TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-20-0066

Number: P-20-0066
TSCA Section 5(a)(3) Determination: The chemical substance is not likely to present an unreasonable risk (5(a)(3)(C))

Chemical Name:
Generic: 2-Propenoic acid, 2-hydroxyethyl ester, reaction products with dialkyl hydrogen heterosubstituted phosphate and dimethyl phosphonate

Conditions of Use (intended, known, or reasonably foreseen)[1]:
Intended conditions of use (generic): Manufacture and process for use as and use as an antiwear additive for lubricants, 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 cause food-chain effects via accumulation in exposed organisms. Based on available test data on the new chemical substance and comparing the chemical substance and its possible hydrolysis products and metabolites to structurally analogous chemical substances for which there is information on human health hazard, EPA estimates that the chemical substance has high environmental hazard and potential for the following human health hazards: skin irritation, eye

[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.

irritation, carcinogenicity, reproductive toxicity, and specific target organ toxicity. 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), data submitted for the new chemical substance, and EPI (Estimation Program Interface) Suite™ (http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface). In wastewater treatment, the new chemical substance is expected to be removed with an efficiency of 25% to 75% 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 low to strong and to soil and sediment is expected to be low to very strong. Migration of the new chemical substance to groundwater is expected to be negligible to rapid due to low 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 and has unknown potential to migrate to 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 degradation half-lives of the new chemical substance using data for analogue(s) and 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[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 to bioaccumulate using data for

[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 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)

[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 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)

analogue(s) and EPI Suite™. EPA estimated that the new chemical substance has low bioaccumulation potential based on BCFBAF model result mitigated by expected metabolism (bioconcentration factor = 1,905 [estimated by linear regression from log Kow] and bioaccumulation factor = 83 [estimated by the Arnot-Gobas method (2003)])[4]. The listed BCFBAF model values are for a representative structure of the new chemical substance. The substance is expected to undergo metabolism, and as a result, the estimated bioaccumulation factor was used to determine the low bioaccumulation potential for the new chemical substance. The measured bioconcentration data for the analogue was also used to support the bioaccumulation potential. 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, by comparing it to structurally analogous chemical substances for which there is information on human health hazard, and other structural information. Absorption is expected to be poor to moderate through the skin, moderate through the gastrointestinal (GI) tract, and poor through the lungs based on physical/chemical properties. EPA expects the new chemical substance to undergo ester hydrolysis in the acidic environment of the stomach to release ethylene glycol. For the new chemical substance, EPA identified hazards for skin and eye irritation based on submitted data on the new chemical substance (OECD 404, OECD 405); systemic toxicity and reproductive/developmental toxicity, based on analogue data; and systemic toxicity and reproductive/developmental toxicity based on a hydrolysis product and two residual compounds. Submitted tests on the new chemical substance reported the test substance as not acutely toxic in rats (OECD 402, OECD 420), slightly irritating to skin in rabbits (OECD 404), mildly irritating

[4] Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. *QSAR and Combinatorial Science* 22: 337-345.

[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.

to eyes in rabbits (OECD 405), positive for skin sensitization in vitro (OECD 442D), but negative for skin sensitization in vitro and in vivo (OECD 442C and OECD 406), and negative for mutagenicity/genotoxicity in vitro with and without metabolic activation (OECD 471, OECD 473, OECD 490). EPA identified a non-cancer NOAEL of 9 mg/kg-bw/day for subchronic/chronic exposures, Oral Slope Factor (OSF) of 9×10^{-3} per mg/kg/day-bw/day, and a Benchmark Dose Limit-1 Standard Deviation ($BMDL_{1SD}$) of 111 mg/kg-bw/day for short-term exposures (<14 days/year). These values were based on systemic effects in 10-week & 2-year repeated-dose oral toxicity studies in rats and decreased weight gain in pregnant rats for an analogue, respectively. EPA considered these values protective for systemic toxicity and reproductive/developmental effects. EPA used the selected values to derive exposure route- and population-specific points of departure for quantitative risk assessment, described below. EPA qualitatively evaluated irritation.

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 upon both the hazard (or toxicity) of the chemical substance and the extent of 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 14 mg/L, 0.56 mg/L, and 39 mg/L, respectively. Chronic toxicity values measured for fish, aquatic invertebrates, and algae are 1.4mg/L, 0.056 mg/L, and 5.5 mg/L, respectively. These toxicity values indicate that the new chemical substance is expected to have high 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 0.02 mg/L (20 ppb) and 0.006 mg/L (6 ppb), respectively. Due to uncertainties in the estimates for this substance (use of an Acute-to-Chronic Ratio (ACR)) and the limitations of analytical tools (e.g., HPLC, GC), the chronic COC is rounded up to 6 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

[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).

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 exposures via the inhalation and dermal routes. Releases to air and landfill were estimated. Exposures to the general population were not assessed via groundwater impacted by landfill leachate or via inhalation because releases to landfill and air were expected to be negligible (below modeling thresholds) or via drinking water and fish ingestion because no releases to surface water are expected. Exposures to consumers were assessed for dermal exposure.

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 substance were evaluated using the route-specific effect levels (i.e. NOAEL, OSF, and $BMDL_{1SD}$), described above. Risks were identified for workers for systemic toxicity via inhalation and dermal exposures based on quantitative hazard data for an analogue ($MOE_{Inhalation}$ = 13; MOE_{Dermal} = 0.54; Benchmark MOE = 100, Fold factor = 8). Risks were identified for workers for cancer via dermal exposure based on quantitative hazard information for an analogue (Cancer risk= 1.1E-03). Risks were identified for workers for cancer via inhalation exposure based on quantitative hazard information for an analogue (Cancer risk= 1.8E-04). Irritation hazards to workers via inhalation and dermal exposure were identified based on submitted test data and the pH of the new chemical substance. 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, eye protection, and respiratory protection. EPA expects that employers will require and workers will use appropriate PPE (i.e., impervious gloves, eye protection, and respiratory protection), consistent with the Safety Data Sheet prepared by the PMN submitter, in a manner adequate to protect them.

Risks to the general population were not evaluated because exposures are below modeling thresholds. Risks were not identified for consumers for systemic toxicity in the Lubricant Scenario for [claimed CBI] via dermal exposure based on quantitative hazard data for an analogue (MOE = 1,004; Benchmark MOE = 100). EPA assumes that skin and eye irritation is not expected from exposure to the consumer product as long as the concentration of the new chemical substance in the consumer product is maintained below 3% and to the extent that remaining unknown components do not exhibit irritating properties[7]. The concentration of the new chemical substance in the final product is [claimed CBI]% by weight.

Risks to the environment were not identified due to no releases to water.

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

9/18/2020
Date:

/s/
Madison H. Le, Director
Chemical Control Division
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U.S. Environmental Protection Agency

[7] EPA is using the *Globally Harmonized System of Classification and Labelling of Chemicals (GHS): Eighth Revised Edition (*UN, New York, https://doi.org/10.18356/f8fbb7cb-en, Chapter 3.2 and 3.3), to establish the cut-off value for the new chemical substance's skin and eye irritation effects in consumer products. EPA will consider a mixture to be irritating to the skin or eye when the concentration of the new chemical substance is ≥ 3% in the mixture. When selecting the cut-off value, EPA assumes that a mixture containing irritant ingredients cannot be classified based on the additivity approach. The theory of additivity assumes that each ingredient contributes to the overall irritant properties of the mixture in proportion to its potency and concentration. However, there are types of chemicals that the theory of additivity might not apply.
Annex 5 of the GHS document states *"[e]stimates of possible exposures and risk to consumers should be based on conservative, protective assumptions to minimize the possibility of underestimating exposure or risks [Section A5.2.1(c)]."* Thus, EPA selected the cut-off value (≥ 3%) under the assumption that the additivity approach does not apply for the new chemical substance in relation to the other ingredients in the consumer product.