United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/petitioned-substances

Document Type:

☐ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☒ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Potassium Sorbate

Crops

Potassium Sorbate

Chemical Names:
2,4-Hexadienoic acid, potassium salt (1:1); 2,4-Hexadienoic acid, potassium salt (1:1), (2E,4E)-; (2*E*,4*E*)-hexa-2,4-dienoic acid; Potassium 2,4-hexadienoate; Potassium (2E,4E)-hexa-2,4-dienoate; Potassium (E,E)-1,3-pentadiene-1-carboxylic acid; 2-propenylacrylic acid; Potassium salt of trans, trans-2,4-hexadienoic acid; Sorbic acid, potassium salt

Other Name:
K sorbate; Sorbistat-K

Trade Names:
Potassium Sorbate, Powder; Potassium Sorbate, Granular

CAS Numbers:
24634-61-5: 2,4-Hexadienoic acid, potassium salt (1:1), (2E,4E)-;
590-00-1: 2,4-Hexadienoic acid, potassium salt (1:1)

Other Codes:
INS Number E202; FEMA 2921; IFN 8-03-761; US EPA PC Code: 075902; California DPR Code: 1132

Summary of Petitioned Use

Potassium sorbate, which will be referred to as KS throughout this report, is petitioned for addition to the National List at 7 CFR 205.601(e) for use as an insecticide, and at §205.601(i) for use as a plant disease control.

Characterization of Petitioned Substance

Composition of the Substance:

KS is a sorbic acid derivative with the chemical formula $C_6H_7O_2K$ or $C_6H_7KO_2$ (Nemes et al., 2020; PubChem, 2022a). Sorbic acid is an unsaturated fatty acid, characterized by a straight-chain, trans-trans isomeric form (Stopforth et al., 2005). The sorbic acid carboxyl group is highly reactive, allowing for the formation of many salts and esters (Stopforth et al., 2005). Common derivatives include KS, calcium sorbate and sodium sorbate, which are used commercially as preservatives in food and drinks (Stopforth et al., 2005; Nemes et al., 2020).

Source or Origin of the Substance:

KS is derived from the reaction of equimolar portions of sorbic acid with potassium hydroxide, as shown in Figure 1 (Probst & Oehme, 1965; PubChem, 2022a). Sorbic acid was first isolated through the distillation of malic acid obtained from the immature fruit of mountain ash, *Sorbus aucuparia,* at which point the reaction of naturally-derived sorbic acid with potassium was described (Hofmann, 1859). The most common method for manufacturing sorbic acid involves the reaction of ketene with crotonaldehyde to create an intermediary polyester, which is subsequently cleaved to produce sorbic acid. This manufacturing process, along with others, is described in greater detail in *Evaluation Question* #2 and *Evaluation Question #3*.

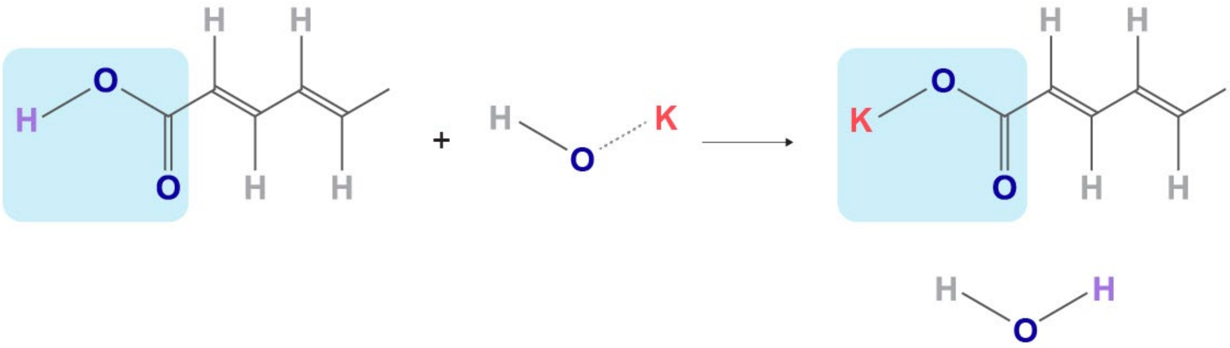

Figure 1: Chemical reaction of sorbic acid with potassium hydroxide, leading to the formation of potassium sorbate and water. Illustration modified from PubChem (2022a; 2022b).

Properties of the Substance:

KS is a potassium salt, generally available as crystals, crystalline powder, or granules in >98% purity (Joint FAO/WHO Expert Committee on Food Additives, 1998). KS is highly soluble (58.2% in water at 20°C) and disassociates into sorbic acid and ionic potassium in solution (Baker & Grant, 2018; Kowalczyk et al., 2015). Specific chemical and physical properties of potassium sorbate are listed in **Table 1**.

Table 1: Properties of potassium sorbate

Property	Values – Potassium Sorbate
Physical State at 20°C	Crystals or crystalline powder
Odor	Characteristic odor
Color	White or yellowish-white
Molecular Formula	$C_6H_7O_2K$
Molecular Weight (g/mol)	150.22
Density (g/cm^3) at 25°C	1.36
Water Solubility at 20°C	58.2%
Dissociation Constant at 20°C	4.69
Melting Point (°C)	270
Stability	Stable at room temperature under normal storage and handling conditions

Sources: (ChemicalBook, 2022; Joint FAO/WHO Expert Committee on Food Additives, 1966, 1998; PubChem, 2022a)

Specific Uses of the Substance:

The petition to add KS to the National List specifies it is for use as an active fungicide and insecticide ingredient for plant disease and insect control/suppressant in field and greenhouse applications. The label for the commercial KS pesticide product referenced in the petition includes directions for foliar spray application to ensure contact with the target organism causing powdery mildew in various crops. These are *Erysiphe necator* in grapes, *Podosphaera xanthii* in cucurbits, *Podosphaera pannosa* in roses, *Leveillula taurica* in solanaceous crops such as tomato, and *Podoshaera* spp., *Erysiphe pistaciae,* and *Microsphaera penicillata* in stone fruit, pome fruit, and nuts. The label additionally indicates control of downy mildew (*Plasmopara viticola*), and sour rot disease complex in grapes, and suppression of white flies in cucurbits, roses, and plants in the Solanaceae family (Oro Agri Inc., 2021). Although KS can be used in agricultural applications as a fungicide, bactericide, and algicide (Baker & Grant, 2018), a review of literature for this report did not identify any studies that specifically address the target organisms identified on the petitioned product's label. The majority of research focuses on the use of KS in post-harvest handling. As such, some of these studies are referenced throughout this report where deemed potentially relevant to crop use. *Appendix 1* presents a summary of KS uses described in the literature reviewed, for various diseases, pathogens, and crops.

In 2001, the National Organic Standards Board (NOSB) received a petition to add KS to the National List for use as a seed treatment in combination with sodium propionate (Patil, 2001). The NOSB requested a Technical Advisory Panel Report (TAP) to consider that use (NOP, 2002b). Following review of the information, on May 7, 2002 at an official public meeting in Austin, TX, the NOSB voted that potassium sorbate was synthetic and recommended that it not be added to the National List (NOP, 2002b).

Generally, KS is an effective antimicrobial agent against many bacteria, molds, and yeasts. It is most efficacious at acidic pH (Stopforth et al., 2005), specifically pH 4-6 (Smilanick et al., 2008). It loses antimicrobial efficacy in more alkaline conditions (Nemes et al., 2020). **Table 2** lists genera of organisms reported as being inhibited by KS.

Table 2. Genera of organisms inhibited by KS

Fungi, including most molds	Yeasts	Bacteria
Alternaria *Aspergillus* *Botrytis* *Cercospora* *Colletotrichum* *Fusarium* *Geotrichum* *Helminthosporium* *Macrophomina* *Monilinia* *Mucor* *Penicillium* *Pythium* *Rhizoctonia* *Rhizopus* *Sclerotinia* *Trichoderma*	*Candida* *Cryptococcus* *Rhodotorula* *Saccaromyces*	*Acetobacter* *Bacillus* *Clostridium* *Pseudomonas* *Salmonella* *Staphylococcus* *Escherichia coli*

Sources: (Arslan et al., 2009; Baker & Grant, 2018; Hervieux et al., 2002; Jabnoun-Khiareddine et al., 2016; Palou et al., 2009; Stopforth et al., 2005)

Bullerman (1983) found that KS not only delayed and prevented spore germination and growth initiation for *Aspergillus flavus* and *Aspergillus parasiticus*, but at a concentration of 0.10-0.15% sorbate, it also reduced or prevented aflatoxin B_1 production by the same species (Bullerman, 1983). Various studies suggest that KS has synergistic[1] antimicrobial effects when combined with other treatments (Ge et al., 2020).

KS is one of the most common food preservatives (Stopforth et al., 2005). While most food preservation with KS occurs as part of food processing, it is the applications during crop production and post-harvest handling of raw agricultural commodities that are considered within the scope of the current petition. Post-harvest use would have to be specifically annotated for any KS listing at §205.601 according to National Organic Program (NOP) Guidance 5023 (NOP, 2016).

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[1] Synergistic effects are combined effects of two or more substances resulting from their interaction, which are greater than the sum of their individual effects (Lexico, 2022).

Seed treatment

El-Mougy et al. (2004) tested the efficacy of KS on the incidence of root rot caused by *F. solani* and *R. solani* on cowpea seeds that had been soaked in 9% solution of KS. The experiment showed a 28.1% reduction in the incidence of pre-emergent root rot, averaged over 2 seasons, as compared to untreated controls, and a 31.5% reduction post-emergence. These reductions were even greater, 38.3% and 39.4% respectively, when the seed-soaking was followed by foliar spray of newly emergent true leaves with a 1.0 g/l solution of KS (El-Mougy et al., 2004).

In vitro tests on soilborne pathogens

KS is fungistatic, inhibiting fungal growth. One in vitro study found concentrations of less than 0.05% w/v KS inhibited the growth of various soil-borne pathogens: *F. oxysporum* f. sp. *melonis*, *M. paseolina*, *R. solani*, and *S. sclerotiorum*, by 50% as compared to controls. Concentrations ranging from 0.5 – 0.6% KS completely inhibited mycelial growth, while 0.1 - >2% KS was required to irreversibly inhibit, or kill the various pathogens (Arslan et al., 2009). These results are consistent with the findings of another in vitro test of 10 tomato pathogens (Jabnoun-Khiareddine et al., 2016). Notwithstanding variable responses to KS among the pathogens depending on KS concentration, the results showed increasing inhibition of fungal mycelial growth with increasing KS concentrations, from 0.25% KS to complete inhibition for all species tested at 1.5% KS (Jabnoun-Khiareddine et al., 2016). Another in vitro study also reported inhibition of *F. oxysporum* isolates, though 6% KS concentration was reported to be required for complete reduction of mycelial cell growth (Ragab et al., 2012). KS application to soil—in field, controlled environment, or greenhouse settings —was not found in the literature searched.

Pre-harvest treatment of crops

Several studies examined pre-harvest applications of KS at various stages of plant growth. One evaluated the efficacy of treating table grapes with a 0.5% concentration of KS at berry set, pre-bunch closure, at the onset of ripening, and two or three weeks before harvest. These applications significantly reduced the incidence of gray mold caused by *Botrytis cinerea* in two out of three study years (Feliziani et al., 2013). Youssef and Roberto (2014) found no significant difference between the efficacy of pre-harvest application of 1% (w/v) KS in reducing gray mold on table grapes compared to pre-harvest application plus post-harvest immersion in KS, suggesting that application one week prior to harvest may be sufficient and even superior, targeting the pathogen *B. cinerea* early in the disease cycle.

Jabnoun-Kiareddine & Abdallah (2016) applied KS to 30-day-old tomato seedlings under a controlled-growth setting, in soil medium inoculated with pathogens. KS treatment resulted in a 50% reduction in Verticillium wilt severity as compared to inoculated, untreated controls, a 78% reduction in wilt caused by *Fusarium*, and a 65% reduction in *Fusarium* crown and root rot severity. They also found KS application to tomato fruits wounded with the various pathogens resulted in significant decreases in the severity of gray mold, Rhizoctonia, Anthracnose, and Alternaria rot (Jabnoun-Khiareddine et al., 2016).

The petition provides efficacy data against the silverleaf whitefly on poinsettia plants (Oro Agri Inc., 2021).

Post-harvest handling

Several studies reported that KS may be effective as a post-harvest handling treatment used to inhibit fresh produce decay. Studies have reported on the post-harvest decay of harvested fresh fruit dipped in KS solutions of varying concentrations (Montesinos-Herrero & Palou, 2016; Ragab et al., 2012) for anywhere from 5 to 120 seconds, often at elevated temperatures ranging from 40-68 ºC (Ge et al., 2020; Palou et al., 2009). Higher temperatures increased the efficacy of KS treatments (Smilanick et al., 2008). KS may also be applied by a controlled droplet applicator (CDA) (Palou et al., 2009). Numerous studies explored the use of KS as a post-harvest antimicrobial agent to substitute for conventional fungicides that pose greater health and environmental risks (Ge et al., 2020; Ragab et al., 2012; Youssef & Roberto, 2014) and which may have diminished efficacy due to pathogen resistance to these conventional fungicides (Hervieux et al., 2002).

Smilanick et al., 2008 found post-harvest applications of KS to citrus effectively inhibited green mold caused by *Pencillium digitatum* and sour rot caused by *Geotrichum citri-aurantii,* particularly when heated to 50 °C. Montesinos-Herrero et al. (2009) also found that treatment with 3% KS solution controlled blue and green molds to varying degrees on citrus artificially inoculated with *P. digitatum* and *P. italicum* based on the species and cultivar of citrus, solution temperature, and the duration of treatment (Montesinos-Herrero et al., 2009). The results were replicated by Thipaksorn et al. (2012). They found the most effective parameters were 60-second dips at 62 ºC. In 2016, Montesinos-Herrero and Palou reported that adding exposure to elevated CO_2 or O_2 at a curing temperature following KS treatment had a synergistic effect on control of green and blue molds (Montesinos-Herrero & Palou, 2016). Potato tubers treated post-harvest via dipping in a KS solution for one minute, or misting prior to washing, showed significantly reduced surface area of silver scurf lesions after four weeks in storage as compared to controls (Olivier et al., 1999).

In a different post-harvest application, KS was used to coat plastic packaging material which delayed the growth of *Botrytis* in raspberries, blueberries, and black berries, thereby extending their shelf-life (Junqueira-Gonçalves et al., 2016).

There may be other benefits resulting from the use of KS treatment post-harvest. Molaei et al. (2021) found that treating pomegranate with KS in combination with chitosan during cold storage not only increased storage life but also the nutritional values of the fruit, and lowered the incidence of chilling injury and decay. Ge et al. (2020) also reported improved fruit quality resulting from KS treatment of kiwifruit post-harvest, as well as increased defense-related enzyme activity in the fruit. Stopforth et al. (2005) noted that although KS is inhibitory to most molds, some species can metabolize sorbates, resulting in the production of off-odors.

Other

KS continues to be widely used in food, cosmetic, and personal care products; washing and cleaning products; pharmaceuticals; and other manufactured industrial products (Dehghan et al., 2018; Hartman, 1983). It is an alternative to benzoates and other preservatives. Annual global production of KS in 2017 was 38,000 tons (Dehghan et al., 2018).

One study reported the use of KS in combination with lactic acid on packed chicken legs in modified atmosphere conditions and 4 ºC storage, and found reduced occurrence of *L. monocytogenes* compared with untreated controls (González-Fandos et al., 2021). KS is also used as a silage additive (Knický & Spörndly, 2009). Sometimes combined with sodium benzoate, this application alters the microbial community composition in silage. It enhances preservation by suppressing spoilage-inducing yeasts, enterobacteria and clostridia, thereby allowing more favorable organisms to ferment the silage and aid in preservation (Zhang et al., 2020). Baker and Grant (2018) noted that sorbates inhibit the growth of yeast on food surfaces during fermentation, but do not inhibit the yeasts and other organisms carrying out the fermentation. KS is used generally as a preservative in animal feed (EFSA, 2014), as well as in cosmetics and pharmaceuticals due to its antibacterial and antifungal properties (Stopforth et al., 2005).

Approved Legal Uses of the Substance:

EPA

KS is permitted as an active ingredient in minimum risk pesticides exempt from EPA registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), also known as ‘25b exempt pesticides,’ per 40 CFR 152.25(f)(1). It is also permitted as an inert ingredient in 25b exempt pesticides for both food and non-food use sites, and residues from such uses are exempt from the requirement of a tolerance at 40 CFR 180.950(e). Tolerance exemptions for all pesticide chemical residues *in food*, including those that are not exempt but subject to EPA registration, are established by EPA regulation at 40 CFR 180. KS and its residues are exempt from the requirement of a tolerance in food, per 40 CFR 180.1233. Prior to receiving 25b exemption, potassium sorbate was used as an active ingredient in several EPA registered pesticides. The last of these registrations was cancelled in 1989 (U.S. EPA, 2022b).

KS is also on the EPA 2004 List 4A – Minimal risk inert ingredients. Thus, it is currently permitted as an inert ingredient in combination with permitted active ingredients in pesticide formulations used in organic crop production according to 7 CFR 205.601(m)(1). NOP Guidance 5023 clarifies that inert ingredients compliant with §205.601(m) of the National List may also be used in post-harvest pest control substances on raw agricultural commodities (NOP, 2016).

FDA

Potassium sorbate is listed as *Generally Recognized as Safe* (GRAS) by the U.S. Food and Drug Administration (US FDA) at 21 CFR 182.3640, with the only specification being that it be used according to good manufacturing practices (GMPs) (U.S. FDA, 2022a).

Action of the Substance:

KS is primarily used as a food preservative and is valued for the bacteriostatic effects (i.e., prevents growth of bacteria) and fungistatic effects (i.e., prevents growth of fungi) imbued by sorbic acid, the weak acid constituent from which it is derived (Montesinos-Herrero & Palou, 2016; Preciado-Iñiga et al., 2018). Sorbic acid has limited solubility in water; therefore the more soluble salt derivatives, and its salts—particularly KS—are more practical to use (Lück, 1990). The subsequent dissociation of KS into ionic potassium and the dissociated form of sorbic acid, which occurs in solution, is shown below (**Figure 2**).

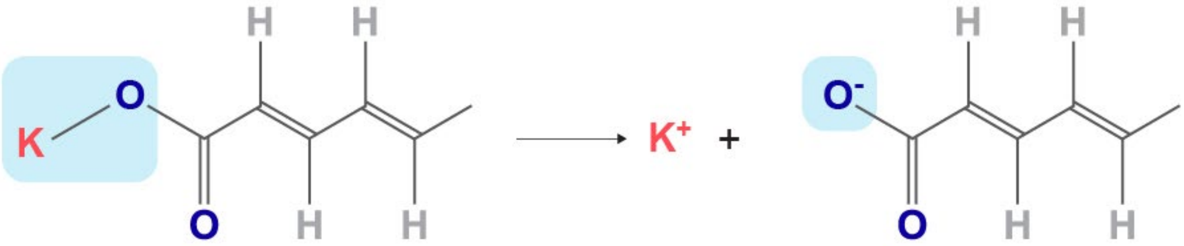

Figure 2. Dissociation of potassium sorbate into ionic potassium and anionic sorbic acid.

Like other weak acid preservatives, sorbic acid inhibits fungal and bacterial growth via diffusion of the acid into the cell, partial dissociation within the cell, and subsequent acidification of the cytoplasm. Study of this process indicated that it does not entirely explain the effects of sorbic acid, and additional mechanisms have been implicated (Stratford et al., 2013). In most instances sorbic acid and its derivatives act directly upon pathogens to inhibit growth, however there is evidence of indirect inhibition of these pathogens through the stimulation of the plant resistance response.

KS and sorbic acid are toxic at the cellular level and inhibit cellular growth through direct and indirect modes of action.

Direct inhibition

Several studies suggest that the cell membrane is the likely target of direct action, where inhibition of H^+-ATPase proton pumps and generation of reactive oxygen species by sorbic acid have been described (Sofos et al., 1986; Stratford et al., 2013). Fungal inhibition following the application of KS and sorbic acid is tied to interference with the proton pump, but this inhibition is dependent on sorbate presence and is rapidly reversed upon its removal (Stratford et al., 2013). This is consistent with the reversible behavior of other unsaturated fatty acids when incorporated into the cell membrane (Freese et al., 1973). The H^+-ATPase proton pump is essential to cellular function, predominantly due to its involvement in establishing and controlling cellular pH at an acidic level between ≤7 to ~4.5 (Maxson & Grinstein, 2014). Membrane damage, such as this proton pump inhibition, can lead to cytoplasmic leakage and cell lysis (Stratford et al., 2013).

Study of resistance in yeasts, which vary in dependency on fermentation versus respiration for energy, provides further insight into the mechanisms of direct action by sorbic acid. When applied to fungal taxa that rely primarily on respiration for energy, sorbates target the mitochondrial membrane, resulting in increased production of reactive oxygen species (ROS). The amplified ROS production subsequently leads to diminished biogenesis of iron-sulfur clusters that are relevant to cellular respiration, and mitochondrial DNA damage that results in the formation of mitochondrion-defective cells (Stratford et al., 2020). The resulting breakdown in cellular respiration appears to be the primary mechanism through which sorbic acid inhibits fungal growth. Alternatively, yeasts that rely on fermentation for energy, either primarily or intermittently, are shown to be most frequently responsible for food spoilage when KS is used as a preservative (Stratford et al., 2020). This variable susceptibility and resistance to sorbic acids is described further in the Focus Question. In bacterial cells, sorbic acid and its derivatives appear to inhibit growth through similar mechanisms (Freese et al., 1973; Sofos et al., 1986).

Indirect inhibition

Indirect inhibition of microbial growth by the induction of plant resistance responses is documented following the application of sorbates to several horticultural crops. Mechanistically, sorbate application initiates an increase in a number of phytochemicals relevant to pathogen resistance, including phytoalexins, chitinases, and phenolic compounds (Feliziani et al., 2013; Soliman & El-Mohamedy, 2017; Ge et al., 2020). Application of potassium sorbate and other salts accelerates the production of peroxidases and other antioxidants as a response to increased production of ROS in the plant cell following salt applications (Feliziani et al., 2013; Youssef & Roberto, 2014; Ge et al., 2020). Sudden, elevated levels of ROS in the plant cell, referred to as oxidative bursts, are an initial response to fungal pathogens like downy and powdery mildew, as well as bacterial pathogens and insect herbivory (Sedlářová et al., 2011; Kerchev et al., 2012; Smith & Heese, 2014; Jing et al., 2019). Oxidative bursts are considered the beginning of the signaling cascade for plant resistance, thus it is understood that the mode of action of KS includes an indirect inhibition of various plant pests via induction of plant immunity (Kerchev et al., 2012).

<u>Combinations of the Substance:</u>

The petition for KS identifies the substance as 100% food grade potassium sorbate, with no ancillary substances (Oro Agri Inc., 2021). OR-159-B, the proposed end-use fungicide/insecticide product referenced in the petition, contains 45% potassium sorbate, with the remaining 55% comprised of inert ingredients: urea and citric acid (Oro Agri Inc., 2021), both of which appear on the 2004 EPA List 4A: Inerts of Minimal Concern. Baker and Grant (2018) also cited the use of citric acid as a stabilizer for sorbic acid and its salts.

There are various reports of KS being combined with other antimicrobial active ingredients to increase efficacy. Thipaksorn et al. (2012) found that combining 1.5% KS with 0.02% peracetic acid (PAA) increased the control of green mold caused by *P. digitatum* on *Sai Nam Phuen* tangerines over treatment with 1.5% KS alone, in terms of reducing disease incidence, severity, and sporulation. KS treatment alone increased chilling injury in pomegranates, but KS combined with chitosan decreased chilling injury more than chitosan alone (Molaei et al., 2021). Sodium benzoate is another food preservative with antifungal properties that has been used in combination with KS (Palou et al., 2002). Sodium benzoate is not permitted in the post-harvest handling of organic commodities. See *Appendix 1* for reports of KS combination with other active ingredients.

Olivier et al. (1999) included the surfactant, Tween, in a 0.2 mol/L KS solution used to treat silver scurf on potato tubers during post-harvest storage but did not find any increase in efficacy compared to KS solutions without Tween. They therefore did not include Tween in subsequent trials.

Status

Historic Use:

KS has historically been used in the food processing industry as a preservative, due to its fungistatic and bacteriostatic properties (Baker & Grant, 2018; Stopforth et al., 2005). It is found in a wide variety of food products including meats, cheeses, baked goods, fresh and fermented vegetables, dried fruit, fish, processed food, and carbonated beverages (Sofos et al., 1986; Somogyi, 2000; Stratford et al., 2020). Additionally, KS is utilized as a preservative in animal feed, as a treatment to encourage the development of an appropriate microbial community composition in silage, and in cosmetics and pharmaceuticals (EFSA, 2014; Knický & Spörndly, 2009; Stopforth et al., 2005; Y. Zhang et al., 2020).

There is little historic use of KS in organic agricultural production, in accordance with the petitioned use or otherwise. KS has been petitioned previously, for use in livestock production as a preservative in aloe vera and in crop production as part of an unspecified seed coating. Neither petition resulted in the addition of KS to the National List (NOP, 2002b, 2002c). KS is currently permitted for use as an inert ingredient used in combination with allowed active ingredients in organic crop and livestock production (U.S. EPA, 2004; USDA AMS, 2022c, 2022b).

Organic Foods Production Act, USDA Final Rule:

Potassium sorbate is not explicitly listed anywhere in the Organic Foods Production Act of 1990 (OFPA), nor in the USDA organic regulations at 7 CFR part 205. It is implicitly on the National List as an inert ingredient of minimal concern [§§ 205.601(m)(i) and 205.603(e)(1)].

International

Canada, Canadian General Standards Board – CAN/CGSB-32.311-2020 Organic Production Systems Permitted Substances List
KS does not appear on Table 4.2 – Substances for crop production - of the CAN/CGSB-32.311 Permitted Substances List, nor on Table 8.3 – Post-harvest substances. Thus, the Canadian Organic Standards do not permit the use of KS as an active ingredient in organic crop production or post-harvest handling.

CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999)
Codex Alimentarius Guidelines Annex 2 Table 2 – Substances for plant pest and disease control – does not include KS, nor is it included in any other section of the guidelines.

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008
Organic regulations of the European Union, EU 2021/1165, do not reference KS in Annex 1 – Active substances contained in plant protection products authorized for use in organic production as referred to in point (a) of Article 24(1) of Regulation (EU) 2018/848. Sorbic acid (E 200), however, is permitted as a preservative in organic livestock feed in Annex III Part B (1)(a).

Japan Agricultural Standard (JAS) for Organic Production
KS is not included in Appended Table 2 – Agricultural chemicals – and is therefore not permitted under the Japan Agricultural Standard for use in organic crop production.

IFOAM – Organics International
KS does not appear in IFOAM standards, Appendix 3 – Crop protectants and growth regulators, or Appendix 4, Table 1 – List of approved additives and processing /post-harvest handling aids.

Evaluation Questions for Substances to be used in Organic Crop or Livestock Production

Evaluation Question #1: **Indicate which category in OFPA that the substance falls under: (A) Does the substance contain an active ingredient in any of the following categories: copper and sulfur compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part 180?**

The substance was previously petitioned as a seed treatment active ingredient (Patil, 2001). It is also used as an inert ingredient that meets the requirements of 7 CFR 205.601(m)(1) and § 205.603(e)(1). Potassium sorbate does not appear to fall into any other categories identified in the OFPA as qualified for exemption from the prohibition of synthetic substances. The current petition did not identify or suggest any other 7 USC 6517(c)(1)(B)(i) category qualified for inclusion on the National List (Oro Agri Inc., 2021).

Evaluation Question #2: **Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).**

KS is most commonly manufactured via the dissolution of sorbic acid in aqueous potassium hydroxide (Dehghan et al., 2018). In this process, potassium hydroxide reacts with the carboxyl group of sorbic acid to form KS and water (Figure 1). The two KS precursors, sorbic acid and potassium hydroxide, are also manufactured through chemical synthesis, with exceptions noted below.

Sorbic acid

Sorbic acid is a naturally occurring weak acid, first isolated from mountain ash (Hofmann, 1859). It is found in the fatty acids of the several aphid species, including large knapweed, potato, and oleander aphids (Lück et al., 2000; Walters et al., 1994). Although these natural sources exist, nearly all sorbic acid manufactured today is a product of chemical synthesis (Lück et al., 2000). The petitioners describe a common manufacturing method that involves the condensation of ketene gas with crotonaldehyde, at temperatures ranging from 20-50°C, in the presence of fatty acid salts of bivalent transition metals and an inert solvent (Fernholz et al., 1962; Lück et al., 2000). The ketene gas for this reaction is produced through the pyrolysis of acetic acid, acetone, or acetic anhydride (PubChem, 2009). An intermediary polyester, 3-hydoxy-4-hexenoic acid, is formed from the condensation reaction and subsequently cleaved to form crude sorbic acid (Lück et al., 2000; Oro Agri Inc., 2021). The polyester is cleaved into sorbic acid through the addition of a strong acid such as hydrochloric acid, base, or metal-complex catalyst in solution (Lück et al., 2000).

The resulting crude sorbic acid product contains contaminant "tars" that may be water soluble or insoluble in nature (Brown et al., 1985). Removal of these impurities may involve centrifugation of water-soluble tars, isolation of water insoluble tars within the aqueous phase, washing of the crude product with acetone, or a water and alcohol mixture, carbon treatment, or steam distillation (Brown et al., 1985; Lück et al., 2000; Oro Agri Inc., 2021). Crude sorbic acid may also be exposed to a number of organic solvents for impurity removal, although a minimal amount of the acid product may be dissolved with this approach (Brown et al., 1985). Water or carbon treatments require significant energy consumption relative to the amount of pure sorbic acid produced, compared to the methods that utilize organic solvents (Brown et al., 1985).

Potassium hydroxide

Historic, nonelectrochemical processes rely on the salt metathesis[2] reaction of potassium carbonate and calcium hydroxide to form solid calcium carbonate and potassium hydroxide solution, as does the historic production method for lye. However, this method does not contribute to modern, commercial production (Ofori & Awudza, 2017; Schultz et al., 2000).

Potassium hydroxide is almost exclusively manufactured currently through the electrolysis of potassium chloride, using either the diaphragm, membrane, or mercury processes (Schultz et al., 2000). Diaphragm and mercury electrolysis were the predominant production methods prior to 1985, with mercury preferred for the purity of final products prior to concentration (Schultz et al., 2000). Both diaphragm and mercury production methods are subject to regulation regarding effluent from manufacturing points (U.S. EPA, 2022c). Modern manufacturing has shifted to the membrane method, wherein electrolytic cells containing membranes comprised of carboxylic acid-substituted polymers produce a cell liquor with low chloride content and a KOH concentration of 32% (Lynch et al., 1983; Schultz et al., 2000). Irrespective of electrolytic cell type, all KOH products are evaporated to a concentration of 45-50% for the final product (Schultz et al., 2000).

The petitioned substance is manufactured through the neutralization of sorbic acid with potassium hydroxide to form KS (**Figure 1**), although other potassium salts, such as potassium carbonate, may be used (Lashley & Myerly, 1964). Several methods are described for the isolation of the KS solid, including filtration, centrifugation spraying, or crystallization of KS and subsequent distillation of water (Lashley & Myerly, 1964; Oro Agri Inc., 2021). The resulting product can be found as white powder or in a white granule form, if a granulation method has been utilized (EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019; Lashley & Myerly, 1964).

<u>Evaluation Question #3:</u> Discuss whether the petitioned substance is formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).

KS is manufactured through chemical processes (Lashley & Myerly, 1964; Lück et al., 2000; Schultz et al., 2000). The most common commercial practice produces KS through the neutralization of sorbic acid with potassium hydroxide (Schultz et al., 2000).

The active constituent, sorbic acid, is synthesized by the condensation of ketene gas with crotonaldehyde (Fernholz et al., 1962; Lück et al., 2000). Ketene gas is obtained through the thermal cracking of acetic acid, acetone, or acetic anhydride (PubChem, 2009). Commercially available crotonaldehyde is produced through the aldol condensation of acetaldehyde, which is naturally occurring in vinegar, milk products, and many plants (PubChem, 2018; Uebelacker & Lachenmeier, 2011). Potassium hydroxide is synthesized through electrolysis of potassium chloride, using one of several electrolytic cell technologies (e.g., including diaphragm, mercury, and membrane cells) (Schultz et al., 2000; U.S. EPA, 2022c).

<u>Evaluation Question #4:</u> Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518 (m) (2)).

Because it inhibits microorganisms from colonizing a "new" substrate, KS is an effective antimicrobial. However, this bacteriostatic effect is likely to be overwhelmed in a natural community, where microorganisms can quickly degrade KS into readily metabolized compounds such as sorbitol, potassium, and sorbic acid (Dehghan et al., 2018). Many microorganisms present in soils are capable of degrading sorbic acid (Lück et al., 2011). Additionally, sorbic acid has a biodegradation half-life of 3.56 days (U.S. EPA, 2020) and shows high degradability (95 % within 6 d) in the Zahn – Wellens test (PubChem, 2022b). At concentrations of 0.05%-0.2%, sorbic acid displays very little toxicity to plants (Lück et al., 2011). Furthermore, sorbic acid and the sorbates are not hazardous in water and are not

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[2] Salt metathesis is a chemical reaction in which two chemical reactants exchange a bond/bonds to create two new products, with identical or similar bonding affiliations (Muller, 1994).

subject to any hazardous materials classification. The acute fish toxicity (LC_{50} for the zebra barbel) is very low: >1000 mg/L after 48 –96 h. Thus, sorbic acid is incorporated in the lowest German water hazard class (WGK"0") (Lück et al., 2011). So far, no hazardous decomposition products of KS are known (ECHA, 2022). In general, sorbic acid and its salts have been considered compounds of very low ecotoxicity (ECHA, 2022; Walker, 1990).

Few studies are found in the literature that report on the use of KS as a crop fungicide; thus, information regarding its persistence or that of its by-products in the environment resulting from this use is limited. No studies on KS used to control the target organisms identified on the petitioned product's label were found to expound on its potential effects on soil microbial communities. The information that is available is related to its more prominent use in food, both as a post-harvest treatment and as a conventional food additive.

As noted in **Table 1**, KS is a solid and stable compound at room temperature, is soluble in water, and exhibits antimicrobial activity. Although crystalline KS is relatively stable, its behavior in solutions and in foods depends on several factors like temperature, pH, food combination, water activity, packaging, and the presence of various metals and other additives (Ferrand et al., 2000; Thakur et al., 1994; Yarramraju et al., 2007). For example, sorbic acid in aqueous solution is known to degrade into acetaldehyde and β-carboxylacrolein, causing a brownish aspect of the product (Thakur et al., 1994). Manufacturers package KS to maintain stability, avoid degradation, and keep it in marketable condition so it will not be released directly into the environment. However, some KS that is off-specification or past expiration date will be disposed rather than consumed. Disposal is addressed further in *Evaluation Question #6*.

Most of the KS consumed by a person (or animal) is metabolized and oxidized to carbon dioxide and water (Ueda et al., 2022), in the same way as fatty acids. Only a small fraction of the KS molecules, between 2-10%, returns to the environment via urine (Dehghan et al., 2018). A second input of KS to the environment will be all the products that are applied directly to the environment (like washing products or aerosols), and those which directly end in the waste stream. KS can be destroyed by incineration, but otherwise will be relatively stable. The presence of KS in natural environments after its commercial use is considered safe (U.S. EPA, 2004, 2016(a), 2016(b); US FDA, 2016).

Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).

KS and sorbic acid inhibit cellular growth through direct and indirect modes of action, the processes of which are discussed in detail in *Action of the Substance*.

Soil, air, and water

KS has an air half-life of 2.6 h, a soil half-life of 416 h and a water half-life of 206 h (EPI, 2012). As noted in *Evaluation Question #4,* many microorganisms present in soils are capable of degrading sorbic acid (Lück et al., 2011). Sorbic acid has a biodegradation half-life of 3.56 days (U.S. EPA, 2020) and shows high degradability (95 % within 6 d) in the Zahn – Wellens test (PubChem, 2022b). Sorbic acid and the sorbates are not hazardous in water and are not subject to any hazardous materials classification. The acute fish toxicity (LC_{50} for the zebra barbel) is very low: >1000 mg/L after 48 –96 h. In general, sorbic acid and KS are considered compounds with very low ecotoxicity (ECHA, 2022; Walker, 1990). Despite this, some studies discussed in *Evaluation Question #9* have shown that KS can impair photosynthetic functions in algae (Engel et al., 2015), negatively affect the microbiome of fishes (Peng et al., 2019), inhibit mycelial growth in fungi (Arslan et al., 2009) and affect the soil pH (Arslan et al., 2009).

Consumption of processed products

As noted in *Evaluation Question #4*, most of the KS consumed is metabolized and oxidized to carbon dioxide and water (Ueda et al., 2022). KS is absorbed via a diffusion process in the stomach, and it can be dissociated into its constituents (potassium and sorbate) and absorbed through small intestine in the form of sorbic acid (Walker, 1990). Regarding the tissue distribution, studies in rats showed that 85% of the sorbic acid was metabolized to carbon dioxide, 3% of it remained in internal organs, 3% of it was found in the skeletal muscles, approximately 2% was excreted in the urine and urea and 0.4% in the feces, and 6.6% was found in other parts of the body (Dehghan et al., 2018; Walker, 1990). Further studies in mice showed that 80-86% of KS was released as carbon dioxide in lung tissue and 2-10% was excreted via urine as urea, and in lower concentrations as muconic acid (Dehghan et al., 2018).

Dehghan et al. (2018) point out that various research results showed that increased KS intake (>25 mg/kg) may lead to cytotoxic and genotoxic effects by producing mutagenic compounds and inducing chromosome aberrations and DNA breakage. These factors can lead to the development of many chronic diseases such as diabetes mellitus and cancers. The wide use of KS in commercial products, such as food, cosmetics, cleaners, and other consumer goods, all contribute to the consumption of KS resulting in consumer uptake higher than the maximum acceptable daily limit for humans of 25 mg/kg of body weight. For more information regarding human health concerns, refer to *Evaluation Question #10*.

Evaluation Question #6: Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).

KS is used in a wide range of industrial and commercial products, many of which are not related to food or beverage production. Environmental contamination already occurring from these uses are beyond the scope of this Technical Report.

The European Union assessed KS and its active constituent, sorbic acid, for human health and environmental risks. These tests determined KS and sorbic acid are readily biodegradable, are somewhat degradable by photolysis or light exposure, and are at low risk for bioaccumulation (European Chemicals Agency, 2015).

KS is manufactured from several other chemical precursors, each with different reactivity and toxicity (see *Evaluation Question* #2). The precursor sorbic acid is often produced from gaseous ketene condensed with crotonaldehyde. Ketene gas is a reactive volatile organic compound (VOC) that has been shown to act as a respiratory poison in a number of animal studies (National Research Council, 2014). One recent study identified ketene within the emissions of a petrochemical facility at a rate similar to the known air pollutant toluene, where it appears to be responsible for tropospheric O_3 production (Sarkar et al., 2021). Crotonaldehyde is a known eye, skin, and respiratory irritant with probable carcinogenicity (Coenraads et al., 1975). Its manufacture is tied to wastewater and air pollution, with particular concern about the recalcitrance and toxicity of by-products such as unsaturated aldehydes, aromatic aldehydes, and esters (Hajizadeh et al., 2018; Liu et al., 2019; Song et al., 2017).

Sorbic acid used to produce KS is neutralized with a potassium salt, usually potassium hydroxide (KOH) (Lashley & Myerly, 1964). The current prevailing manufacturing method for KOH involves the electrolysis of potassium chloride (KCl) in a manner that is similar to the chloralkali process for producing sodium hydroxide (NaOH) (Schultz et al., 2000; U.S. EPA, 2022c). Three forms of electrolysis have been used, as summarized in *Evaluation Question #2*. Diaphragm and mercury-based electrolytic cells are known to be point sources of pollution for mercury, chlorine, and total suspended solids; as a result, this effluent is regulated by the EPA (U.S. EPA, 2022c). Furthermore, potassium hydroxide is considered a category 1 hazardous substance under the Clean Water Act, due to its impact on pH and potassium levels in wastewater (U.S. EPA, 2022d). Although KOH itself may be corrosive in solid form, and is listed as a hazardous substance under the Clean Water Act, it is considered a GRAS substance when produced with good manufacturing practice and currently appears on the National List at 7 CFR 205.605(b) for use in processed products (U.S. EPA, 2022e; U.S. FDA, 2022b; USDA AMS, 2022a).

KS does not appear on the U.S. EPA's Consolidated List of Chemicals subject to various reporting requirements for intentional or accidental release (U.S. EPA, 2022a). Disposal of KS and its by-products are by landfilling in closed containers or incineration. Disposal in the sewage system is not recommended (Guidechem, 2017). KS is then decomposed or biodegraded into carbon dioxide and water. KS has no potential for accumulation in the environment (ECHA, 2022).

<u>Evaluation Question #7:</u> Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).

No report of chemical interactions between KS and other substances used in crop production were found in the literature reviewed for this report. In fact, there are very few studies that report the use of KS in crop pesticide applications, even on conventional crops, suggesting that it is not widely used for these applications. Thus, there is a lack of available information regarding potential interactions of KS with other crop production inputs.

In the case of processed food, products with both sorbate and nitrite preservatives may form several species of direct-acting mutagens and genotoxic agents under certain conditions. In particular, when both are present together at pH's mimicking gastric conditions the moieties will form the mutagens ethylnitrolic acid and 1,4-dinitro-2-methylpyrrole (Hartman, 1983). Kitano et al. (2002) found Ames test and rec-assay mutagenicity and DNA-damaging activity when KS, ascorbic acid and iron (Fe) salts were combined. The Fe salts used were ferric citrate, ferrous gluconate, ferric pyrophosphate and ferrous sulfate. The authors assumed that KS was oxidized by hydrogen peroxide, which was generated by ascorbic acid and Fe salt, to produce mutants and toxicants (Kitano et al., 2002). The four Fe salts used are currently approved for use as food additives in the U.S. by the FDA, as is citric acid.

In vitro studies on bone marrow chromosomes of mice showed that the combination of sorbic acid (15 mg/kg) and nitrite (2 mg/kg) creates a synergistic effect, severely affecting spindle apparatus and chromosomal structure (Banerjee & Giri, 1986). Further study is required to determine the toxic impact of sorbic acid in conjunction with nitrite on humans.

Evaluation Question #10 describes in greater detail other health effects of sorbic acid and KS.

<u>Evaluation Question #8:</u> Describe any effects of the petitioned substance on biological or chemical interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).

Crops

KS was tested for phytotoxicity in cotton seedlings (Davis, 1970). The treatments caused a reduction in the primary root elongation at concentrations of 40, 80 and 120 ppm. In the same study, KS severely affected the dry weight of the cotton seedlings shoots and roots at all KS concentrations tested. The article observed that the conditions used in the experiments might not hold true for soil-cultured plants, where available fungicidal activity would be expected to decrease as a result of soil absorption, leaching, plant uptake, or through root growth away from the immobile fungicide. This study concluded that KS is not as phytotoxic as the fungicides used to treat seeds in conventional agriculture, Pimaricin (natamycin) and Vitavax (carboxin).

Arslan et al. (2009) demonstrated that KS addition slightly increased the pH of soil. Soil pH is important in determining variation in bacterial community structure and diversity (Tripathi et al., 2018). In addition, a concentration of 0.6% KS completely inhibited mycelial growth of four soil-borne pathogenic fungal species tested in the experimental conditions (Arslan et al., 2009). Further field research is needed on any possible negative effects that KS could have on the bacterial communities necessary for a healthy soil and optimal microbe-plant interactions. This information is not reported in the scientific literature.

Livestock

One study evaluated several combinations of antimicrobial silage additives (Knický & Spörndly, 2009). The combination of KS, sodium benzoate, and sodium nitrate proved to be one of the most effective at controlling yeast that cause aerobic spoilage in high-dry matter silage, and at reducing clostridia spores and the formation of butyric acid in low-dry matter silages. The resulting silage did contain more residual nitrate-N than the untreated control, but the treatment was considered to improve the overall quality of the silage.

Considering the antibacterial, antifungal, bacteriostatic and fungistatic properties of KS, it is possible that when used as an additive in livestock feed, its presence in the rumen could affect the microbiome and therefore the ruminant metabolism. This concern was voiced by a reviewer during the Potassium Sorbate Livestock CFNP TAP Review Analyses (NOP, 2002a): *"[…] one should in fact determine directly at what level KS, as an anti-bacterial will interfere with ruminant metabolism. Presumably if used in significant quantities (whatever that may be), then the product would presumably do its "antibacterial" thing in the rumen."* However, no research was found that addresses this topic. Future research that identifies the concentrations of KS affecting the ruminant microbiome is needed.

Processed products

In the context of food, the two preservatives, sorbate and nitrite, can together form several direct-acting mutagens and genotoxic agents, including ethylnitrolic acid and 1,4-dinitro-2-methylpyrrole (Hartman, 1983). Hartman's study evaluated the interactions of sorbate and nitrate when used as food additives. Sodium nitrate can be used as a fertilizer in organic crop production. Thus, potential interactions of nitrate and sorbate in an agricultural context requires more research to understand the extent of these possible interactions and guarantee that mutagens and genotoxic agents are not formed by the reaction of sorbate and nitrate in the soil.

<u>Evaluation Question #9:</u> Discuss and summarize findings on whether the use of the petitioned substance may be harmful to the environment (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).

Our research did not uncover any information to suggest that KS is currently used as a conventional pesticide, nor any reports of its effects on beneficial organisms that would be associated with such use. Furthermore, while some field studies have examined the impacts on soilborne pathogens, these studies have not measured the impacts on non-target beneficial soil organisms.

Tripathi et al. (2018) confirmed a strong influence of pH in the soil bacterial community assembly. While KS may be less harmful to the environment than other synthetic fungicides used to treat soilborne pathogens, its broad spectrum anti-fungal and localized effects on soil pH suggest that it may have adverse effects in laboratory studies (Arslan et al., 2009). The authors recommended replication of the studies in field conditions, so the actual efficacy against pathogens and impact on beneficial soil organisms in the environment could be investigated (Arslan et al., 2009).

KS released into the environment eventually biodegrades into water and carbon dioxide, but as noted above in *Evaluation Question #4.*, it is stable as a solid, may have toxic intermediate degradants, and can remain active against fungi, bacteria, algae, and other non-target species before it is degraded. Newer studies call for research on possible effects of KS at higher concentrations than those previously considered. High concentrations of KS can impair photosynthetic function in algae even with short exposure times (Engel et al., 2015), or can have negative effects on the microbiome of fishes (Peng et al., 2019).

<u>Evaluation Question #10:</u> Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4)).

Health impacts of KS when used as a pesticide

No information was found regarding the effects on human health from the use of KS as an insecticide or fungicide in crop production. As noted in the 2002 TAP review on KS for livestock production, "…there are few references that potassium sorbate has been used as a seed treatment or for any other crop uses in either organic or conventional agriculture. Only a few experimental references were found in the literature, and there is no indication that potassium sorbate was ever used commercially." (NOP, 2002a). The present review reports similar findings.

Health impacts of KS as a food additive

An evaluation performed by the World Health Organization in 1973 concluded that sorbic acid is readily metabolized. Both humans and rats appear to utilize identical metabolic mechanisms for oxidation of sorbate, and long-term studies suggest that the same no-effect level applies to the salts as to the free acid. Sorbic acid and KS that meet food grade specifications do not cause tumors when administered orally or subcutaneously. This evaluation also estimated the acceptable daily intake for humans at 0-25 mg/kg body weight (World Health Organization, 1974).

Some older studies addressing KS toxicity demonstrated no evidence of mutagenic or genotoxic potential. In experiments conducted by Shtenberg and Ignatev (1970), sorbic acid was the preservative that showed the lowest toxicity compared to nisin, sodium bisulphite and benzoic acid in mice and rats. In general, the doses showed some adverse effect in both rats and mice, particularly on growth, survival and susceptibility to stress, but sorbic acid appeared to be the least toxic (Shtenberg & Ignat'ev, 1970). The FDA reviewed four animal studies for carcinogenesis in conducting the GRAS evaluation of sorbic acid and its sodium and potassium salts. Three showed no carcinogenesis and one was inconclusive (LSRO, 1975).

Toxicology has new methods and technologies to investigate damage to cells and tissues that were not available when the initial studies of sorbic acid and sorbate salts were conducted. Researchers continue to screen the effects of these additives and the consequences of their long-term, large-scale dietary consumption (Piper & Piper, 2017). New evidence about the genotoxicity and potential risks to humans raises questions about the classification of KS as GRAS (Dehghan et al., 2018; Piper & Piper, 2017). Consumers exposed to KS have complained of "burning mouth syndrome" (Haustein, 1988; Lamey et al., 1987).

Some studies reported observed genotoxic reactions to KS on various test animals. Banerjee & Giri (1986) showed that sorbic acid itself had a marked effect on chromosomes of mice. However the combination of sorbic acid (15 mg/kg) and nitrite (2 mg/kg) used together, at half the concentration than when tested independently, gave a synergistic effect that severely affected spindle apparatus and chromosomal structure of the mice (Banerjee & Giri, 1986). Sorbic acid and nitrates are among the most common chemical preservatives used to reduce microbial spoilage of foods. Sorbic acid is added to a broad spectrum of food types such as cheese, wine, baked goods etc., while nitrates are usually added to meats and cured meats products. Therefore, the interaction between these two chemicals is likely when consuming conventional processed foods. Notably, the dose of sorbic acid and nitrite used by Banerjee & Giri (1986) was below the daily acceptable limit of each for humans.

Tsuchiya & Yamaha (1983) reported positive results in an Ames test conducted on the feces and urine of mice fed a diet containing KS. Hasegawa et al. (1984) found KS to be weakly genotoxic, inducing in vitro chromosome aberrations, sister chromatid exchanges (SCE)[3] and gene mutations in cultured Chinese hamster V79 cells. In this study, sorbic acid and KS showed significant effects only at the highest concentrations tested (1 and 20 mg/ml, respectively). It is well documented that chromosomal aberrations such as these can lead to cancer (Lobo, 2008). Münzner et al. (1990) re-examined potassium sorbate for possible genotoxic potential, demonstrating that stored sorbic acid salts kept for four weeks at room temperature in daylight highly compromised the survival percentage of mammalian cells (CHO cells).

Mamur et al. (2010) studied the genotoxic potential of KS in cultured and isolated human lymphocytes, finding that the KS treatment significantly increased the chromosomal aberrations and SCEs. This study

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[3] Sister chromatid exchanges (SCEs) are reciprocal exchanges of chromatid segments that occur at low levels in untreated cells. Following the exposure to DNA-damaging agents, their frequency increases substantially so they have been commonly used as an indicator of genotoxic effects in cells (Eastmond, 2014).

concluded that KS is clearly genotoxic to the human peripheral blood lymphocytes in vitro (Mamur et al., 2010). Kitano et al. (2002) found mutagenicity and DNA-damaging activity of the decomposed products when combining KS, ascorbic acid and Fe salt, by means of the Ames test and rec-assay. The Fe salts used were ferric citrate, ferrous gluconate, ferric pyrophosphate and ferrous sulfate. The authors assumed that KS was oxidized by hydrogen peroxide, which was generated by ascorbic acid and Fe salt, to produce mutants and toxicants (Kitano et al., 2002). The four Fe salts used are currently approved for use as food additives in the USA by the FDA, as is citric acid.

Health impacts of KS used as a plant disease control and insecticide

KS was also evaluated for acute dermal toxicity in humans. One literature review concluded that a "small but ill-defined subgroup may suffer idiosyncratic reactions to [sorbic acid and its salts]" (Walker, 1990). Soschin & Leyden (1986) found that there was a high prevalence of a transient localized erythema, with edema and flare, in human subjects treated with sorbic acid at different concentrations. Intense reactions were present in 100% of the subjects treated with 1% on the upper portion of the back, compared to the 76% that had an intense reaction to 0.5% and 17.6% to 0.1% (Soschin & Leyden, 1986). Dermal exposure to KS was also linked to urticaria (hives) (Hannuksela & Haahtela, 1987). Consumers exposed to KS have complained of "burning mouth syndrome" (Haustein, 1988; Lamey et al., 1987). KS was linked to severe rashes in a farmer and dairy plant worker who was repeatedly exposed to potassium sorbate in an occupational setting (Le Coz, 2005).

<u>Evaluation Question #11:</u> Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).

KS is petitioned for use as a fungicide and insecticide to control pathogens and insect pests in crops. The brand name product label referenced in the petition indicates application via foliar spray (Oro Agri Inc., 2021). A literature review for this report uncovered somewhat limited information on the use of KS as a foliar spray on growing crops, while there are numerous nonsynthetic substances and allowed synthetic substances that may be potential alternatives to KS for the petitioned uses.

Crop fungicides and insecticides

Biological controls are nonsynthetic pesticides widely employed in organic systems. At the time of this report, the OMRI Products List included over 750 biological controls approved for use as crop pest, weed and disease controls under NOP standards (OMRI, 2022). *Trichoderma harzianum*, *T. viride*, *Bacillus subtilis*, *Paenibacillus polymyxa* and *Serratia marcescens* are known to significantly reduce powdery mildew severity and area in cucumbers, under in-vitro tests and in greenhouse spray applications (Sarhan et al., 2020). Dagostin et al. (2011) also reported efficacy of *T. harzianum* in the control of downy mildew in viticulture, along with plant-extracts: *Yucca schidigera* and *Salvia officinalis*. Biological control techniques to control plant pathogens continue to advance (Scortichini, 2022). Instead of a single-antagonist / single-target approach, researchers are developing products that use combinations of organisms to protect crops against a wide range of potential diseases, such as potatoes in storage being treated with a combination of *Bacillus, Lysobacter, Streptomyces,* and *Trichoderma* antagonists (Osei et al., 2022).

Plant-based pesticides constitute another important nonsynthetic alternative to KS. Numerous plants have chemical defense mechanisms mediated by secondary metabolites[4], which ward off pathogens through chemical barriers that inhibit bacterial and fungal growth (Martínez, 2012). Enhanced production of these compounds can occur in response to pathogen attack or other stressors (Martínez, 2012). Thymol and carvacrol are antifungal terpenes found in the essential oils of thyme and oregano (Rathod et al., 2021). Eugenol, found in clove and cinnamon oil, has shown antimicrobial activity against *Penicillium* and *Apsergillus* pathogenic species (Martínez, 2012). An Aloe vera extract was shown to inhibit *Penicillium digitatum*, *P. expansum*, *Botrytis cinerea* and *Alternaria alternata* (Barkai-Golan, 2001). A number of plant-derived antimicrobial compounds can be applied as fungicides in lieu of synthetic substances. In one

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[4] Secondary metabolite refers to a chemical compound produced by a plant that is not involved in the plant's primary metabolic processes such as respiration and photosynthesis (Martínez, 2012).

study, foliar applications of mustard oil and garlic extract reduced the incidence of powdery mildew from the genus *Oidium* by 29.89% and 44.69%, respectively, on Indian jujube trees (Choudhary et al., 2020). Other studies have reiterated the powdery mildew disease control imbued by mustard and garlic extracts on other horticultural crops, including squash and cucumber (Frem et al., 2022; Morsy et al., 2009). Control of downy mildew in pearl millet using plant extracts has been explored as well, and a number of ornamental and edible crops are known to have zoospore-inhibiting properties (Sa et al., 2007). Several studies point to the antifungal compounds found in chili peppers (*Capsicum* spp.) and black pepper (*Piper nigrum*), which may be useful for the control of fungi in both field and post-harvest storage settings (Buitimea-Cantúa et al., 2020; Maracahipes et al., 2019; Soumya & Nair, 2012). One study found that a mixture of cooking oil and egg yolk was able to control powdery mildew in organic lettuce production with an efficacy comparable to that of conventional controls (Jee et al., 2008). At the time of this report, there are over 500 pesticides that formulate with plant-derived active ingredients on the OMRI Products List (OMRI, 2022).

Section 205.601(e) of the National List enumerates synthetic insecticides, and section (i) describes plant disease controls that are permitted in organic crop production. Detailed information regarding each of these substances is available in their respective technical reports, TAP reports and NOSB recommendations, published in the NOP's Petitioned Substances Index (NOP, 2022b). A brief review of information from these sources is included below.

Fixed coppers and copper sulfate are used as fungicides to control downy mildew in grapes, as well as a host of other plant diseases affecting a variety of crops (NOP, 2022a). Copper products are some of the most heavily used and relied upon pesticides in organic operations. However, efforts are underway to identify suitable alternatives to copper, due to the toxic effects of excess copper on plants, animals, invertebrates, and microorganisms. The allowance of copper products for plant disease control in organic agriculture is currently undergoing sunset review, which will include evaluation of copper toxicity and impacts on human health (NOP, 2022a). KS may be an alternative that could be used in lieu of or in rotation with copper-based fungicides.

Aqueous potassium silicate is permitted as an insecticide and plant disease control. It is applied preventively via spray as a broad-spectrum fungicide. It also suppresses mites, whiteflies and other insects (NOP, 2014a).

Lime sulfur is used to control plant diseases such as powdery mildew, black rot, brown rot, anthracnose, scab, plum pockets, spot of rose, San Jose scale, peach leaf curl and several raspberry diseases. It is also used against mites, including spider mites. Post-harvest treatment of peaches with lime sulfur has been shown to reduce the incidence of brown rot caused by *Monilinia fructicola*. *Elemental sulfur* is also a fungicide and insecticide registered for use on a wide range of food crops, in field or in greenhouse settings (NOP, 2014b).

Hydrogen peroxide is a well-known broad-spectrum fungicide used in greenhouses, on seeds, as a plant root and stem dip, a soil drench, and a foliar spray. It is used both preventively and in post-infection control of plant diseases caused by *Pythium*, *Phytophthora*, *Rhizoctonia*, *Fusarium* or *Thielaviopsis*. It is marketed for control of powdery mildew, downy mildew and bunch rot in viticulture, and downy mildew control in cucurbits. It is also a post-harvest control of diseases caused by *Botrytis cinerea*, *Rhizopus stolonifer*, *Penicillium digitatum*, and *P. italicum* in strawberries and organs, and of pink rot resulting from *Phytophthora erythroseptica* in potatoes (NOP, 2015a).

Horticultural oils are widely used as insecticides and fungicides to control, for example, powdery mildew on various crops and sooty mold in citrus (NOP, 2019).

Potassium bicarbonate is used to control plant pathogens such as *Sphaerotheca fuliginea* causing powdery mildew in cucurbits, and *Alternaria cucumerina* causing early blight in tomatoes. It is also used against scab in pome fruit. Laurent et al. (2021) found that potassium bicarbonate was an effective control for gray mold (*Botrytis cinerea*) in grapes (NOP, 2015b). Youssef and Roberto (2014) also applied potassium bicarbonate to table grapes at one week pre-harvest and found this to be effective at reducing the incidence of gray mold to zero after 20 days of cold storage (Youssef & Roberto, 2014). The authors determined in this study that potassium bicarbonate and KS both significantly inhibited *B. cinerea* mycelia growth at 0.25% concentration in vitro. They then treated grapes both pre- and post-harvest with KS and potassium bicarbonate, and evaluated them for decay incidence after one month of cold storage. Results showed that spray application with potassium bicarbonate one week prior to harvest was slightly more effective (100% inhibition of gray mold) than pre-harvest treatment with KS, but post-harvest immersion in 1% (w/v) KS resulted in a slightly lower incidence of decay (100% inhibition of gray mold) than grapes immersed in potassium bicarbonate post-harvest (Youssef & Roberto, 2014).

Jabnoun-Khiareddine et al. (2016) compared the effects of KS and potassium bicarbonate on 10 different pathogens affecting tomatoes in Tunisia and found them both effective controls. The more effective or less effective fungicide differed depending on the pathogen.

Polyoxin D zinc salt is a fungicide used to control diseases of various crops including downy mildew, powdery mildew, anthracnose, and diseases caused by *Alternaria*, *Botrytis*, and *Rhizoctonia* (NOP, 2017). It is a relatively new alternative for organic farmers.

Post-harvest handling fungicides

As noted, most studies examining the use of KS as an antimicrobial agent in agriculture focus on post-harvest handling applications. Thus, **Table 3** lists materials discussed in the literature that are allowed for post-harvest handling per NOP Guidance 5023 (NOP, 2016), as potential alternatives to KS treatment.

Table 3. Nonsynthetic and allowed synthetic post-harvest handling disease control alternatives.

Nonsynthetic	Synthetic
Nonsynthetic salts • Sodium bicarbonate • Sodium carbonate • Calcium sulfate Biological controls • *Candida sp.* • *Trichoderma sp.* • *Bacillus subtilis* • *Pseudomonas* Plant products including essential oils • Turmeric • Clove oil • Thyme oil • Peppermint oil • Lemongrass oil Ethanol	Synthetic salts • Potassium bicarbonate • Sodium citrate • Sodium lactate • Potassium lactate Other § 205.605(b) materials • Chlorine materials • Peracetic acid

Biological controls can be used for post-harvest prevention of decay in raw organic agricultural commodities. One study that isolated various microbes from table grapes found the *Candida sp.* to be a more effective post-harvest treatment of sweet cherries than *C. oleophila* at reducing the percentage of decayed fruits (Akgun Karabulut et al., 2001). Although the study also evaluated potassium sorbate, it did not compare those results to the biological controls. Ragab et al. (2012) found *Trichoderma viride, B. subtilis, and P. fluorescens* to be more effective controls against *Fusarium oxysporum*, a wilt disease agent, than *T. harzianum*, *T. aureiviride*, *Bacillus subtilis* and *Pseudomonas fluorescens*, based on in vitro tests on the suppression of linear growth. The study also evaluated salts, including KS, and essential oils, finding a variety of these types of controls to be efficacious, though there was not specific comparison of the different types of controls with one another.

Nonsynthetic salts such as sodium bicarbonate and sodium carbonate are used to prevent post-harvest decay of citrus. Thipaksorn et al. (2012) found sodium bicarbonate and KS to both be effective at controlling green mold from *P. digitatum* on tangerines at a concentration of 1.5%. In another study, sodium bicarbonate was found to be more effective than KS and antimicrobial yeasts in the control of post-harvest decay of sweet cherries (Akgun Karabulut et al., 2001). Potato tubers immersed post-harvest in a KS dip completely inhibited *H. solani* spore germination, as did sodium bicarbonate and sodium carbonate dips (Hervieux et al., 2002). KS was slightly more effective at inhibiting mycelial growth than sodium bicarbonate, but not as effective as sodium carbonate (Hervieux et al., 2002). Calcium sulfate was included in a study along with KS and other materials tested for efficacy against gray mold of 'Italia' table grapes. Calcium sulfate was not reported to be effective; KS and potassium bicarbonate, discussed below, were the most effective (Youssef & Roberto, 2014). Smilanick et al. (2008) evaluated the effect of KS and sodium bicarbonate treatments on green mold, blue mold, and sour rot in Valencia oranges. The authors noted several advantages of KS over sodium bicarbonate, principally the absence of sodium, making for easier and more environmentally-friendly disposal (Smilanick et al., 2008). Sodium bicarbonate and sodium carbonate also inhibited germination of sclerotia from the pathogens *Sclerotinia rolfsii* as effectively as KS, and displayed greater fungicidal properties against germinated sclerotia (Punja & Grogan, 1982).

Ethanol is another reported alternative for controlling *B. cinerea* and related post-harvest decay in table grapes (Karabulut et al., 2005; Lichter et al., 2002). Karabulut et al. (2005) measured germination of *B. cinerea* spores in potato dextrose agar (PDA) medium, and the incidence of correlated gray mold in grapes in the presence of, or treatment with, different concentrations of ethanol, KS, and the two combined. 10% ethanol was slightly less effective than 0.5% KS at preventing spore germination in vitro, but more effective at higher concentrations (20% ethanol vs. 1.0% KS). KS was slightly more effective than ethanol at lowering gray mold incidence in grapes at both concentrations tested. However, in all cases, the combination of ethanol and KS showed the antifungal efficacy greater than either treatment alone, suggesting a strong synergism (Karabulut et al., 2005).

Plant products, including essential oils, can also be used to prevent post-harvest pathogens. Dry treatment of stored rice with 0.1% turmeric showed 62.9% control of aflatoxin production, as compared to 67.2% control with 0.125% KS treatment (Gupta, 2010). Essential oils including clove, thyme, lemon grass, and peppermint showed complete reduction in fungal linear growth of *Fusarium oxysporum* (causal agent of wilt disease in peppers) at 4% concentration (Ragab et al., 2012). KS was also shown to be effective in this study but was compared to other salts rather than the essential oils. Other edible essential oils that demonstrate antimicrobial activity include anise, cinnamon, coriander, eucalyptus, juniper, lavender, lemon, neroli, rosemary, fennel, citronella, rosemary, and nutmeg (Pauli & Schilcher, 2009).

According to NOP Guidance 5023 (NOP, 2016), substances listed at §205.605 of the National List may be used for post-harvest handling of raw agricultural commodities either on farms or in handling facilities, provided that there is no restriction limiting their use. This includes post-harvest pest control substances, formulated with compliant inerts. The following materials appear at §205.605 without limiting restrictions that would preclude their use in post-harvest handling.

Synthetic salts potassium bicarbonate, sodium citrate, and sodium and potassium lactate may all be used for post-harvest prevention of decay. As noted above, Youssef and Roberto (2014) found post-harvest immersion of table grapes in potassium bicarbonate to be an effective control of gray mold after 20 days of cold storage, albeit slightly less effective than the post-harvest KS dip. Hervieux et al. (2002) reported post-harvest immersion of potato tubers in either KS or sodium citrate inhibited the spore germination of *H. solani*. In the same study, sodium lactate showed only modest inhibition of *C. elegans* spore germination and mycelial growth and promoted conidiation[5] (Hervieux et al., 2002). Of the salts tested,

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[5] Conidiation is the asexual reproduction of filamentous fungi (Jung et al., 2014).

KS and sodium carbonate were among the most effective at reducing the severity of silver scurf when applied four days after inoculation. (Hervieux et al., 2002). Note that sodium carbonate is permitted as a nonsynthetic salt in organic crop production, and a nonsynthetic substance permitted in food processing per §205.605(a). Either allowance covers its use in post-harvest handling. Germination of sclerotia from the pathogens *Sclerotinia rolfsii* was completely inhibited by potassium bicarbonate as well as KS; unlike KS, potassium bicarbonate also displayed fungicidal properties to sclerotia (Punja & Grogan, 1982).

The literature cites the use of other inorganic salts having antimicrobial activity as alternatives to conventional fungicides, however, these are not permitted in post-harvest handling of organic crops, as they do not appear on §§205.601 or 205.605 of the National List: ammonium bicarbonate, calcium citrate, calcium propionate (Arslan et al., 2009; Olivier et al., 1999; Palou et al., 2009; Punja & Grogan, 1982). Challenges to the use of KS and other inorganic salts for post-harvest decay prevention include limited persistence and lack of preventive effect, inconsistent activity, potential for fruit injury, and the issue of disposal of salt solutions following their use (Palou et al., 2002; Smilanick et al., 2008). Other conventional alternatives to KS are also noted in **Appendix 1**.

Chlorine materials are a common post-harvest disinfectant in flume and wash water. One study found a significant decrease in the incidence of black root rot on artificially wounded and inoculated carrots when treated with a 0.05 or 0.1M solution of KS as compared to treatment with a 100-µg/ml Cl sodium hypochlorite solution (Punja, 1993). KS may be a less toxic and more environmentally benign alternative to chlorine.

Peracetic acid at 0.02% and KS at 1.5% were both effective dips for controlling green mold in tangerines (as was 1.5% w/v sodium bicarbonate) during 5 days of storage at room temperature and approximately 95% relative humidity, though KS was superior (Thipaksorn et al., 2012). However, the authors found a synergistic effect when combining peracetic acid and KS, as this mixture was more effective than either the KS or peracetic acid alone. A similar synergy was not found with the combination of peracetic acid and sodium bicarbonate (Thipaksorn et al., 2012).

While there are many alternative substances available to prevent decay in the post-harvest handling of raw organic commodities, there are far fewer options than in conventional post-harvest handling. The myriad different pathogens, diseases, and types of crops requires a diversity of control measures to adequately prevent decay to meet marketing needs. Palou et al. (2009) noted that different fruits have different peel characteristics and physical and physiological conditions that affect the interaction of water activity and pH on the fruit surface, and these parameters affect the toxicity of low-toxicity antimicrobial agents. Thipaksorn et al. (2012) suggested that cultivars should be matched with appropriate antimicrobials in post-harvest handling to effectively protect against post-harvest decay.

Evaluation Question #12: Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).

Organic farming manages plant diseases and insect pests primarily by preventive cultural practices and ecological processes, designed to promote beneficial microbial diversity in the soil and biodiversity generally in the farm ecosystem. Diverse microbial soil communities can naturally suppress pathogenic organisms through competition, antagonism, hyper-parasitism, and predation. Similarly, insect pest pressure is reduced when a biodiverse system attracts and supports beneficial insects. These natural controls follow from management practices such as cover cropping, which adds organic matter to the soil and fodder for the soil microbial community. Crop rotation can disrupt the life cycles of pests and pathogens that rely on a particular crop host, as can managing cropping schedules and spatial arrangements (Mohler & Johnson, 2009; Parry et al., 2020).

Planting disease resistant crop varieties is another alternative to the use of KS and other biocides to prevent losses from plant diseases. Grapevine varieties bred for resistance to powdery and downy mildew contain genetic factors that confer some protection against pathogens, though research continues to monitor resistance to ensure it does not break down over time when challenged by virulent pathogens

(Merdinoglu et al., 2018). Cucurbits (Dhillon et al., 2018), spinach (Bhattarai et al., 2020), wheat (Kang et al., 2020), and other crops have also been bred for powdery mildew resistance. One study examined cauliflower genotypes that imparted resistance to downy mildew (Singh et al., 2022). Some crops have been bred for host plant resistance to insect herbivory such as by white fly (Leckie et al., 2012; Parry et al., 2020; Yao et al., 2019).

Sanitation and exclusion of pathogens are important techniques to prevent post-harvest handling losses. Various washing regimes and storage parameters have been examined to maximize the shelf life of produce. Physical techniques, such as modified atmosphere and temperature control, can also enhance shelf-life. In one study, modified atmosphere packaging combined with cold storage enhanced post-harvest antimicrobial treatments. (Akgun Karabulut et al., 2001). Preciado-Iñiga et al. (2018) promote what they called "hurdle technology," where various physical and non-biocidal chemical techniques are applied in combination. These include pH control, reduction of water activity, and cold storage with both oxygen and light protection, as well as antimicrobial treatment (Preciado-Iñiga et al., 2018). Microwave heat has also been explored as a physical post-harvest preservation technique. Rice grains subjected to 100% microwave power for 2 minutes showed over 50% inhibition of fungal growth during storage, without detriment to the cooking quality of the grains (Gupta, 2010).

<u>Focus Question:</u> Is KS considered a weak acid antimicrobial known to cause resistance?

Bacteria, molds, and yeasts are the three main types of microorganisms that cause food spoilage incidents. Thus, the answer to this question focuses on the documented resistance that these three types of microorganisms can present in the context of the food industry. Studies have documented in detail resistance to weak acid preservatives and specifically to sorbates and sorbic acid on yeast models. Fewer studies are available for bacteria and molds, but some have documented resistance with these types of microorganisms as well. **Table 4** summarizes the resistance mechanisms that have been described.

Table 4. Documented resistance to sorbate and sorbic acid and its reported mechanism.

Organism	**Species / Type**	**Resistance mechanism**	**Reference**
Yeast	*Zygosaccharomyces rouxii*	Change in fatty acid composition of the cell membrane	Golden et al., 1994
		Sorbic acid degradation to pentadiene	Casas et al., 2004
	Zygosaccharomyces bailii	Reduced permeability to preservative	Warth, 1989
		Sorbic acid degradation	Mollapour & Piper, 2001
		Population heterogeneity: certain cells possess lowered pHi[6] in addition to other resistance mechanisms	Stratford et al., 2013
	Saccharomyces cerevisiae	Expression of proton pumps to expel excess protons and regulate pHi	Holyoak et al., 1996 Lambert & Stratford, 1999
		Induction of transporters (Pdr12[7])	Papadimitriou et al., 2007
		Sorbic acid degradation to pentadiene	Stratford et al., 2007
	Debaryomyces hansenii	Sorbic acid degradation to pentadiene	Casas et al., 2004
Mold	*Penicillium spp*	Sorbic acid degradation to pentadiene	Kinderlerer & Hatton, 1990
	Aspergillus niger	Sorbic acid degradation to pentadiene	Plumridge et al., 2008
		Weak acid resistance (WarA) transcription factor activation	Geoghegan et al., 2020
	Aspergillus fumigatus	Weak acid resistance (WarA) transcription factor activation	Geoghegan et al., 2020
Bacteria	*Staphylococci spp*	Sporulation	Russell, 1991
	Gram-negative bacteria	Outer membrane possible degradation of preservative	Russell, 1991
	Bacillus subtilis	Plasma membrane remodeling	Beek et al., 2008

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[6] Intracellular pH.

[7] Plasma membrane transporter that mediates the energy-dependent extrusion of water-soluble carboxylate anions from the cell (P. Piper, 1998).

Yeasts

Some yeasts can adapt and resist exposure to different weak acids, including sorbates and sorbic acid. Among the species that can present such resistance, *Saccharomyces cerevisiae*, *Zygosacharomyces bailii*, and *Z. rouxi* have been studied in detail. Sorbates are able to inhibit yeast growth on food surfaces during fermentation, but do not inhibit the organisms used in the fermentation process (Somogyi, 2000). When exposed to the inhibitory sorbate concentrations, the yeast cells can activate a number of molecular responses: internal pH recovery to maintain homeostasis, detoxification through multidrug resistance transporters and remodeling of the cellular envelope (Mira et al., 2010). Some studies have also found that certain yeasts are able to degrade sorbic acid (Casas et al., 2004; Stratford et al., 2007). Additionally, the high resistance yeast, *Z. balii,* can use weak acids such as sorbic acid as a carbon source in the presence of oxygen (Mollapour & Piper, 2001; Stratford et al., 2007).

Steels et al. (2000) studied the resistance of *Z. bailii* to sorbic acid, finding that a bigger inoculum of *Z. bailii* contains a greater and more diverse population, and that a small fraction of these cells can present resistance to sorbic acid. This study also concluded that the phenotype of cells presenting a high resistance to sorbic acid, also called “super cells” was not heritable; this resistance is not conferred by a genetically-stable heritable trait within the population (Steels et al., 2000).

Papadimitriou et al. (2007) studied the reported role of Pdr12 in *S. cerevisiae* sorbic acid resistance, finding that the induction of Pdr12 to maximal amounts did not provide the cells with an acquired resistance to the compound. In this same study, *S. cerevisiae* cells were treated with sorbic acid at 0.9 mM for two-hours. The pre-stressed cells exhibited no resistance to a higher concentration of sorbic acid after this conditioning period.

Stratford et al. (2013) studied the resistance of *Z. bailii* and hypothesized that its extreme resistance is due to population heterogeneity, with a small proportion of cells having a lower intracellular pH (pHi). The pHi of this subpopulation, in addition to other unidentified factors, determines its extreme resistance. This study showed that the phenotype of the weak-acid resistance subpopulation was not stably inherited. Phenotypic heterogeneity is another antimicrobial resistance determinant. This phenomenon is observed within isogenic cell populations, whereby individual cells can display a markedly different phenotype despite being genetically identical (Geoghegan et al., 2020).

Molds

Current understanding of resistance mechanisms of mold fungi to weak acids is limited, especially compared to yeasts (Geoghegan et al., 2020). Weak acid resistance can be attributed in part to the enzymatic degradation of sorbic acid (Plumridge et al., 2008) together with other as-yet-uncharacterized mechanisms of resistance. Recently, Geoghegan et al. (2020) identified a transcription factor that they called weak acid resistance A (warA). This transcription factor activates the WarA regulon[8], conferring weak acid resistance to *Aspergillus fumigatus* and *A. niger*. During this study, some experiments with sorbic acid determined that genetically uniform populations of *A. niger* conidia[9] demonstrate different levels of resistance, or heteroresistance, to this weak acid. This is the first report of heteroresistance to weak acids in fungal conidia. It is important to note that the heteroresistance decreased within 6 h of conidial germination, suggesting that at least some factors underlying this heterogeneity are limited to ungerminated conidia and are lost upon germination (Geoghegan et al., 2020). Experiments conducted in the 1980s exposed the molds *Penicillium digitatum* and *Penicillium italicum* to sorbic acid and KS at various doses over prolonged periods. *Penicillium italicum* developed some tolerance to potassium sorbate, but *Penicillium digitatum* did not (Schroeder & Bullerman, 1985). No resistance mechanism was identified or hypothesized.

Bacteria

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[8] A regulon is a group of several genes that are turned on or off in response to the same signal by the same regulatory factor (Clark et al., 2019), in this case the WarA transcription factor.

[9] Asexual spores formed by certain Fungi divisions (Osherov & May, 2001).

In bacteria, the mechanisms of insusceptibility to agents such as KS and sorbic acid are less well understood than those that convey tolerance to antibiotics (Russell, 1991). Bacterial resistance can be classified in two types: Intrinsic resistance and acquired resistance (Russell, 1991). Intrinsic resistance is not caused by horizontal gene transfer and can be triggered by genes that mediate the impermeability of cellular envelopes or the activity of multidrug efflux pumps[10] (Zhang & Feng, 2016). Acquired resistance, on the other hand, results from genetic changes arising either from mutation or horizontal gene transfer (Russell, 1991).

In the case of gram-positive bacteria, intrinsic resistance is lower because the preservatives enter these cells more easily than the cells of gram-negative bacteria (Russell, 1991). The lipopolysaccharides that form the gram-negative bacterial membrane can act as a barrier. Another type of intrinsic resistance is the possession of enzymes that enable bacteria to degrade preservatives (Russell, 1991).

Phenotypically-acquired resistance to lipophilic acid preservatives such as benzoic acid and sorbic acid is well documented in yeasts (Warth, 1977, 1978). It results from the enhanced ability of adapted cells to catalyze energy-dependent extrusion of the acids. No such mechanism has been claimed with bacteria. However, the levels of acquired resistance of bacteria to most organic acids rarely exceeds two- to threefold (Russell, 1991).

Bacterial spores are not usually killed by sorbic acid, but in some cases the presence of KS (Russell, 1991) can have inhibiting or bacteriostatic effects. For example, at pH values below 6, sorbic acid inhibits *Clostridium botulinum* spore germination and KS delays the growth and toxin production of *C. botulinum* (Russell, 1991).

Report Authorship

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All individuals are in compliance with Federal Acquisition Regulations (FAR) Subpart 3.11—Preventing Personal Conflicts of Interest for Contractor Employees Performing Acquisition Functions.

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[10] Multidrug efflux pumps are elements with conserved organization both at the genetic and at the protein levels, which are encoded in bacterial genomes and that can extrude a wide range of substrates that include, beside antibiotics: heavy metals, organic pollutants, plant-produced compounds, etc (Blanco et al., 2016).

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Appendix 1

Reports of plant pests and diseases controlled through the application of potassium sorbate, either as the sole active or in combination with other active ingredients, at various stages of production.

Disease	**Pathogenic organism**	**Crop**	**Alone or with other active substances**	**Stage and method of application**	**Reference**
Root rot	*Fusarium oxysporum* f. sp. *melonis, Macrophomina phaseolina, Rhizoctonia solani,* and *Sclerotinia sclerotiorum*	Field and horticultural crops subject to various root rots	Alone	In vitro test, including in soil medium	(Arslan et al., 2009)
Root rot	*Fusarium solani; Rhizoctonia solani*	Cowpea	Alone	Seed soaking; foliar spray on emergent leaves; combination of both	(El-Mougy et al., 2004)
Root rot and crown rot	*Pythium aphanidermatum, Sclerotinia sclerotiorum*	Tomatoes	Alone	In vitro test on growth media; Foliar spray in growth chamber	(Jabnoun-Khiareddine et al., 2016)
Brown rot	*Botrytis cinerea, Geotrichum candidum, Alternaria alternata, Penicillium expansum, Mucor piriformis,* and *Rhizopus stolonifer*	Nectarines	Alone (pre-screening) and with half-strength fludioxonil and sodium benzoate	Post-harvest dip; controlled droplet applicator	(Palou et al., 2009)
Brown rot	*Monilinia fruticola*	Sweet cherry	Alone	Post-harvest	(Akgun Karabulut et al., 2001)
Black root rot	*Chalara elegans*	Carrots	Alone	Post-harvest dip	(Punja, 1993)
Sour rot	*Geotrichum candidum*	Nectarines	Alone and with sodium benzoate, sodium propionate, or sodium acetate(?)	Post-harvest dip	(Palou et al., 2009)
Sour rot	*Geotrichum citri-aurantii*	Citrus	Conventional fungicides: imazalil, thiabendazole, pyrimethanil, and fludioxonil.	Post-harvest	(Smilanick et al., 2008)
Silver scurf	*Helminthosporium solani*	Potatoes	Alone	Post-harvest dip	(Hervieux et al., 2002; Olivier et al., 1999)
Gray mold	*Botrytis cinerea*	Tomatoes	Alone	Foliar spray of 30-day-old tomato seedlings	(Jabnoun-Khiareddine et al., 2016)
Gray mold	*Botrytis cinerea*	Table grapes	Alone and with a program that included applications of pyrimethanil, cyprodinil + fludioxonil, pyraclostrobin + boscalid, or fenhexamid for two out of four years	Pre-harvest (at berry set, pre-bunch closure, ripening onset, and 2 or 3 weeks before harvest)	(Feliziani et al., 2013)
Gray mold	*Botrytis cinerea*	'Italia' table grapes	Alone	Pre-harvest spray, post-harvest dip & combination of both	(Youssef & Roberto, 2014)
Gray mold	*Botrytis cinerea*	Kiwifruit	Alone and with a hot water treatment	Post-harvest	(Ge et al., 2020)

Disease	**Pathogenic organism**	**Crop**	**Alone or with other active substances**	**Stage and method of application**	**Reference**
Gray mold	*Botrytis cinerea*	Peaches, nectarines, plums	Alone (pre-screening) and with half-strength fludioxonil and sodium benzoate	Post-harvest	(Palou et al., 2009)
Gray mold	*Botrytis cinerea*	Sweet cherries	Alone in modified atmosphere packaging.	Post-harvest	(Akgun Karabulut et al., 2001)
Gray mold	*Botrytis cinerea*	Berries	Post-consumer recycled polyethylene terephthalate (PCPRPET) and aqueous silicone solution	Post-harvest packaging	(Junqueira-Gonçalves et al., 2016)
Gray mold	*Botrytis cinerea*	'Flame Seedless' and 'Thompson' Grapes	Alone or in combination with ethanol	In vitro test and post-harvest dip of detached grapes	(Karabulut et al., 2005)
Blue mold	*Penicillium expansum*	Sweet cherries	Alone in modified atmosphere packaging.	Post-harvest	(Akgun Karabulut et al., 2001)
Green mold; blue mold	*Penicillium digitatum* and *P. italicum*	Citrus (oranges and mandarins)	Carbon dioxide (CO$_2$) and hyperoxygenation (O$_2$)	Post-harvest dip	(Montesinos-Herrero & Palou, 2016)
Green mold; blue mold	*Penicillium digitatum* and *P. italicum*	Citrus (mandarins, lemons and oranges)	Optionally imazalil (conventional fungicide)	Post-harvest dip	(Montesinos-Herrero et al., 2009)
Green mold; blue mold	*Penicillium digitatum* and *P. italicum*	Citrus (lemons and oranges)	Optionally sodium benzoate, sodium propionate or sodium acetate	Post-harvest dip	(Palou et al., 2002)
Green mold	*Penicilium digitatum*	Citrus (tangerines)	Optionally peracetic acid	Post-harvest	(Thipaksorn et al., 2012)
Green mold	*Penicilium digitatum*	Citrus	Sodium bicarbonate; conventional fungicides	Post-harvest	(Smilanick et al., 2008)
Early blight	*Alternaria solani*	Tomatoes	Alone	In vitro test	(Jabnoun-Khiareddine et al., 2016)
Wilt	*Fusarium oxysporum*	Pepper (*Capsicum annum* L.)	Alone in five concentrations; comparison study with biological antagonists, essential oils, other salts, and a conventional fungicide	In vitro test	(Ragab et al., 2012)
Wilt	*Verticillium dahliae*, *Fusarium oxysporum* f. sp *lycopersici* and *F. oxysporum f. sp. radicis-lycopersici*	Tomatoes	Alone	In vitro tests and pre-harvest foliar spray of 30-day-old tomato seedlings	(Jabnoun-Khiareddine et al., 2016)
Fruit rot	*Rhizoctonia solani*, *Colletotrichum coccodes*	Tomatoes	Alone	In vitro test	(Jabnoun-Khiareddine et al., 2016)
Chilling injury, nutrient loss	Abiotic	Pomegranate	Chitosan	Post-harvest, during cold storage	(Molaei et al., 2021)
Aflatoxin production	*Aspergillus flavus*	Rice	Alone	Post-harvest, dry application	(Gupta, 2010)