

United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet

<https://www.ams.usda.gov/rules-regulations/organic/national-list/petitioned>

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.

Aspirin

Livestock

Identification of Petitioned Substance

Chemical Names:	Endosprin
Acetylsalicylic acid	Magnecyl
<i>o</i> -acetylsalicylic acid	Micristin
2-(Acetyloxy)benzoic acid	Poloirin
	Polopiryna
Other Name:	Solprin
Aspirin	Soluspan
Rhodine	Zorprin
Trade Names:	CAS Numbers:
Acetysal	50-78-2
Easprin	
Aloxiprimum	Other Codes:
Colfarit	ELINCS number: 200-064-1
Dispril	FDA UNII Code: R16CO5Y76E
Ecotrin	

Summary of Petitioned Use

Aspirin is listed at 7 Code of Federal Regulations (CFR) 205.603 as a synthetic substance allowed for use in organic livestock production and is approved for health care use to reduce inflammation.

Characterization of Petitioned Substance

Composition of the Substance:

Aspirin or acetylsalicylic acid (C₉H₈O₄, CAS No. 50-78-2) is a synthetic, aromatic organic compound, with the following structural formula:

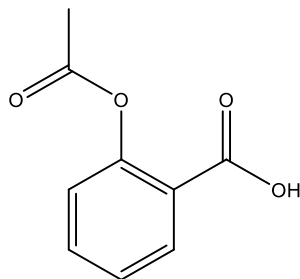
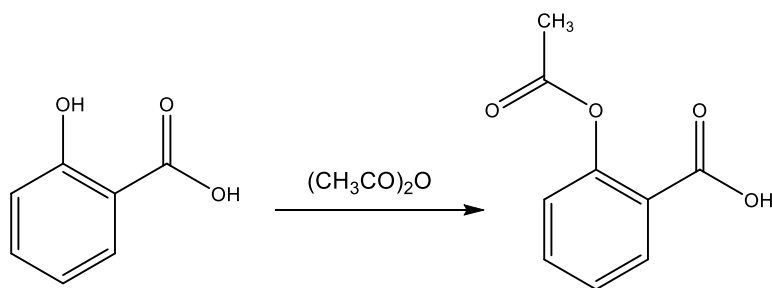


Figure 1. The structural formula of aspirin
(Budavari 1989)

Aspirin is described by the National Institute for Occupational Safety and Health as odorless and occurs as a colorless to white, crystalline powder with a slight bitter taste. Upon exposure to moisture, aspirin develops the vinegar-like odor of acetic acid (NIOSH 2016).

Source or Origin of the Substance:

Aspirin is a synthetic compound that is produced from the reaction of ortho-(hydroxy)benzoic acid with acetic anhydride (Held 2005):



29

Figure 2. Synthetic route for aspirin

30

Properties of the Substance:

Physical and chemical properties of the substance are summarized in Table 1.

33

Table 1: Physical and Chemical Properties of Aspirin (Lide 2003)

Property	Value
Chemical formula	$\text{C}_9\text{H}_8\text{O}_4$
Molar mass	180.16 g/mol
Appearance	colorless to white, crystalline powder
Solubility, water	1 g in 300 mL
Melting point	135 °C
pK _a	3.49 (25 °C)

35

Aspirin is stable in dry air. Upon exposure to moisture, the compound is gradually hydrolyzed into salicylic and acetic acids (Budavari 1989).

38

Specific Uses of the Substance:

Aspirin (i.e., acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) used for temporary relief of minor aches and pains due to headache, muscular aches, minor arthritis pain, toothache, backache, the common cold, and premenstrual and menstrual cramps. It is also used for temporarily reducing fever, the prevention of cardiovascular events, and the treatment of rheumatologic disorders.

44

Approved Legal Uses of the Substance:

Aspirin is considered a pain reliever and fever reducer in the over-the-counter, tentative final monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use by the U.S. Food and Drug Administration (FDA) (53 Federal Register 46204, Nov. 16, 1988 and 21 CFR 343). Aspirin is included under 21 CFR 343.12 and 343.13 for the prevention of cardiovascular events and the treatment of rheumatologic disorders.

51

Aspirin is also listed at 7 CFR 205.603 as a synthetic substance allowed for the use in organic livestock production and is approved for health care use to reduce inflammation.

54

Action of the Substance:

Aspirin inhibits the biosynthesis of certain hormonelike substances called prostaglandins, which accounts for most of its clinical effect. Depending on where in the body these prostaglandins are produced, they may trigger pain, inflammation, fever, or blood clotting. Following absorption, aspirin is hydrolyzed to salicylic acid, which is the active metabolite for its major clinical effects. Aspirin also inhibits platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase (Desborough 2017).

61

Combinations of the Substance:

Additional excipients, or inactive ingredients, such as carnauba wax, corn starch, hypromellose, powdered cellulose, and triacetin are generally added to commercially available forms of the petitioned substance. Any excipients used in the manufacture of drugs used to treat organic livestock must comply with the requirements of 7 CFR 205.603(f), which requires the excipient to be identified by the FDA as Generally

66

67 Recognized As Safe; approved by the FDA as a food additive; or included in the FDA review and approval
68 of a New Animal Drug Application or New Drug Application.
69

70 Status

71 Historic Use:

72 Aspirin is used in livestock production to mitigate pain and inflammation associated with injury or
73 procedures such as castration, dehorning, and branding.
74

75 Organic Foods Production Act, USDA Final Rule:

76 Aspirin is listed at 7 CFR 205.603 as a synthetic substance allowed for the use in organic livestock
77 production and is approved for health care use to reduce inflammation.
78

79 International

80 The Canadian General Standards Board includes aspirin as a permitted substance for organic production
81 systems under CAN/CGSB-32.311-2015 for pain mitigation and inflammation reduction in livestock
82

83 Aspirin was not found to be listed under any other international standard for organic livestock production.
84
85

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

87
88 **Evaluation Question #1: Indicate which category in OFPA that the substance falls under: (A) Does the**
89 **substance contain an active ingredient in any of the following categories: copper and sulfur**
90 **compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated**
91 **seed, vitamins and minerals; livestock parasiticides and medicines and production aids including**
92 **netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is**
93 **the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological**
94 **concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii)? Is the synthetic substance an inert**
95 **ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part**
96 **180?**
97

98 The petitioned substance is an active ingredient falling under the category of livestock parasiticides and
99 medicines and production aids. Aspirin is a not classified as a synthetic inert ingredient, nor is the
100 substance exempt from a requirement of a tolerance per 40 CFR 180.
101

102 **Evaluation Question #2: Describe the most prevalent processes used to manufacture or formulate the**
103 **petitioned substance. Further, describe any chemical change that may occur during manufacture or**
104 **formulation of the petitioned substance when this substance is extracted from naturally occurring plant,**
105 **animal, or mineral sources (7 U.S.C. § 6502 (21)).**
106

107 The most prevalent method of synthesizing aspirin is via an esterification. Salicylic acid is treated with
108 acetic anhydride, an acid derivative, causing a quantitative chemical reaction that turns salicylic acid's
109 hydroxyl group into an ester group ($R-OH \rightarrow R-OCOCH_3$; Figure 2). This process yields aspirin and acetic
110 acid, which are considered byproducts of this reaction. Small amounts of sulfuric acid (and occasionally
111 phosphoric acid) are almost always used as a catalyst (Held 2005).
112

113 The chemical feedstocks for synthesizing aspirin are also manufactured through a chemical process.
114 Salicylic acid is produced commercially via the Kolbe-Schmitt process. Here, phenol and sodium hydroxide
115 react to make sodium phenoxide. The phenoxide comes into contact with CO_2 to form sodium salicylate.
116 The salicylate is acidified to give salicylic acid. The acid is usually crystallized from aqueous solution to
117 give a technical grade 99.5% salicylic acid product. For a pharmaceutical grade product, salicylic acid is
118 further purified by sublimation.
119

120 The commercial process for acetic anhydride was developed by Wacker Chemie in 1922 and uses a
121 chemical reaction between acetic acid and ethenone at a low temperature and pressure (Held 2005).

122
123 **Evaluation Question #3: Discuss whether the petitioned substance is formulated or manufactured by a**
124 **chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).**
125

126 Aspirin is a synthetic material solely manufactured by a chemical process, not extracted from naturally
127 occurring plant, animal, or mineral sources. Aspirin is produced through the esterification of salicylic acid
128 using acetic anhydride (Held 2005).

129
130 **Evaluation Question #4: Describe the persistence or concentration of the petitioned substance and/or its**
131 **by-products in the environment (7 U.S.C. § 6518 (m) (2)).**
132

133 While no Findings of No Significant Impact (FONSI) provided by the U. S. Food and Drug Administration
134 (FDA) were found, the FDA has released a FONSI for proprietary formulations of aspirin (i.e., Provacol®
135 and Bufferin®) in 2003 (NDA 21-387). Aspirin and its major active metabolite, salicylic acid, are expected to
136 biodegrade and/or hydrolyze rapidly in the environment. In addition, less than 1% of an oral dose is
137 excreted unchanged aspirin. Salicylic acid constitutes 10% of the excreted metabolites with the remainder
138 comprised of salicyluric acid (75%) and the ether/ester glucuronide conjugates, which are biologically
139 inactive. In addition, salicylic acid is a naturally-occurring substance in the environment. It is found in
140 microorganisms, common fruits (e.g., apples, oranges, grapes, etc.), and plants (Malakar 2017). Sewage
141 treatment has also been reported to remove 81% of aspirin and 90% of salicylic acid from waste streams.

142
143 The reported occurrence of the aspirin metabolite in water environments is 6.7 nanogram/liter (ng/L) in
144 surface water (Vulliet 2011). Estimates suggest that human exposure to metabolites of aspirin (i.e., salicylic
145 acid) is approximately 1.5 milligrams (mg) over an estimated lifetime of 70 years (l_{70}) and an estimated
146 water consumption of 2 liters/day (Vulliet 2011). This corresponds to approximately 0.05 % of a typical
147 recommended daily dose when used as needed or prescribed.

148
149 **Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its**
150 **breakdown products and any contaminants. Describe the persistence and areas of concentration in the**
151 **environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).**
152

153 There is a significant knowledge gap existing in the literature regarding pharmaceuticals including the
154 identity of metabolites, excretion fraction, eco-toxicity, and environmental fate properties (Han 2017).
155 However, pharmaceuticals do not appear to pose as great a risk to aquatic wildlife or humans as do many
156 metals and triclosan (Donnachie 2016). There are concerns about the nature and relevance of ecotoxicity
157 effects. However, only a very small proportion of pharmaceuticals has been studied sufficiently (and to a
158 reliable standard) to make even preliminary judgments on whether they pose a risk (Donnachie 2016).
159 Preliminary studies have shown that aspirin and/or its corresponding metabolite (i.e., salicylic acid) can be
160 chronically toxic to certain aquatic invertebrates (Henschel 1997, Crane 2006). The mode of action and the
161 source of metabolite toxicity are unknown.

162
163 **Evaluation Question #6: Describe any environmental contamination that could result from the**
164 **petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).**
165

166 There is no significant risk of environmental contamination that could result from manufacture, use,
167 misuse, or disposal of aspirin. Manufactures are not required by the emergency release notification
168 provisions of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA; 40
169 CFR 355.40) to notify the National Response Center of an accidental release of aspirin; there is no
170 reportable quantity for this substance. Aspirin (i.e., acetylsalicylic acid) is not listed as a hazardous waste
171 under the Resource Conservation and Recovery Act (RCRA; 40 USC 6901).

173 **Evaluation Question #7: Describe any known chemical interactions between the petitioned substance**
174 **and other substances used in organic crop or livestock production or handling. Describe any**
175 **environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).**
176

177 To the best of our knowledge, there are no known reports that suggest any specific chemical interactions
178 between aspirin and other substances used in organic crop or livestock production or handling.
179

180 **Evaluation Question #8: Describe any effects of the petitioned substance on biological or chemical**
181 **interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt**
182 **index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).**
183

184 To the best of our knowledge, there are no reported effects of aspirin or resulting metabolites on biological
185 or chemical interactions in the agro-ecosystem.
186

187 **Evaluation Question #9: Discuss and summarize findings on whether the use of the petitioned**
188 **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)**
189 **(i)).**
190

191 Due to the rapid biodegradation/hydrolysis of aspirin and its active metabolite, salicylic acid, and the
192 effectiveness of sewage treatment, there are no known reports of aspirin causing appreciable harm to
193 surface or groundwater, soil, or agro-ecosystems. The background levels present in drinking water would
194 result in the average exposure of approximately 0.05% of a typical daily dose over an average 70-year
195 lifetime in humans. There is some evidence that acetylsalicylic acid (and/or active metabolites) can be toxic
196 to aquatic invertebrates; however, current research into the impact of aspirin and pharmaceuticals in
197 wastewater and aquatic ecosystems is not sufficient for definite conclusions.
198

199 **Evaluation Question #10: Describe and summarize any reported effects upon human health from use of**
200 **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**
201 **(m) (4)).**
202

203 Aspirin has been used for over 100 years for the treatment of minor aches and pains and fever reduction.
204 Aspirin continues to hold prominent position in the treatment of cardiovascular disease and
205 rheumatological disorders. Recent evidence has shown aspirin and other NSAIDs have been demonstrated
206 as key mediators and treatment for gastrointestinal cancers (e.g., colorectal and esophageal cancers).
207 However, there are well-recognized side effects that represent a major drawback in their routine usage,
208 which are summarized below (Thiagarajan 2012).

209 Upper gastrointestinal hemorrhage

210 Gastrointestinal (GI) bleeding is perhaps the most common complication of long-term aspirin use. This is
211 thought to occur via inhibition of the COX-1 enzyme, thereby reducing synthesis of prostaglandins, which
212 protect the gastric mucosa from acid-induced damage. A recent study demonstrated an increased risk of
213 major GI hemorrhage in subjects using low-dose aspirin alone (75–325 mg/day) compared with placebo
214 (Lanas 2011). The risk of GI hemorrhage increases with age in the general population (Jankowski 2011).

215 Intracranial hemorrhage

216 Hemorrhagic stroke is another potential consequence of long-term NSAID use, with studies reporting an
217 increased incidence in populations taking aspirin for prevention of occlusive vascular events (He 1998).
218 There is also evidence that preceding regular aspirin use increases overall mortality from intracranial
219 hemorrhage due to rapid hematoma enlargement (Saloheimo 2006).

220 Macular degeneration

221 There have been reports of an association between regular aspirin use and development of age-related
222 macular degeneration (AMD). A recent European study of approximately 4700 patients showed a dose-

223 dependent increase in the development and severity of AMD among patients regularly taking aspirin (de
224 Jong 2012).

225 Aspirin-exacerbated asthma

226 Aspirin is known to trigger bronchospasms in patients with asthma. Aspirin-exacerbated asthma (AEA) is
227 well-recognized in asthmatic populations has been reported to be as high as 21% (Jenkins 2004). Aspirin is
228 thought to induce bronchospasm through COX-1 inhibition, and its asthmatic effects may be severely
229 debilitating.

230 Age-related side effects

231 As a group, NSAIDs have significantly decreased as a viable treatment for elderly patients due to their
232 potential to cause acute renal failure and interstitial nephritis. One recent study of elderly inpatients
233 reported a significant deterioration in renal function after 2 weeks of low-dose (100 mg/day) aspirin
234 therapy (Segal 2006). Renal function improved after aspirin withdrawal, suggesting a causative effect. The
235 risk of other aspirin-related side effects, such as GI hemorrhage, also increases with advancing age.

236 Drug interactions

237 Aspirin is known to interact with other drugs (Thiagarajan 2012). For example, acetazolamide and
238 ammonium chloride are known to enhance the intoxicating effect of salicylates, and alcohol also increases
239 the gastrointestinal bleeding associated with these types of drugs. Aspirin is known to displace a number
240 of drugs from protein-binding sites in the blood, including antidiabetic drugs and other NSAIDs.
241 Corticosteroids may also reduce the concentration of aspirin in the body. Ibuprofen can negate the
242 antiplatelet effect of aspirin used for cardioprotection and stroke prevention. Aspirin may also inhibit the
243 absorption of vitamin C.

244 Occupational Environments

245 Aspirin (i.e., acetylsalicylic acid) is an allergen and irritant of the eyes, mucous membranes, upper
246 respiratory tract, and skin. Individuals who are intolerant of aspirin can develop hives, rhinorrhea, and
247 bronchospasms upon exposure (USDHHS 1992). The Occupational Safety and Health Administration
248 (OSHA) has established a permissible exposure limit (PEL) for acetylsalicylic acid of 5 mg/m³ of air as an
249 8-hour, time-weighted average (TWA) concentration (29 CFR 1910.1000).

250
251
252 **Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be
253 used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed
254 substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).**

255
256 Extract from the willow tree contains salicin, which produces salicylic acid, the active metabolite from
257 aspirin metabolism, and can be used to ease pain or inflammation (Stone 1763). Salicylic acid can be
258 isolated from the herb meadowsweet (*Filipendula ulmaria*) (Lowig 1839). However, the extract from this
259 herb can cause digestive problems such as gastric irritation, bleeding, diarrhea, and mortality when
260 consumed in high doses.

261
262 There are two other synthetic substances listed under 7 CFR 205.603 for pain management or reducing
263 inflammation in livestock from injury or procedures used in organic livestock production, such as
264 castration, dehorning, and tail-docking. Flunixin is a NSAID, analgesic, and antipyretic used in horses,
265 cattle, and pigs. Its use is typically limited to alleviation of inflammation and pain associated with
266 musculoskeletal disorders. It is regulated by the US FDA (21 CFR 520.970 and 522.970) and can only be
267 administered by or on the order of a licensed veterinarian. Also, it is approved for only intravenous
268 administration in cattle. Flunixin use is limited to a period no longer than 5 days due to toxicity concerns.
269 For its use under 7 CFR 205, cattle must not be slaughtered for human consumption within 8 days of last
270 treatment. Milk that has been taken during treatment and for 72 hours after the last treatment must not be
271 used for food. Flunixin cannot be used in dry dairy cows or calves to be processed for veal. Pigs treated
272 with flunixin cannot be slaughtered for human consumption within 24 days of the last treatment.

273 Butorphanol (21 CFR 522.246) is a synthetic opioid partial agonist analgesic. However, it is restricted by
274 federal law and its use under 7 CFR 205 requires it to be used by or lawful written order of a licensed
275 veterinarian and a meat withdrawal period of at least 42 days after administering to livestock intended for
276 slaughter; and a milk discard period of at least 8 days after administering to dairy animals.

277
278 **Evaluation Question #12: Describe any alternative practices that would make the use of the petitioned**
279 **substance unnecessary (7 U.S.C. § 6518 (m) (6)).**
280

281 Alternative practices that would make the approved substance unnecessary would be to cease the practice
282 of permitted procedures such as castration, dehorning, and tail-docking. Cessation of these practices would
283 not remove the necessity of an anesthetic for the treatment of injury or lameness. There are no other
284 anesthetics for treating pain and inflammation approved for use in organic livestock production; however,
285 there are alternative drugs. There are other NSAIDs (e.g., Loxicorn) or steroids (e.g., Colvasone), but it
286 should be noted that steroids are accompanied by more potential side effects (Norbrook 2017).
287

Report Authorship

289
290 The following individuals were involved in research, data collection, writing, editing, and/or final
291 approval of this report:
292

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297 All individuals are in compliance with Federal Acquisition Regulations (FAR) Subpart 3.11 – Preventing
298 Personal Conflicts of Interest for Contractor Employees Performing Acquisition Functions.
299

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