation potential based on BCFBAF model result < 1000 (bioconcentration factor = 174 [estimated] and bioaccumulation factor = 300 [estimated]). Although EPA estimated that the new chemical substance could be very persistent, the substance has a 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 is likely to present an unreasonable risk because the significance of the risk is dependent upon

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 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 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

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both the hazard (and 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, available PMN data, and by comparing it to structurally analogous chemical substances for which there is information on human health hazard.

Absorption of the new chemical substance is expected to be poor to moderate through the skin, moderate through the GI tract, and poor through the lungs based on physical/chemical properties. For the new chemical substance, EPA identified GI tract effects, liver and thyroid toxicity, and blood biochemistry effects as hazards based on submitted test data on the PMN, as well as skin irritation and sensitization based on submitted test data on the PMN and information provided in the SDS. Submitted tests of the new chemical substance reported negative findings in an Ames assay (OECD 471) and chromosome aberration assay in human lymphocytes (OECD 473). The PMN substance was reported to be irritating to the skin in vitro (OECD 439), non-corrosive to the skin in vitro (OECD 431), non-irritating and non-sensitizing to skin in a human repeat insult patch test, non-irritating to eyes in vitro (OECD 437 and OECD 4992), mildly irritating to rabbit eyes (OECD 405), positive for skin sensitization (OECD 429), negative (minimal reactivity) in a Direct Peptide Reactivity Assay (OECD 442c), positive in a KeratinoSens assay (OECD 442D). In a 28-day repeated-dose dietary study in rats, a NOAEL of 4500 ppm (340.5 and 311.9 mg/kg-day for males and females, respectively) was reported based on liver effects and corresponding biochemistry changes. EPA quantitatively assessed the new chemical substance using test data on the new chemical substance and identified a NOAEL of 311.9 mg/kg based on liver effects and corresponding biochemistry changes, which was used to derive exposure route- and population-specific points of departure for quantitative risk assessment, described below.

Environmental Hazard⁶: 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

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](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>).

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exposure to the substance. EPA determined the environmental hazard for this new chemical substance based on acute toxicity data submitted for the new chemical substance. Acute toxicity values measured for fish, aquatic invertebrates, and algae are 1.01 mg/L, 3.1 mg/L, and 1.7 mg/L, respectively. Chronic toxicity values measured for fish, aquatic invertebrates, and algae are 0.101 mg/L (ACR of 10), 0.31 mg/L (ACR of 10), and 0.83 mg/L, 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 0.202 mg/L (202 ppb) and 0.010 mg/L (10 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 new chemical assessment, EPA assessed exposure to workers via the dermal and inhalation routes. Releases to water, air, and landfill were estimated. EPA assessed general population exposure via drinking water, fish ingestion, and groundwater ingestion (from landfill leaching). Exposure to the general population via inhalation was not assessed because releases to air are expected to be negligible (below modeling thresholds). EPA assessed exposures to consumers via the dermal and inhalation routes.

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.

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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 substance were evaluated using the route-specific effect levels (i.e., NOAEL) described above. Risks were identified for workers for GI tract effects, liver and thyroid toxicity from dermal exposure (MOE = 26; benchmark MOE = 100). Risks would be mitigated if exposures can be controlled by the use of appropriate PPE, including impervious gloves. Risks were not identified for workers for GI tract effects, liver and thyroid toxicity from inhalation exposure (MOE = 2,496; benchmark MOE = 100). Irritation and sensitization hazards to workers via dermal contact were identified based on submitted information and the SDS. 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. 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 the general population for GI tract effects, liver and thyroid toxicity, and blood biochemistry effects via drinking water, fish ingestion, or ground water ingestion (from landfill leaching) based on quantitative hazard data for the new chemical substance (MOEs > 45,000; benchmark MOE = 100). Risks were not identified for the general population for sensitization and via drinking water, fish ingestion, or ground water ingestion (from landfill leaching) since these concerns are expected to be mitigated by dilution in the media. Risks were not assessed for the general population via inhalation because estimated air releases are below modeling thresholds.

Risks were not identified for consumers for GI tract effects, liver and thyroid toxicity, and blood biochemistry effects via dermal or inhalation exposure based on quantitative hazard data for the new chemical substance (MOEs > 8,500; benchmark MOE = 100). Skin irritation and sensitization hazards were identified for the new chemical substance; however, they are not expected at the low percent of the new chemical substance present in formulation in consumer products.

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

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chronic COC of 10 ppb for less than 20 days/year⁷, indicating organisms would not be exposed long enough for chronic effects to occur.

It is reasonably foreseen that the new chemical substance could be used at a higher concentration in formulation based on information provided in the original PMN submission, though EPA does not expect this would result in unreasonable risk, based on further dilution of the formulation in consumer products. EPA assessed conditions of use consistent with the increased concentration in formulation in the initial assessment and did not identify risks to consumers. It is also reasonably foreseen that the new chemical substance could be manufactured domestically, based on manufacture of similar chemical substances by the submitter within the United States. EPA was not able to assess domestic manufacture, and is therefore unable to conclude whether it may present an unreasonable risk to human health or the environment. The SNUR that has been proposed for this chemical substance defines certain conditions of use as significant new uses. The proposed significant new use includes domestic manufacture. 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).

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Date:

/s/

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