TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-16-0314

Number: P-16-0314
TSCA Section 5(a)(3) Determination: The chemical substance is not likely to present an unreasonable risk (5(a)(3)(C))

Chemical Name:
Specific: Ethanone, 1-(5-propyl-1,3-benzodioxol-2-yl)-

Conditions of Use (intended, known, or reasonably foreseen)[1]:
Intended conditions of use (generic): Import for processing and use as part of a fragrance formula, consistent with the manufacture, processing and use 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 non-risk 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. EPA estimated that the new chemical substance would have low persistence and a low potential for bioaccumulation, such that repeated exposures are not expected to be cumulative. Based on 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: liver toxicity for the intact new chemical substance and oncogenicity of a ketone/aldehyde hydrolysis product(s) that may be formed under the acidic conditions in the stomach. EPA concludes that the new chemical substance is not likely to present an unreasonable risk under the conditions of

[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.

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 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). In wastewater treatment, the new chemical substance is expected to be removed with 90% efficiency based on sorption, biodegradation, and stripping. Migration of the new chemical substance to groundwater is expected to be moderate due to rapid biodegradation. Due to estimated vapor pressure, the new chemical substance is expected to undergo moderate volatilization to air. Overall, these estimates indicate that the new chemical substance has moderate potential to volatilize to air and moderate 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 biodegradation half-lives of the new chemical substance using 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). EPA estimated that the aerobic and anaerobic biodegradation half-lives of the new chemical substance are less than 2 months. Based on these estimates, EPA expects the new chemical substance not to be persistent in aerobic environments (e.g., surface water) or 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 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). These estimates indicate that the new chemical substance has low bioaccumulation

[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)

potential (bioconcentration factor = 28; bioaccumulation factor = 41). EPA estimated that the new chemical substance would have low persistence and 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 non-cancer hazard of this chemical substance based on data on the new chemical substance. For this new chemical, absorption is estimated to be good through the skin, lungs, and GI tract based on physical/chemical properties. The new chemical substance was tested for genotoxicity (OECD Test Guidelines (TG) 471 and 473) and results were negative. The new chemical substance was not irritating in submitted eye and skin irritation tests (OECD TG 404 and 405), and was not a skin sensitizer in a submitted Guinea Pig Maximization Test (OECD TG 402). Acute toxicity tests conducted via oral (OECD TG 423), inhalation (OECD TG 403), and dermal (OECD TG 402) exposures all indicated the new chemical substance has low acute toxicity. A NOAEL of 300 mg/kg/day based on increased liver weights and effects on clinical chemistry parameters was identified in a 28-day oral gavage repeated-dose toxicity test (OECD TG 407) of the new chemical substance. This NOAEL was used to derive exposure route- and population-specific points of departure for quantitative risk assessment.

Although there are no oncogenicity concerns for the intact new chemical substance, there are oncogenicity concerns for hydrolysis products that are expected to be formed in the acidic condition of the stomach, 2-hydroxy-4-propyl-phenol (also known as 4-propyl-catechol) and beta-ketopropanal. Both breakdown products present cancer concerns. 4-Propyl-catechol is an analog of catechol, which is mutagenic and carcinogenic. For quantitative risk assessment, catechol should be the best analog for the new chemical substance; however, the available study only used 30 animals per group and one dose and thus is not ideal. Therefore, EPA used the results of a National Toxicology Program (NTP) study on hydroquinone as the basis for the

[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.

quantitative assessment of cancer risk. Hydroquinone (benzene, 1,4-dihydroxy) and catechol (benzene, 1,2-dihydroxy) are expected to have comparable modes of action. A Provisional Peer Review Toxicity Value (PPRTV) is available for hydroquinone. EPA calculated an oral slope factor of $6x10^{-2}$ $(mg/kg\text{-}day)^{-1}$ based on the NTP study. Risks were not evaluated for cancer via dermal or inhalation exposures since carcinogenic metabolites are unlikely to be produced via these exposure routes.

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 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 test data on the new chemical substance and 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 neutral organics. Based on submitted test data on the new chemical substance, acute toxicity values for fish, aquatic invertebrates, and algae are 23 mg/L, 21.7 mg/L, and 7.45 mg/L, respectively. Chronic toxicity values for fish (estimated using ECOSAR), aquatic invertebrates (estimated applying an acute to chronic ratio assessment factor of 10 based on submitted test data on the new chemical substance), and algae (based on submitted test data on the new chemical substance) are 4.29 mg/L, 2.17 mg/L, and 2.96 mg/L, respectively. These toxicity values indicate that the new chemical substance is expected to have moderate environmental hazard. Application of assessment factors of 4 and 10 to acute and chronic toxicity values, respectively, results in acute and chronic concentrations of concern of 1.863 mg/L (1,863 ppb) and 0.217 mg/L (217 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-

[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).

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. Exposure to the general population was assessed via inhalation, drinking water and fish ingestion. EPA also assessed inhalation and dermal exposures to consumers.

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. 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).

Non-cancer risks to human health for the new chemical were evaluated using the points of departure (i.e., NOAEL) described above. Risks were not identified for workers for liver effects via inhalation exposure (All MOEs > 3,428,571; benchmark MOE = 100). Risks were identified for workers for liver effects via dermal exposure (MOE = 11; benchmark MOE = 100). Risks will be mitigated if exposures can be controlled by the use of appropriate PPE, including impervious gloves. EPA expects that employers will require and workers will use appropriate personal protective equipment (i.e., impervious gloves), consistent with the Safety Data Sheet prepared by the PMN submitter, in a manner adequate to protect them.

Non-cancer risks were not identified for the general population for liver effects via drinking water (MOE_{Adult} = 1,600,000; MOE_{Infant} = 450,000; benchmark MOE = 100) or fish ingestion (MOE = 1,300,000; benchmark MOE = 100). Risks were not identified for consumers for liver

effects via inhalation exposure (MOE = 50,676; benchmark MOE = 100) or dermal (MOE for Bar Soap Scenario = 24,390; MOE for General Purpose Cleaners Scenario = 139,535; benchmark MOE =100).

Risks were not identified for the general population for cancer via drinking water exposure based on quantitative data for an analog for an expected metabolite of the new chemical substance, hydroquinone (Cancer risk = 8.0E-08).

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 because the estimated surface water concentrations did not exceed the acute or chronic COCs.

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.

5/28/2019
Date:

/s/
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