TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-20-0011

Number: P-20-0011
TSCA Section 5(a)(3) Determination: The chemical substance is not likely to present an unreasonable risk (5(a)(3)(C))

Chemical Name:
Generic: Tetraoxaspiro[5.5]alkyl-3,9-diylbis(alkyl-2,1-diyl) bis(2-cyano-3-(3,4-dimethoxyphenyl)acrylate)

Conditions of Use (intended, known, or reasonably foreseen)[1]:
Intended conditions of use (generic): Import and process for use as and use as a light stabilizer, consistent with the 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 substance has low potential for bioaccumulation, such that repeated exposures are not expected to cause food-chain effects via accumulation in exposed organisms. Based on EPA's TSCA New Chemicals Program Chemical Category for Esters and Vinyl Nitriles,[2] available data on the new chemical substance, and test data on analogous chemical substances, EPA estimates that the

[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] 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.

chemical substance has high environmental hazard and potential for the following human health hazards: specific target organ toxicity and reproductive toxicity (for the potential metabolite). 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 the new chemical substance using data for analogue(s) (compounds with large molecular volume) and data submitted for the new chemical substance. In wastewater treatment, the new chemical substance is expected to be removed with an efficiency of 90% due to sorption. Removal of the new chemical substance by biodegradation is negligible. Sorption of the new chemical substance to sludge is expected to be strong and to soil and sediment is expected to be very strong. Migration of the new chemical substance to groundwater is expected to be negligible due to very strong sorption to soil and sediment. Due to low estimated vapor pressure and Henry's law constant, the new chemical substance is expected to undergo negligible volatilization to air. Overall, these estimates indicate that the new chemical substance has low potential to volatilize to air or migrate to groundwater.

Persistence[3]: 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 submitted for the new chemical substance. EPA estimated that the new chemical substance's aerobic and anaerobic biodegradation half-lives are > 6 months. These estimates indicate that the new chemical substance may be very persistent in aerobic environments (e.g., surface water) and anaerobic environments (e.g., sediment).

Bioaccumulation[4]: 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 data for analogues (compounds with large molecular volume). EPA estimated that the new

[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 if 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 if there are equivalent or analogous data. (64 FR 60194; November 4 1999)

chemical substance has low bioaccumulation potential based on large predicted molecular volume, which limits bioavailability. Although EPA estimated that the new chemical substance could be very persistent, the substance has low potential for bioaccumulation, such that repeated exposures are not expected to cause food-chain effects via accumulation in exposed organisms.

Human Health Hazard[5]: 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, available data on the new chemical substance, 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 nil to poor through the skin, lungs, and gastrointestinal (GI) tract based on physical/chemical properties. There are concerns for aliphatic nitriles to produce neurotoxicity, developmental effects upon metabolism based on the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationships (QSAR) ToolBox metabolites lacking the cyano group and test data on the metabolites. There are concerns for sensitization based on the OECD QSAR ToolBox alert for reactive functional groups, but this concern is reduced based on negative results in the Local Lymph Node Assay (LLNA) method. Submitted tests on the new chemical substance reported the test substance as non-irritating to skin and eyes in vitro (OECD 437 and 439), non-sensitizing in an LLNA in mice (OECD 429), non-mutagenic in a bacterial reverse mutation assay (OECD 471), and did not identify effects in an acute oral study in rats (OECD 423). EPA identified a NOAEL of 8 mg/kg-day based on significant and dose related increases in absolute and relative liver and kidney weights that were used to derive exposure route- and population-specific points of departure.

Environmental Hazard[6]: Environmental hazard is relevant to whether a new chemical substance is likely to present unreasonable risk because the significance of the risk is dependent

[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 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.

[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

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 the Ecological Structure Activity Relationships (ECOSAR) Predictive Model (https://www.epa.gov/tsca-screening-tools/ecological-structure-activityrelationships-ecosar-predictive-model); specifically the QSAR for vinyl/allyl/propargyl nitriles and polyaliphatic nitriles as well as acute toxicity data submitted for the new chemical substance. This substance falls within the TSCA New Chemicals Category of Esters and Vinyl Nitriles. Acute toxicity values estimated for fish, aquatic invertebrates, and algae are 0.36 mg/L, 51.8 mg/L, and 13.7 mg/L, respectively. Chronic toxicity values estimated for fish, aquatic invertebrates, and algae are 0.007 mg/L, 5.7 mg/L, and 1.8 mg/L, respectively. These toxicity values indicate that the new chemical substance is expected to have high environmental hazard. Application of an assessment factor of 5 to acute toxicity values, results in an acute concentration of concern (COC) of 0.072 mg/L (72 ppb). Application of an assessment factor of 10 to chronic toxicity values results in a chronic concentration of concern of 0.0007 mg/L (0.7 ppb). Due to uncertainties in the modeling estimates for this substance (e.g. log Kow, toxicity values) and the limitations of analytical tools (e.g. high performance liquid chromatography, gas chromatography), the chronic COC is rounded up to 1 ppb.

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.

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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).

For this new chemical assessment, EPA assessed worker exposure via dermal and inhalation routes. Releases to water, air, and landfill were estimated. Exposure to the general population was assessed via drinking water. Exposure to the general population via fish ingestion was not assessed because bioaccumulation potential was evaluated to be low or via groundwater impacted by landfill leaching because migration of the new chemical substance to groundwater was expected to be nil, or via inhalation because releases to air were expected to be negligible (below modeling thresholds). Consumer exposures were not assessed because consumer uses were not identified as conditions of use.

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 (UF) 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 Lowest Observed Adverse Effect Level (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 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., NOAEL) described above. Risks were identified for workers for liver and kidney effects via inhalation based on quantitative hazard data for an analogue (MOE_{total} = 6; Benchmark MOE = 100; Fold Factor = 17, and $MOE_{respirable}$ = 18; Benchmark MOE = 100; Fold Factor = 6). Risks were identified for workers for liver and kidney effects via dermal exposure based on quantitative hazard data for an analogue (MOE= 1.9; Benchmark MOE = 100). Risks will be mitigated if exposures are controlled by the use of appropriate PPE, including chemically impervious gloves and respiratory protection. EPA expects that employers will require and workers will use appropriate PPE (i.e., impervious gloves and respiratory protection), consistent with the Safety Data Sheet prepared by the PMN submitter, in a manner adequate to protect them.

Risks were not identified for the general population for liver and kidney effects via drinking water exposure based on quantitative hazard data for a an analogue (Drinking Water MOE_{Adult} = 137,931; MOE_{Infant} = 32,841; Benchmark MOE = 100). Risks were not evaluated for the general population via fish ingestion because bioaccumulation potential was evaluated to be low, or via groundwater impacted by landfill leaching because migration to groundwater was nil, or via inhalation because exposures are expected to be negligible. Risks to consumer were not evaluated because consumer uses were not identified as conditions of use.

Risks to the environment were evaluated by comparing estimated surface water concentrations with the acute and chronic concentrations of concern. Risks from acute exposure to the environment were not identified due to releases to water that did not exceed the acute COC. Risks from chronic exposure to the environment were not identified due to releases to water that exceeded the chronic COC of 1 ppb for less than 20 days/year[7] (10/30 days/year during processing of the new chemical substance).

Because worker exposures can be controlled by PPE, no unreasonable risks to the general population or environment were identified, and there are no expected consumer exposures, 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.

07/17/2020
Date:

/s/
Madison H. Le, Director
Chemical Control Division
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[7] The 20-day criterion for concluding chronic risk is not likely is based on partial life cycle tests (daphnid chronic and fish early life stage tests) that typically range from 21 to 28 days in duration.