### **Propionic Acid**

Handling/Processing

1 2 **Identification of Petitioned Substance** 3 4 Chemical Name (IUPAC): **CAS Number:** 5 Propanoic acid 79-09-4 6 7 **Other Codes:** Other Names: 8 Propionic acid EINECS 201-176-3 9 RTECS UE 5950000 Methylacetic acid 10 Ethylformic acid UN 1848 11 Ethanecarboxylic acid EC 607-089-00-0 12 Carboxyethane 13 14 **Trade Names:** Luprosil 15 16 Prozoin 17 Tenox P grain preservative 18 Tenox P 19

#### **Characterization of Petitioned Substance**

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#### **Composition of the Substance:**

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Propionic acid is a three-carbon carboxylic acid,  $CH_3CH_2COOH$ , which occurs naturally as the free acid or in the form of its esters. It can be produced by chemical synthesis or by fermentation. The chemical structure of propionic acid is shown below:

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#### **Properties of the Substance:**

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35	Product Chemistry (EPA, RED, 1991)	
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37	Physical State	Oil liquid
38	Appearance	Colorless
39	Odor	Rancid, pungent odor
40	Molecular Weight	74.08
41	Boiling Point (760 mmHg)	141 ℃
42	Melting Point	-22.4 °C
43	Solubility	Complete in water, ethanol, chloroform, diethyl ether
44	Vapor Pressure	3 mm Hg at 20 ℃
45	Specific Gravity	0.99 at 20 °C
46	Dissociation Constant	$1.32 \times 10^{-5}$ at 25 °C
47	pН	Around 5 (- log K=4.87) based on the dissociation constant

48 49 **Specific Uses of the Substance:** 

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 Propionic acid is an active ingredient for use as fungicides and bactericides on stored grains, hay, storage areas for silage and grains, poultry litter, and drinking water for poultry and livestock. According to the petition, there is 48% of propionic acid in their product (DMX-7) which is used primarily for animal feed preservation as a mold inhibitor. It is used in shipping and storage and is applied either as a solution or on an absorbent (vermiculite) to prevent mold in corn gluten meal, corn, rice and other grains. Propionic acid is applied with a spray nozzle. Application rates of propionic acid depend on the moisture content of the grain at the time it is placed in storage, and also varies depending on whether the grains are in "open" storage or "closed" storage. The following information is provided in the petition:

Moisture Level	Amount of DMX-7
Up to 14%	Minimum 2 pounds per ton
16%	Minimum 3 pounds per ton
18%	Minimum 4 pounds per ton

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#### **Approved Legal Uses of the Substance:**

1. The U.S. Environmental Protection Agency (EPA) approved propionic acid under 40 CFR Part 180—Tolerances and Exemptions from Tolerances for Pesticide Chemicals Infood. It is stated as "§180.1023 Propanoic acid; exemptions from the requirement of a tolerance." It is exempted from the requirement of a tolerance on all crops when used as an active/inert ingredient in accordance with good agricultural practice in pesticide formulations applied to growing crops, to raw agricultural commodities (before and after harvest), and to animals (including applied as bactericide/fungicide to livestock drinking water, poultry litter, and storage areas for silage and grain). Propionic acid has an EPA Pesticide Chemical (PC) Code Number: 0777702; and Registration No. 8596-24—fungicide for external application.

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- 2. The U.S. Food and Drug Administration (FDA) approved propionic acid under:
  - "Animal Drugs, Feeds, and Related Products" listed on "Substances Generally Recognized As Safe" in "Chemical Preservatives", 21 CFR §582.3081. Propionic acid is generally recognized as safe (GRAS) when used in accordance with good manufacturing or feeding practice; and
  - "Food for Human Consumption" listed on "Direct Food Substances Affirmed as Generally Recognized As Safe", 21 CFR §184.1081. Propionic acid is used, as an antimicrobial agent and a flavoring agent, infood with no limitation other than current good manufacturing practice.

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#### **Action of the Substance:**

Propionic acid is permitted in animal feed and human foods primarily as a mold inhibitor. It tends to be highly specific against molds, with the inhibitory action being primarily fungistatic rather than fungicidal. Propionic acid acts against microorganisms by inhibiting the cellular uptake of substrate molecules (Jay, 2005).

The undissociated form of propionic acid is essential to the antimicrobial activity. It can penetrate the semi-permeable membrane of the bacterial cell wall and enter cytoplasm. After that, propionic acid dissociates at the internal pH of bacteria (around pH 7.0) and causes the internal pH of the microbe to decrease, which the bacteria are unable to tolerate. This phenomenon consumes energy and eventually stops the growth of the bacteria or even kills them.

#### Status

#### **United States:**

1. Environmental Protection Agency – propionic acid was first registered for pesticidal use in the early 1970's. In 1975, EPA first exempted propionic acid from tolerances for residues following post-harvest application in grains or hays. As the active ingredient, propionic acid is a fungicide/bactericide used to (a)

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preserve stored grains for animal and human consumption, (b) inhibit bacterial growth in drinking water for poultry and livestock, (c) control mold and fungi in poultry litter and animal feed, and (d) sanitize precleaned food contact surfaces. Propionic acid is also identified as an inert ingredient, on the Agency's "List 4B", in pesticide formulations.

2. Food and Drug Administration— in May 1984, propionic acid was affirmed as Generally Recognized As Safe (GRAS) for use as direct food additives (i.e., as chemical preservatives in animal feeds and antimicrobial/flavoring agents in human food) with no limitation other than current good manufacturing practice.

#### **International:**

- 1. The Canada Food Inspection Agency, Food and Drug Regulations propionic acid as a preservative is listed under Food Additives Permitted for Use in Canada. (Last modified 2006)
- The European Union (EU) propionic acid is listed under the Preservatives group in the List of
  Additives Currently Permitted in Food.
  - 3. The Joint FAO/WHO Expert Committee on Food Additives propionic acid (INS¹: 280) functional uses as preservative, antimould and antirope agent, or flavoring agent. (Latest evaluation 1997)
  - 4. The EU Organic Regulation No 2092/91 the use of propionic acid as a preservative in the production of silage shall be only permitted when weather conditions do not allow for adequate fermentation.
  - 5. The Codex Guidelines for Organically Produced Foods propionic bacteria and its natural acid product may be used as a silage additive when the weather conditions do not allow for adequate fermentation, and with approval of the competent authority.

#### Evaluation Questions for Substances to be used in Organic Handling

# <u>Evaluation Question #1:</u> Is the petitioned substance formulated or manufactured by a chemical process? (From 7 U.S.C. § 6502 (21).)

According to the petition, the manufacture involves reacting ethylene (petroleum based) and synthetic gas (a mixture of carbon monoxide and hydrogen, produced by partial oxidation of natural gas or oil with air under controlled conditions) with a catalyst (rhodium or cobalt) to produce propionaldehyde. Propionaldehyde is further oxidized to yield propionic acid by a treatment with air or pure oxygen in a carefully controlled reactor. Propionic acid is then concentrated by distillation.

Propionic acid can also be synthesized from ethanol and carbon monoxide using boron trifluoride catalyst (Merck, 2006).

<u>Evaluation Question #2:</u> Is the petitioned substance formulated or manufactured by a process that chemically changes the substance extracted from naturally occurring plant, animal, or mineral sources? (From 7 U.S.C. § 6502 (21).)

As described above, propionic acid is derived from petroleum raw materials. It is manufactured by reacting ethylene, which was produced from petroleum, and carbon monoxide with a catalyst (rhodium or cobalt) to produce the intermediate, propionaldehyde. Further oxidation yields propionic acid.

# <u>Evaluation Question #3:</u> Is the petitioned substance created by naturally occurring biological processes? (From 7 U.S.C. § 6502 (21).)

Propionic acid can be produced biologically from the metabolic breakdown of fatty acids containing odd numbers of carbon atoms, and in the breakdown of some amino acids. It is formed in the oxidation of fatty acids and

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<sup>&</sup>lt;sup>1</sup> A number assigned to a food additive in accordance with the Codex Class Names and the International Numbering System (INS) for Food Additives.

from the side chain of cholesterol. In addition, bacteria of the genus *Propionibacterium* also can produce propionic acid as the end product of the anaerobic metabolism. These bacteria are commonly found in the stomachs of ruminants and play important roles in the development of the characteristic flavor of Swiss cheese. Several carbon sources (such as glucose, xylose, maltose, sucrose, and whey lactose) have been used for propionic acid fermentation, but the results are not economically viable (Kumar et al., 2006).

#### Evaluation Question #4: Is there a natural source of the petitioned substance? (From 7 CFR § 205.600 (b) (1).)

As stated above in Evaluation Question #3, propionic acid naturally occurs in animals and in dairy products in small amounts. Propionic acid was first described in 1844 by Gottlieb who found it among the degradation products of sugar. Propionic acid can also obtained from natural gas by the Fischer-Tropsch process, as a byproduct in the pyrolysis of wood, and by the action of microorganisms on a variety of materials in small yields (Merck, 2006).

# <u>Evaluation Question #5:</u> Is there an organic agricultural product that could be substituted for the petitioned substance? (From 7 CFR § 205.600 (b) (1).)

Organic acids are known in the feed industry as an effective and affordable tool to control mold growth. According to the published scientific data, a variety of organic acids (such as acetic acid, lactic acid, propionic acid, or blends of acids) was used to help control mold contamination.

In 1991, Higgins and Brinkhaus conducted a study to determine the relative efficacy of eight organic acids (propionic, acetic, lactic, undecylenic, butyric, valeric, benzoic, and sorbic) against six molds (*Aspergillus spp., Geotrichum spp., Mucor spp., Fusarium spp., Penicillium spp., and Scopulariopsis spp.*) commonly found in animal feeds. The results showed that valeric acid, propionic acid, and butyric acid displayed the highest efficacy against all mold with the effective concentrations ranging from 0.05 to 0.25%. They concluded that due to its high efficacy and its relatively good palatability at lower inclusion rates, as well as its relatively low cost, propionic acid may reasonably be considered one of most economical organic acids for field application (Higgins et al., 1991). Similar results were obtained by Pelhate in a 1973 study. He examined the relative efficacy of propionic, sorbic, acetic, and formic acids and found propionic acid to be the most effective of these four organic acids (Pelhate, 1973).

 However, there is no information available to suggest that an organic agricultural commodity or product could be substituted for the petitioned substance, propionic acid. The petition mentioned that acetic acid or butyric acid is an alternative, which can be used in place of propionic acid, but both acids have a distinctive pungent odor. For example, butyric acid has a rotten butter odor at ppm levels in air.

# <u>Evaluation Question #6:</u> Are there adverse effects on the environment from the petitioned substance's manufacture, use, or disposal? (From 7 CFR § 205.600 (b) (2).)

In the environment, propionic acid acts as a carbon source for various microbes and is metabolized to carbon dioxide and water. Since propionic acid has little outdoor use and is metabolized (bio-degradation) into carbon dioxide and water, there is no adverse effect on the environment. The available ecotoxicity studies indicate that propionic acid is only slightly toxic to birds, fish, aquatic invertebrates and mammals. Since it has limited outdoor use and low toxicity, its hazard to nontarget organisms is expected to be minimal. EPA has waived all environmental fate and ecological effects data requirements (RED, 1991). Propionic acid is also identified on the EPA's List 4B as inert ingredients. For those ingredients listed on List 4B, EPA has sufficient data to reasonable conclude that the current use pattern in pesticide products will not adversely affect public health or the environment.

# Evaluation Question #7: Does the petitioned substance have an adverse effect on human health as defined by applicable Federal regulations? (From 7 CFR § 205.600 (b) (3).)

Propionic acid is rapidly absorbed from the mammalian gastrointestinal tract and utilized by most organs and tissues. It is a normal metabolite in the human body. It can be further metabolized to glucose,

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carbohydrates, amino acids, and lipids; and eventually eliminated from the body as carbon dioxide in the Krebs cycle<sup>2</sup>. Therefore, it is not bioaccumulable. People also consume naturally occurring propionic acid in common foods, such as butter and cheese, and as an added ingredient in other foods. Technical propionic acid is of moderate to low acute toxicity via the oral, dermal, and inhalation routes of exposure (toxicity category III), and is not a skin sensitizer. However, propionic acid is highly irritating to the eyes and skin (toxicity category I).

In February 2002, EPA's Health Effects Division (HED) concluded that based on its low toxicity, limited use pattern, and affirmation as a GRAS chemical when used as a food additive, propionic acid is not expected to result in any adverse health effects via the food, drinking water, or residential exposure pathways. There is a possibility of eye and skin irritation to occupational handlers; the use of personal protective equipment is required. A review of the toxicology database, with an emphasis on sensitivity to infants and children, shows no significant findings since the date of the original propionic acid Reregistration Eligibility Document (RED) from 1991.

# Evaluation Question #8: Is the nutritional quality of the food maintained when the petitioned substance is used? (From 7 CFR § 205.600 (b) (3).)

There is no information available to demonstrate that either there is an impact on the nutritional value of the food treated with propionic acid and of the products derived from livestock fed the feeds treated by propionic acid, or adding propionic acid on grain/other feeds could affect feed digestibility in ruminants. In addition, through communication with Dr. Limin Kung of University of Delaware, who is an expert in this area, he does not believe propionic acid treated silages would impact digestibility of cows.

### **Evaluation Question #9:** Is the petitioned substance to be used primarily as a preservative? (From 7 CFR § 205.600 (b) (4).)

As described by the petition, propionic acid is used primarily for animal feed preservation as a mold inhibitor.

According to published scientific literature, propionic acid is used primarily for animal feed preservation (including hay, silage, and grains) and in human foods (mainly in baked goods and cheeses). Propionic acid can also be used as an intermediate in the synthesis of herbicides, cellulose acetate–propionate plastics and pharmaceuticals.

<u>Evaluation Question #10:</u> Is the petitioned substance to be used primarily to recreate or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law, e.g., vitamin D in milk)? (From 7 CFR § 205.600 (b) (4).)

As stated in Evaluation Question #9, propionic acid is used primarily for animal feed preservation as a mold inhibitor. There is no information available to suggest that propionic acid is used primarily to recreate or improve colors, textures, or nutritive values lost in processing. Propionic acid can also be used as a flavoring agent.

# <u>Evaluation Question #11:</u> Is the petitioned substance generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices? (From 7 CFR § 205.600 (b) (5).)

Propionic acid is generally recognized as safe (GRAS), in 21 CFR §582.3081 and §184.1081, by FDA. It is used as a chemical preservative (21 CFR §582.3081) in animal feeds and related products with good manufacturing or feeding practice. Propionic acid is also used as an antimicrobial agent and a flavoring agent (21 CFR §184.1081) infood for human consumption with no limitation other than current good manufacturing practice.

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<sup>&</sup>lt;sup>2</sup> Krebs cycle is a series of chemical reactions of central importance in all living cells.

### <u>Evaluation Question #12:</u> Does the petitioned substance contain residues of heavy metals or other contaminants in excess of FDA tolerances? (From 7 CFR § 205.600 (b) (5).)47

Commercially, the chemical process for manufacturing propionic acid starts with ethylene (petroleum based) and synthetic gas (a mixture of carbon monoxide and hydrogen, produced by partial oxidation of natural gas or oil with air under controlled conditions) with a catalyst (rhodium or cobalt). The distilled propionaldehyde is then treated with air or pure oxygen in a carefully controlled reactor to partially oxidize it to propionic acid. The resulting product is then distilled. The manufacturing process employed in the production of propionic acid, does not include any specific purification steps. Impurities occurring in propionic acid are comprised of unreacted staring materials (e.g., ethylene) as well as reaction byproducts (e.g., propionaldehyde). Heavy metals may not occur in the final product due to the distillation process. In addition, there is no other published information to suggest that heavy metals or contaminants may be present in the petitioned substance.

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