TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-19-0035

Number: P-19-0035
TSCA Section 5(a)(3) Determination: The chemical substance is not likely to present an unreasonable risk (5(a)(3)(C)).

Chemical Name:
Specific: Acetamide, 2-(4-methylphenoxy)-N-1H-pyrazol-3-yl-N-(2-thienylmethyl)-; CASRN: 1374760-95-8

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 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. Although EPA 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 hazard data on analogous chemicals and 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: severe eye irritation,

[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.

sensitization, lung effects, and histopathological effects on the nasal passages. EPA concludes that the new chemical substance is not likely to present an unreasonable risk under the conditions of use.

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 submitted data on the new chemical substance and EPI (Estimation Programs Interface) Suite™, a suite of physical/chemical property and environmental fate estimation programs (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 - 10% based on low biodegradability, low sorption, and low stripping. Sorption to sludge is estimated to be low, and sorption to soil and sediment is estimated to be moderate, resulting in moderate migration to groundwater. Volatilization to air is expected to be negligible because the substance is estimated to have a low vapor pressure and a low Henry's Law constant. Overall, these estimates are indicative of low 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. EPA estimated biodegradation half-lives of this new chemical substance using submitted data for the new chemical substance and EPI Suite™. EPA estimates the aerobic and anaerobic half-lives of the new chemical substance to be greater than six months. These estimates indicate that this substance may be very persistent in aerobic environments (e.g., surface water) and 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 using received data for the new chemical substance and EPI Suite™. The new chemical substance is estimated to have

[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)

low bioaccumulation potential (bioconcentration factor = 18; bioaccumulation factor = 17). Although EPA estimates that this 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 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 physical/chemical properties, and available data on the new chemical substance. For this new chemical substance, absorption is estimated to be nil via all routes as a neat material and good through the skin and moderate through the lung and GI tract when in solution based on physical/chemical properties. EPA identified severe eye irritation, sensitization, lung effects, and histopathological effects on the nasal passages based on data for the new chemical substance submitted with the PMN. EPA identified a LOAEC of 5 mg/m^3 for the inhalation route based on histopathological changes in the nasal passages identified in a 28-day inhalation study (OECD TG 412), and a NOAEL of 100 mg/kg-bw/day for the oral route identified based on no adverse or systemic effects at the highest dose tested in a 90-day oral repeated-dose toxicity study (OECD 417), which were used to derive exposure route- and population-specific points of departure for quantitative risk assessment, described below.

Environmental Hazard[5]: Environmental hazard is relevant to whether a new chemical substance is likely to present unreasonable risk because the significance of the risk is dependent

[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).

upon both the hazard (or toxicity) of the chemical substance and the extent of exposure to the substance. EPA estimated environmental hazard of this new chemical substance using hazard data on analogous chemicals, the Ecological Structure Activity Relationships (ECOSAR) Predictive Model (https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-releationships-ecosar-predictive-model), specifically the QSAR for thiopenes, and submitted test data on the new chemical substance. Based on test data on the new chemical substance, the acute toxicity values for fish, aquatic invertebrates, and algae are > 13.1 mg/L, 2.18 mg/L, and > 6.49 mg/L, respectively. Chronic toxicity values estimated for fish, aquatic invertebrates, and algae are 0.15 mg/L (ECOSAR), 0.21 mg/L (ECOSAR), and 2.22 mg/L (test data on the new chemical substance), respectively. Based on these toxicity values, EPA expects the new chemical substance 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 0.436 mg/L (436 ppb) and 0.015 mg/L (15 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 releases of the 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 has assessed risks to workers under the conditions of use of the new chemical substances and identified potential risk concerns for this PESS under the conditions of use. 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 route, and inhalation exposure to workers is not expected. Releases to water and air were estimated. EPA assessed exposure to the general population via drinking water and fish ingestion. Exposure to the general population via inhalation was not assessed because releases to air are expected to be negligible (below modeling thresholds). Consumer exposures were assessed via dermal and inhalation exposures.

Risk Characterization: EPA applies a margin of exposure approach, which compares an effect level to an estimated exposure concentration, 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. 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 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 and LOAEC) described above. Risks were not identified for workers via dermal exposures based on quantitative data for the new chemical substance which showed no adverse effects observed at the highest dose tested (MOE = 101; benchmark MOE = 100). Risks were not identified for workers via inhalation exposure because estimated exposures are negligible. Irritation and sensitization hazards to workers via dermal contact were identified, but risks for these hazard endpoints were not quantified due to a lack of dose-response for the hazards. Risks would be mitigated if exposures can be controlled by the use of appropriate PPE, including impervious gloves and eye protection. EPA expects that workers will use appropriate PPE, including impervious gloves and eye protection, consistent with the Safety Data Sheet prepared by the submitter, in a manner adequate to protect them.

Risks were not identified for the general population via drinking water (MOE_{Adult} = 1,169,590; MOE_{Infant} =278,473; benchmark MOE = 100) or fish ingestion (MOE = 2,100,840; benchmark MOE = 100). Risks were not identified for the general population for irritation via drinking water because irritation effects are expected to be mitigated by dilution in the media. Risks were not identified for the general population via inhalation exposure because exposures are expected to be negligible (below modeling thresholds).

Risks were not identified for consumers via inhalation (MOE = 6,200,000; benchmark MOE = 1,000) or dermal exposure (MOE = 193,573; benchmark MOE = 100). Risks were not identified for consumers for the identified irritation and sensitization hazards because risks for these endpoints are not expected at the low exposure levels and formulation concentrations estimated for consumers.

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 due to relevant estimated surface water concentrations that did not exceed the acute and chronic COCs.

TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-19-0035

Because worker exposures can be controlled by PPE, and no unreasonable risks to the general population, consumers, and 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.

03/28/19
Date:

/s/
Tala R. Henry, Ph.D.
Acting Deputy Director for Programs
Office of Pollution Prevention and Toxics