TSCA Section 5(a)(3) Determination for Premanufacture Notice (PMN) P-19-0037

Number: P-19-0037
TSCA Section 5(a)(3) Determination: The chemical substance is not likely to present an unreasonable risk (5(a)(3)(C))

Chemical Name:
Generic: D-Glucaric acid, mixed alkali metal salt

Conditions of Use (intended, known, or reasonably foreseen)[1]:
Intended conditions of use (generic): Manufacture for use as a chemical intermediate, consistent with 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 has identified the following reasonably foreseen uses based on patent searches: manufacture, processing, or use, other than for the use described in the PMN, including preparation of modified polymers, preparation of biomass-based colloidal carbon, coating gravel packs and with polymeric breaker, nanotextured silicone hydrogel lenses, anti-freeze composition; and based on analogue information: use as a sequestering agent in detergents, and plasticizer retardant for concrete.

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.

[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.

EPA estimated that the new chemical substance is not persistent due to rapid biodegradation and has low potential for bioaccumulation, such that repeated exposures are not expected to be cumulative. Based on test data on the new chemical substance and on analogous chemical substances, EPA estimates that the chemical substance has moderate environmental hazard and has identified the following human health hazards: irritation and possibly developmental and blood toxicity. EPA determines that the new chemical is not likely to present unreasonable risk to human health or the environment 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 new chemical substance is likely to present an unreasonable risk. EPA estimated physical/chemical and fate properties of this 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), as well as measured data on analogues. Based on this information, EPA estimates that the new chemical substance will be rapidly and completely biodegraded during wastewater treatment. The chemical substance is estimated to be removed with an efficiency of 95-99.9% during wastewater treatment due to destruction by biodegradation. The rapid biodegradation is also estimated to result in negligible migration to groundwater. Biodegradation in aquatic aerobic and anaerobic environments is also estimated to be fast, with half-lives on the order of weeks. Volatilization to air is estimated to be negligible because the substance is estimated 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 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 EPI (Estimation Programs Interface) Suite™. EPA estimated that the aerobic and anaerobic biodegradation half-lives of the chemical substance will be less than 2 months. These estimates for biodegradation indicate that the new chemical substance is not expected to be persistent in aerobic environments (e.g., surface water) or in anaerobic environments (e.g., sediment).

[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)

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 EPI Suite™. These estimates indicate that the chemical substance has low bioaccumulation potential (bioconcentration factor = 3; bioaccumulation factor = 1), indicating that 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[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 estimated physical/chemical properties, and by comparing it to structurally analogous chemical substances for which there is information on human health hazard. For this new chemical substance, absorption is estimated to be nil to poor through the skin based on physical/chemical properties and good through the lung and gastrointestinal tract based on analogues. EPA identified irritation and possibly developmental and blood effects as hazards based on structural alerts. EPA also identified developmental and blood effects as potential hazards based on analogues and the chelating ability of metals; however the analogue data available for this endpoint showed no effects at the highest dose tested and has also been assessed in EPA's Safer Chemicals Ingredients List (SCIL) and is "expected to be of low concern based on experimental

[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)

[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.

and modeled data.". The NOEL for this study was 274 mg/kg-bw/day – the highest dose tested, at which no effects were observed in a prenatal developmental toxicity study in mice (OECD 414). This NOEL was used to derive exposure route- and population-specific points of departure for quantitative risk assessment, described below. Although as noted, there were no effects at this dose, so this will result in a conservative estimate of risk. A benchmark MOE of 100 was used.

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 hazard data on an analogous chemical (tartaric acid; CASRN: 87-69-4). Acute ecotoxicity values measured for fish, aquatic invertebrates and algae are >100 mg/L, 93.3 mg/L and 51.4 mg/L, respectively. Chronic ecotoxicity values for fish, aquatic invertebrates, and algae are >10 mg/L, 9.33 mg/L, 4.42 mg/L, respectively. These toxicity values indicate the new chemical substance is expected to have moderate hazard. Application of assessment factors of 4 and 10 to acute and chronic toxicity values, respectively, results in an estimated acute concentration of concern (COC) of 12.85 mg/L (12,850 ppb) and a chronic COC of 0.442 mg/L (442 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 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 also considers PESS

[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).

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 dermal exposure, and inhalation exposure to workers is not expected. Releases to water were estimated. Exposure to the general population was assessed 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). Exposures to consumers were not assessed because consumer use was not identified as an intended condition 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 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).

Risks to human health for the new chemical substances were evaluated using the points of departure (i.e., NOEL) described above. Risks were not identified for workers for developmental effects via dermal exposure when moderate absorption was assumed (MOE = 406; benchmark MOE = 100). EPA also calculated risks assuming a maximum allowable concentration of 100%, and also did not identify risks for workers for developmental effects via dermal exposure when an estimate of poor absorption was assumed (i.e., high end of the estimated range of absorption) and the conservative POD (NOEL) for an analogue (MOE = 406; benchmark MOE = 100). Irritation hazards to workers via dermal contact were identified based on analogue data. Risks for these endpoints were not quantified due to a lack of dose-response for these hazards. However, exposures can be mitigated by the use of appropriate PPE, including impervious gloves and eye protection. EPA expects that employers will require and workers will use appropriate PPE consistent with the Safety Data Sheet prepared by the new chemical submitter, in a manner adequate to protect them.

Risks were not identified for the general population for developmental effects via oral exposure or inhalation exposure (all MOEs >= 3,545; benchmark MOE = 100). General population risks for irritation cannot be quantified due to a lack of dose-response information; however, irritation risks are expected to be mitigated by dilution of the new chemical substance upon release into environmental media.

Risks to the environment are evaluated by comparing estimated surface water concentrations with the acute and chronic COCs. Estimated surface water concentrations did not exceed the acute COC, and the chronic COC was exceeded less than 20 days[6], indicating organisms would not be exposed long enough for chronic effects to occur.

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 intended conditions of use.

It is reasonably foreseen, based on a number of patents, that the new chemical substance may be manufactured, processed, or used in ways other than those described in the PMN, including in consumer products. Because no unreasonable risks were identified under the intended conditions of use and at a maximum concentration of 100% using conservative estimates for absorption and effects level, EPA determines that unreasonable risk for developmental effects under reasonably foreseen conditions of use is not likely. If the new chemical substance is used at a concentration that may result in irritation, EPA expects that workers will use PPE or otherwise handle products appropriately to limit exposure. EPA also expects that, if the chemical substance were ever used in consumer products, such products would only contain the new chemical substance at concentrations that are not irritating. Although the new chemical substance is estimated to have moderate environmental hazard, it is also predicted to biodegrade rapidly such that EPA believes that this chemical substance would be unlikely to present an unreasonable risk even if releases to the environment were high. Therefore, EPA concludes that the new chemical is not likely to present unreasonable risk to human health or the environment under reasonably foreseen conditions of use.

4/12/2019 /s/

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[6] 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.