TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-16-0510

Number: P-16-0510
TSCA Section 5(a)(3) Determination: Chemical substance not likely to present an unreasonable risk (5(a)(3)(C))

Chemical Name:
Specific: Oxirane, 2-methyl-, polymer with oxirane, bis[2-[(1-oxo-2-propen-1-yl)amino]propyl] ether (CASRN: 1792208-65-1).

Conditions of Use (intended, known, or reasonably foreseen)[1]:
Intended conditions of use (specific): Import in solution at a concentration of approximately 50% for processing and use as, a deodorizer in industrial, commercial, and household consumer products such as floor cleaners, cat litters, fabric refresher sprays, etc. at a maximum concentration of 2% by weight in the formulation of the final product, consistent with the manufacturing, processing, use, distribution, and disposal information described in the PMN.
Known conditions of use: None.
Reasonably foreseen conditions of use: 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 chemical substance has low potential for bioaccumulation, such that repeated exposures are not expected to be cumulative. Based on EPA's TSCA New Chemicals Program Chemical Categories for Acrylates and Acrylamides[2] and test data on analogous chemical substances, EPA estimates that the chemical substance has low to moderate environmental hazard and the potential for the following human health hazards: irritation, mutagenicity, developmental/reproductive toxicity,

[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. 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.

neurotoxicity, and carcinogenicity. Based on test data on structural analogues to the low molecular weight components of the PMN substance, systemic effects were used as the endpoint for evaluation. EPA determines that the conditions of use would not present unreasonable risk because the PMN submitter would import the chemical substance in solution at a concentration of 50% or less for processing which would result in a deodorizer for use at a concentration of 2% by weight in the formulation of the final product.

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 data for analogous polymers. The chemical substance is expected to be removed with an efficiency of 90% during wastewater treatment due to strong sorption to sludge and partial destruction by biodegradation. Polymers are expected to sorb via Van der Waals interactions that result in binding to solids found in sludge and soil, so sorption to sludge is estimated to be strong, and sorption to soil and sediment is expected to be very strong, resulting in negligible migration to groundwater. Volatilization to air is expected to negligible because the substance is expected to have 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 low potential for this chemical to migrate into ground water.

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. Based on data for analogous polymers, EPA estimated the aerobic biodegradation half-life to be between two and six months and the anaerobic biodegradation half-life to be greater than six months. These estimates for biodegradation indicate that the chemical substance may be persistent in aerobic environments (e.g., surface water) and very persistent in 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

[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)

food chains. The chemical substance has low bioaccumulation potential based on estimates from analogous polymers and large predicted molecular volume, which inhibits bioavailability. Although EPA estimated that the new chemical substance could be very persistent, the chemical 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, analogues, and other structural information. Absorption of the low molecular weight components of the PMN substance is expected to be good through the lungs and poor through the skin and GI tract based on physical/chemical properties. Should there be exposure to the LMW components, EPA may, depending on the extent of exposure, have potential concerns for mutagenicity, developmental toxicity, reproductive effects, neurotoxicity, and a marginal potential concern for oncogenicity based on the potential for Michael addition of functional groups to DNA or other biological molecules. EPA quantitatively assessed hazard for the low molecular weight (LMW) components of the PMN substance, which are expected to be more bioavailable and therefore present the greatest potential risk concern, based on read across data for two analogues, 1,6-hexamethylene diacrylate (HDDA), and dipropylene glycol diacrylate (DPGD) (ECHA, 2011)[6]. The analogues are structurally similar to the PMN substance and are expected to exhibit a similar mode of action (MOA). EPA also considered acrylamide as a potential analogue, but selected DPGD/HDAA as the more predictive analogue for conducting risk calculations due to expected greater reactivity of DPGD/HDDA with potential cellular targets (cysteine residues). However, for comparison, EPA also included in the assessment quantitative hazard/risk calculation for the LMW components based on data

[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 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] ECHA (2011) *Oxybis(methyl-2,1-ethanediyl) diacrylate, EC number: 260-754-3, CAS number: 57472-68-1*, European Chemicals Agency (ECHA), available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14685/1

for acrylamide evaluated in the Toxicological Review of Acrylamide (EPA, 2010)[7].

EPA identified a NOAEL of 250 mg/kg/day for DPGD/HDDA systemic toxicity in a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) (ECHA, 2011) and a $BMDL_{05}$[8] of 0.27 mg/kg/day for acrylamide neurotoxicity observed in a chronic rodent drinking water study (EPA, 2010), which were used to derive exposure route- and population-specific points of departure for quantitative risk assessment.

Environmental Hazard[9]: 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 estimated environmental hazard of this new chemical substance using hazard data on analogous chemicals. The new chemical substance falls within the TSCA New Chemicals Program Chemical Categories of Nonionic Polymers and Acrylamides and the SAR chemical classes of nonionic polymers and acrylamides. The acute (LC50) and chronic (ChV) values are >100 and >10 mg/L, indicating low ecotoxicity. Application of acute and chronic assessment factors of 5 and 10 to the acute and chronic values, respectively, results in concentrations of concern (COCs) of 20 mg/L (20,000 ppb) and 1 mg/L (1,000 ppb), respectively, for the PMN substance at its average molecular weight. For the LMW components of the PMN substance, the acute (LC50) and chronic (ChV) values are 1.7 and 0.43 mg/L, indicating moderate ecotoxicity. Application of acute and chronic assessment factors of 4 and 10 to the acute and chronic values, respectively, results in concentrations of concern of 0.425 mg/L (425 ppb) and 0.043 mg/L (43 ppb), respectively, for the LMW components. Based on these estimated hazard values, EPA concludes that this chemical has low to moderate environmental hazard.

Exposure and Risk Characterization: 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.

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[7] EPA (2010) *Toxicological Review of Acrylamide (CAS No. 79-06-1), In Support of Summary Information on the Integrated Risk Information System (IRIS)*, EPA/635/R-07/009F, 459 pp., available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0286tr.pdf

[8] The term "$BMDL_{05}$" refers to the lower bound confidence limit (L) on the dose, derived by benchmark dose modeling methods (BMD), and the "05" signifies a 5% change in biological response. See https://www.epa.gov/bmds for additional information.

[9] 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).

EPA estimated occupational exposure and environmental release 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 used 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. Specifically, EPA assessed exposure via dermal and inhalation routes to workers during processing and consumers during use of the chemical substance. EPA assessed exposure to the general population via drinking water and fish ingestion.

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, unreasonable risk is considered unlikely.

Risks to human health for the PMN substance were evaluated using the route-specific effect levels (i.e., NOAEL) described above. The exposures predicted under the intended conditions of use are not expected to present unreasonable risk because the MOEs calculated using the DPGD/HDAA analogues, exceeded the benchmark MOEs (100 for inhalation exposure and 30 for dermal and oral exposures). EPA does not have concern for risk to workers for systemic toxicity from either inhalation or dermal exposure, when processed at a concentration of 50%, because the MOEs exceeded the benchmark MOE. EPA does not have concern for risk to consumers for systemic effects from dermal or inhalation exposure, when used at a concentration of 2% by weight in the formulation of the final product, because the calculated MOEs exceeded the benchmark MOEs. Notably, EPA also estimated the percentage of PMN substance in solution that could be used without exceeding the benchmark MOE for both inhalation and dermal exposures and found that there was no upper limit of PMN substance in solution for which risk would be identified (*i.e.*, no risk was identified at up to 100% PMN in solution). EPA does not have concern for risk to the general population for systemic effects from oral exposure to water or consumption of fish because the MOEs exceeded the benchmark MOE of 30.

Risks to the environment were evaluated by comparing estimated surface water concentrations with the estimated acute and chronic COCs of 425 ppb and 43 ppb, respectively, for the LMW components. EPA does not have concern for risk to the environment because the estimated maximum and chronic surface water concentrations did not exceed the ecological acute or chronic COCs.

Potentially Exposed or Susceptible Subpopulation(s) (PESS): EPA considers workers to be a 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 PMN substance and concludes that workers are not expected to be exposed to the PMN substance at levels that would present an unreasonable risk. 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. Using this approach, no unreasonable risks were identified for the general population for any life stage, as the calculated MOEs exceeded the benchmark MOE. 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 consumer exposure to this PMN substance when used at a concentration of 2% by weight in the formulation of the final product, the calculated MOEs exceeded the benchmark MOE.

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Date:

/s/
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