ORIGINAL SUBMISSION

INTERNATIONAL Food Additives Council

EFFCA
European Food & Feed Cultures Association

GRN 000668

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OFFICE OF
FOOD ADDITIVE SAFETY

GRAS DOSSIER

Sodium Formate Use in the Industrial Production of Microbial Food Cultures

July 25, 2016

July 25, 2016

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Re: GRAS Notice-Exemption claim for the use of sodium formate in the industrial production of microbial food cultures

Dear Office of Food Additive Safety:

In accordance with the US Food and Drug Administration's (FDA) proposed rule of April 17, 1997 (62 FR 18938) relating to the filing of notices for substances that are considered to be generally recognized as safe (GRAS), please accept this claim and the attached information, submitted in triplicate, for that purpose as it relates to the use of sodium formate to compensate for the formate lost in the industrial production of microbial food cultures. Specifically, we claim that the use of sodium formate during the fermentation process of specific microbial food cultures is exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act based on its determination that such uses are GRAS. In conformity with the requirements outlined in the proposed rule, the following information is included with this exemption claim:

(i) Name and Address of the Notifier:

International Food Additives Council (IFAC)
750 National Press Building
529 14th Street NW
Washington, D. C. 20045

(ii) Common or Usual Name of Notified Substance:

Sodium Formate

(iii) Applicable Conditions of Use:

Sodium formate is manufactured in in compliance with current Good Manufacturing Practice as specified in 21 CFR Part 110. Sodium formate is the sodium salt of formic acid. It is a white crystalline powder which does not have flammable or explosive properties. It is also completely soluble in water. The proposed use of sodium formate is to support the symbiotic growth of streptococcus, lactobacillus and leuconostoc species in fermented dairy and soy

products, where the level initially added does not exceed 20 ppm, and the final concentration after fermentation is not increased over the naturally-occurring formate concentration in the fermented product when formate is not added.

(iv) Basis for the GRAS Determination:

Scientific procedures, supported by a history of use.

(v) Availability to FDA of Data and Information that are the Basis of Determination:

The data and information forming the basis for this GRAS determination and the exemption claim asserted herein are available for FDA review and copying during reasonable business hours at the following address, or will be sent to FDA upon request:

Robert Rankin, Executive Director
International Food Additives Council (IFAC)
750 National Press Building
529 14th Street NW
Washington, D. C. 20045
Phone: (202)207-1127
rrankin@kellencompany.com

Consequently, on the basis of the above specified information, and the additional requested information as specified in the proposed rule and as attached hereto and submitted with this letter, please accept this GRAS notification and claim of exemption from the statutory premarket approval requirements for the use of sodium formate in the industrial production of microbial food cultures.

Should you have any questions regarding the submission of this notice, please contact IFAC. Thank you for your prompt consideration of, and response to, this notice.

Sincerely,

(b) (6)

Robert Rankin
Executive Director
International Food Additives Council

(b) (6)

Maria-Teresa Scardigli
Secretariat
European Food and Feed Cultures Association

Attachment

1 Introduction

Sodium formate is the sodium salt of formic acid. It is a white crystalline powder which does not have flammable or explosive properties. It is also completely soluble in water.

The proposed use of sodium formate is to support the symbiotic growth of streptococcus, lactobacillus and leuconostoc species in fermented dairy and soy products, where the level initially added does not exceed 20 ppm, and the final concentration after fermentation is not increased over the naturally-occurring formate concentration in the fermented product when formate is not added.

The Microbial Food Culture (MFC) industry produces a variety of dairy cultures which are used by food producers for the manufacture of specific cheese and fermented milk products (yogurt, sour cream, cream cheese, etc.). In most cases, two or more species of MFCs are used for the fermentation. Some of these MFCs utilize symbiotic growth and benefit from a mutual exchange of metabolites. One metabolite, formate is produced by both *Streptococcus thermophilus* and *Lactococcus lactis* species, which then is used as an essential nutrient in the fermentation of other species as well as the species themselves. During the harvesting and concentration of industrially produced MFC through centrifugation or ultrafiltration, the formate which is naturally formed during the growth of the MFCs, is washed out in the supernatant liquid.

Formate also occurs naturally in milk; however, the concentration varies depending on geography, season and feed for the cows as well as the heat treatment used on the milk. A low level of formate results in a delayed and uneven growth of the cultures, slow development of lactic acid and inconsistent quality. Some industrial MFCs are therefore standardized with formate to achieve optimal growth conditions in the start-up of the fermentation process of the food product, where formate is essential. When the MFCs grow, *S. thermophilus* and *L. lactis* will produce formate, which then can be used, for example, by lactobacilli or cocci as a part of their metabolism. Standardization of formate in the MFCs results in a uniform quality in all cases independent of milk conditions, regardless of the amount of formate lost during concentration of MFCs.

Since food ingredients in the United States must either be approved food additives, or exempted GRAS substances, the industry has undertaken a determination of the safety of sodium formate for use in fermented dairy and soy products in which addition of sodium formate supports the growth of the MFCs in the finished food product. Application areas are currently envisioned to include cultured milk products, such as cultured milk, sour cream, yogurts; frozen fermented milk products, e.g. frozen yogurt; strained cultured milk products, e.g. quark, fresh cheese, greek yogurt; fermented soy milk and fermented soy milk products; and cheeses, e.g. asiago cheese, caciocavallo siciliano cheese, cheddar cheese, colby cheese, cottage cheese, gruyere cheese, monterey and monterey jack cheese, mozzarella and scamorza cheese, blue cheese, provolone cheese, romano cheese, and swiss cheese.

For the safety determination, we have established (1) general recognition by experts that use of this substance in processing of MFCs is safe; (2) the experts are qualified by scientific training and experience; and (3) the experts have based their safety judgment on scientific procedures 21 CFR 170.30.

2 Importance of Formate in the Production of Microbial Food Cultures

Formate production by *S. thermophilus* and *L. lactis* has been reported since late1960's (Galesloot et al., 1968) and its importance for improving mixed starter culture performance has been acknowledged since the 1970's as described in a thesis by Tamime 1977 reported in 2000 in Yogurt Science and Technology (Tamime and Robinson, 2000). The growth of *S. thermophilus* in milk is limited by the availability of peptides and free amino acids which are present in relatively low concentrations in milk (Higashio et al., 1978; Goff and Hill, 1993). Streptococcus and lactococcus bacteria produce formate, pyruvate and carbon dioxide all of which stimulate the growth of streptococcus, lactobacillus and lactococcus (Driessen et al., 1982; Chandan and O'Rell, 2006; Verdamuthu, 2006). Due to a formate-induced increase in proteolytic activities by the *Lactobacillus bulgaricus*, it in turn provides sufficient amino acids and peptides to stimulate growth of *S. thermophilus* and its own growth (Sieuwerts et al., 2010). This association is necessary for consistent manufacturing of fermented foods and can be briefly described as each organism providing compounds which benefits itself and the other organisms.

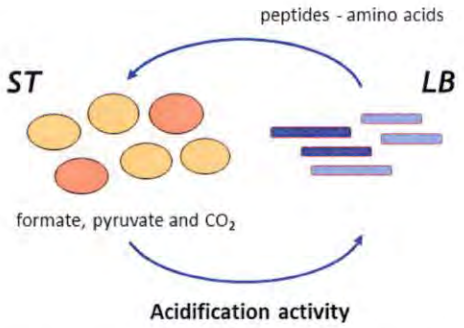


Figure 1: Favorable interactions of *S. thermophilus* and *L. bulgaricus*

This relationship is also referred to as proto-co-operation which means that they have mutually favorable interaction but are not dependent on this coexistence (Courtin and Rul, 2004). Each will grow as a mono-culture in milk but when present together, will grow and acidify the final food product faster (Tamime and Robinson, 2000).

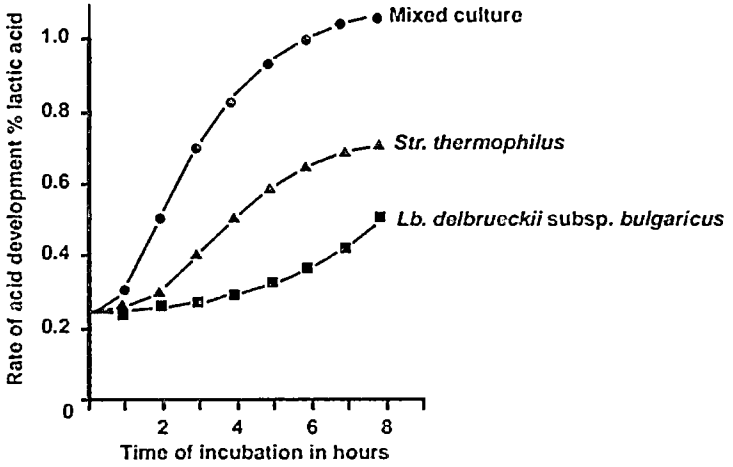


Figure 2: Mutually favorable interaction. Figure from page 417 in Tamime, 2000

Formate is produced by MFCs during fermentation when pyruvate is converted into acetyl-CoA and formate via the pathway catalyzed by the enzyme pyruvate formate lyase (PFL) (Derzelle et al., 2005). The activity of the PFL enzyme in *L. lactis* and *S. thermophilus* is regulated in the presence of oxygen; hence, it is active only under strict anaerobic conditions (Yamada et al., 1985; Arnau et al., 1997; Chandan, 2006). When the milk is inoculated with the starter cultures, the conditions are, in the beginning, aerobic - if no deaeration is performed - and the capability of the cultures to produce formate is inhibited by the oxygen resulting in delayed growth. Even a small amount of oxygen has a negative effect on the symbiotic growth between *Lactobacillus bulgaricus* and *S. thermophilus* (Galesloot et al., 1968; Driessen et al., 1982; Horiuchi and Sasaki, 2012). Stimulation of growth of *L.bulgaricus* and *S. thermophilus* in individually as well as in mixed fermentation was tested by adding different essential nutrients. Beneficial effects were measured as higher cell count, higher acidification rate, and the reduced time to reach the stationary phase. The strongest single stimulation effect seen in all cases was with 20 ppm formate add to the milk (Sieuwerts et al., 2010).

The natural formate present in milk varies in concentration due to multiple factors, such as geography, season and feed (silage inoculated with formic acid) (Goff and Hill, 1993; Suzuki et al., 1986). Heating the milk also affects the level of formate as the lactose is degraded to formate, (Kern et al., 1954) increasing the concentration up to at least 200 ppm depending on the heat treatment technology - from lower levels produced by pasteurization to highest levels produced by autoclaving (Suzuki et al., 1986). Pasteurization is generally the standard treatment.

Traditionally, MFCs known as bulk starter cultures in liquid form have been used to inoculate milk in the manufacture of fermented food products. The traditional bulk starter production is carried out in incremental steps. A fermenter is inoculated with a late-exponential-phase culture and added in a volume that is 5 to 10 percent of the total volume of milk in the fermenter. This inoculum is then built up in a series of stages, starting with the initial culture added to a flask, this ferment is in turn inoculated to a 5 liter flask, further this ferment goes to a small fermenter and finally the 200 to 1,000 liter

ferment is transferred to a 10,000 to 20,000 liter fermentation tank. At all stages, all metabolites (i.e. including formate) are transferred to the next step; thus, no formate is lost (Brock, 1974).

This is a time consuming process which takes several days and at each stage there is a risk of contamination. It is critical in this process to ensure that the culture is behaving normally at all stages.

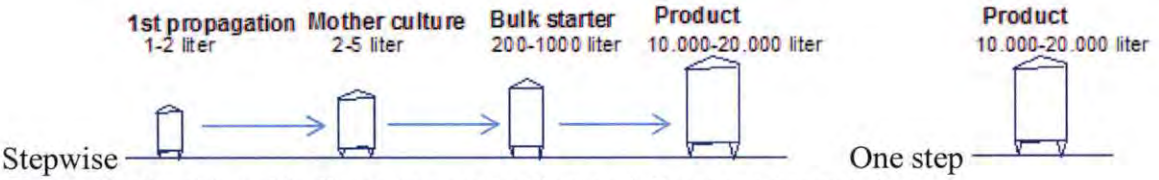


Figure 3: Traditional bulk starter production and direct vat inoculation

Technological developments in production have made it possible to produce highly concentrated commercial MFC's with a defined quantified mixture of strains that can be added in a single step, directly to the milk fermentation tank, eliminating the traditional step process of bulk starter culture production. This reduces the potential risk of under- or overproduction of bulk starter and reduces fermentation time, resulting in a more reproducible and consistent quality product and also decreases the risk of contamination.

During harvest and concentration of industrially produced MFC cells either by centrifugation or ultrafiltration, formate naturally formed during the growth of the cultures is washed out with the supernatant liquid. The loss of formate and subsequent reduction in the initial formate concentration in milk inoculated with MFC can slow down initial growth of the cultures, thereby delaying development of lactic acid. Since the natural concentration of formate in milk being used at the dairy, varies from a few ppm up to more than 200 ppm of formate in heated milk, standardization of formate is necessary to assure a consistently quick and even start of the fermentation. The formate to be added to the commercial starter culture corresponds to an additional level in the milk fermentation tank of 10-20 ppm sodium formate, corresponding to 6.6 to 13 ppm formate, disregarding the natural concentration in the milk, and is sufficient to guarantee optimal condition for the necessary mixtures of cultures resulting in better quality and more consistent process times for fermented food manufacturers.

Formate is continually produced and consumed by the cultures throughout the food fermentation process. Laboratory analysis show that addition of formate to the fermentation medium for MFCs does not significantly alter the content measured at the end of the fermentation, regardless of the type of milk used (Arioli et al., 2015).

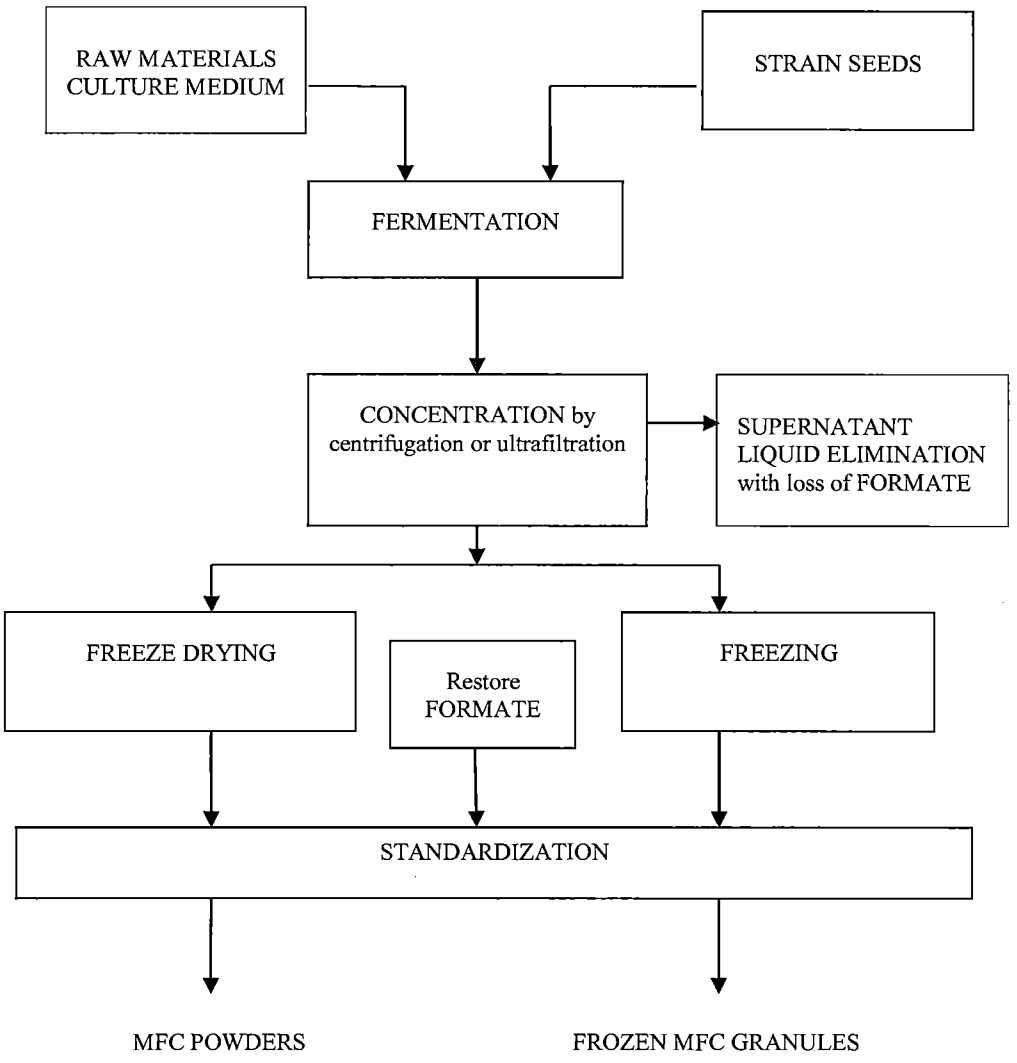


Figure 4: Example of Typical Manufacturing Process for Microbial Food Cultures

3 Description of Sodium formate

Identity Chemical Name: Sodium Formate
CAS Number: 141-53-7
Molecular Formula & Weight: $CHNaO_2$, 68.007 g/mol

Sodium formate is the sodium salt of formic acid. It is a white crystalline powder which does not have flammable or explosive properties. It is also completely soluble in water.

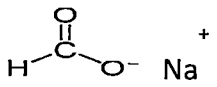
Chemistry

Formic acid (CAS no 64-18-6) (Codex: INS 236), the simplest carboxylic acid with just one carbon is a volatile, weak (pK_a 3.7), organic acid. Formic acid is dissociated into H^+ and $HCOO^-$ (formate) in aqueous liquid, such as the milk.

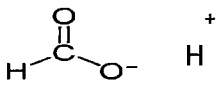
Sodium formate (CAS No 141-53-7) (Codex: INS 237), the salt of formic acid, dissociates into Na^+ and $HCOO^-$ in the milk used to make some fermented dairy products. Sodium formate is used to restore the naturally produced metabolite, formate, lost during industrial production, as sodium formate is much less hazardous and more user-friendly than formic acid. Sodium formate can be used as an intermediate in the production of formic acid.

Sodium formate, formic acid, and formate are used interchangeably in literature as the active constituent (formate) is the same in all three cases.

Sodium formate,
(Mw 68.007 g/mol)



Formic Acid,
(Mw 46.025 g/mol)



Formate
(Mw 45.017 g/mol)

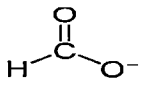


Figure 5: Chemical structure of sodium formate, formic acid, and formate

4 Manufacturing Process

4.1 Typical Starting Materials

Carbon monoxide (CO) and sodium hydroxide (NaOH) are used as starting materials in the production of sodium formate.

4.2 Typical Process for Sodium Formate

Sodium formate can be produced by the reaction of carbon monoxide with sodium hydroxide (FDA Code of Federal Regulation, 1976 (SCOGS) 186.1756).

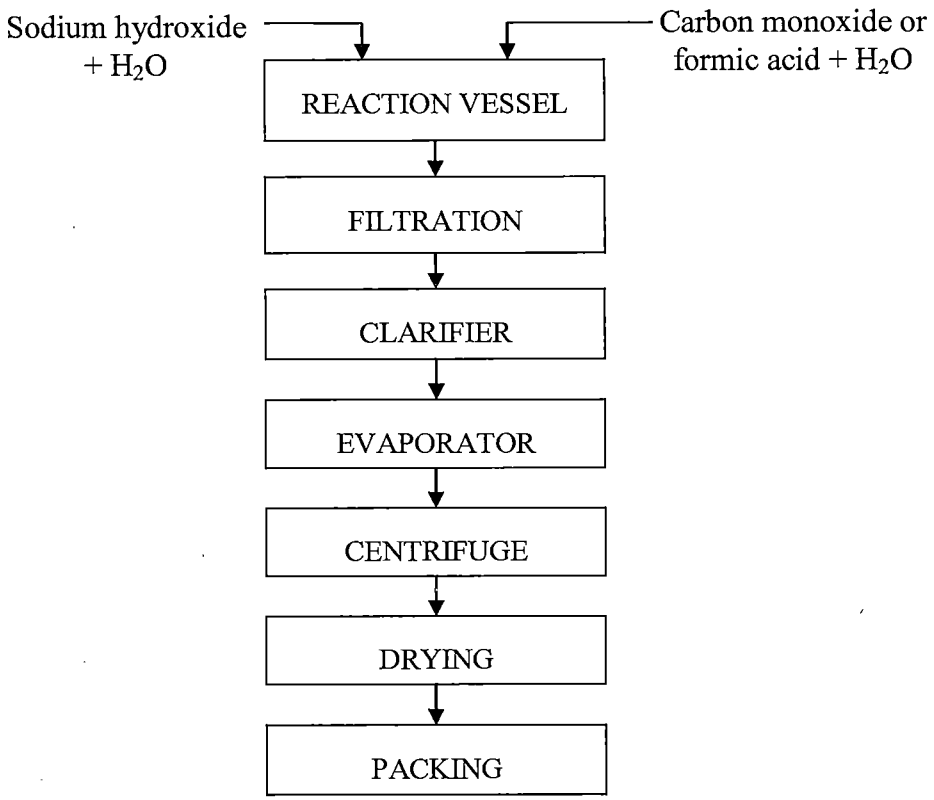


Figure 6: Example of Typical Manufacturing Process of Sodium Formate

5 Quality Control for Sodium Formate

Examples of possible Sodium Formate specification:

Test	Specification
ID	Passes
Description	White Crystal Powder
Arsenic	<3 ppm
Lead	<10 ppm
Copper & Zinc	<50 ppm
Zinc	<25 ppm
Loss on drying	<2.0%
Assay	>98.0%

This list of tests is not all-inclusive

Confidential Information – Do Not Copy or Duplicate

6 Common use in Food

6.1 Formic Acid

Formic acid is naturally occurring in many foods, such as milk, yogurts, cheeses, fruits, honey, wines and coffee (FDA Code of Federal Regulation, 1976 (SCOGS) 186.1316; Jelleff Carr, 1976). It is also *"a normal component of human blood and tissues; it is highly important within the metabolism for carrying C_1-bodies"* (Malorny, 1969). It is permitted for use as a component of synthetic flavoring substances and adjuvant permitted for direct addition to food for human consumption in the United States (FDA 21 CFR 172.515, 1976). It is also permitted as a constituent of paper and paperboard used for food packaging and included on a list of indirect food substances affirmed GRAS by the US FDA (FDA Code of Federal Regulation, 1976 (SCOGS) 186.1316). Formic acid has FEMA GRAS No. 2487 and is listed in the FCC (Food Chemicals Codex 9, 2015) for use as a flavoring agent and preservative. It is also approved for use as an additive in feed and drinking water consumed by animals in the US (FDA 21 CFR 573.480, 2011). JECFA set an ADI of 0-3 mg/kg for human consumption (JECFA 03, 2003) and the European Food Safety Authority (EFSA) Panel on Additives and Products or Substances Used in Animal Feed (FEEDAP) has deemed it safe for all animal species at the use level proposed for feed flavorings with no limitations (EFSA FEEDAP, 2013) and at a level of 12,000 ppm for swine and 10,000 ppm for all other species for preservation (EFSA FEEDAP, 2015). EFSA has evaluated formic acid as safe to use as flavouring in food with no restrictions of use (EFSA AFC, 2008).

6.2 Sodium Formate

Sodium formate has been used by the culture industry for at least 20 years under self GRAS assessment in the manufacturing of starter cultures. Further the US FDA (FDA Code of Federal Regulation, 1976 (SCOGS) 186.1756), affirmed sodium formate as GRAS as an indirect food substance as a component of paper and paperboard for food packaging. Sodium formate has been approved under the Australia/New Zealand (Australian New Zealand Food Standards Code 1.3.3, 2015) Food Standard code for use as a microbial culture nutrient/adjunct in the manufacture of any food since 2005. The European Food Safety Authority (EFSA) Panel on Additives and Products or Substances Used in Animal Feed (FEEDAP) has deemed it safe for all animal species at the use level proposed for food flavorings, with no restrictions for use (EFSA AFC, 2008) and, in agreement with allowances for formic acid, at a level of 12,000 ppm for swine and 10,000 ppm for all other species for preservation (European Commission, DG 1831/2003).

7 Intended Uses/Use Levels

The use of sodium formate is limited to the production of fermented dairy and soy products where addition of sodium formate supports the symbiotic growth of streptococcus, lactobacillus and leuconostoc MFCs. Depending on the species and physiological activity, the MFC with added sodium formate is added to the milk so that the level of formate is less than or equal to 20 ppm in the milk. Because of the anabolic and catabolic reactions which occur during the fermentation process, the total concentration of formate in the final product is not increased over that which can be measured in fermented products where formate is not added (Arioli et al., 2015).

8 Exposure

Variable concentrations of formic acid naturally found in milk, yogurt and cheese have been reported in the literature. In finished dairy products, formate production by *S. thermophilus* is an extremely variable feature that depends on strain, culture medium, and temperature (Perez et al., 1991), analytical methods, ripening time of cheese, and the packaging used for the finished food product.

The following Table 1 summarizes the results found in the literature for yogurt (concentrations ranged from 40 and 2100 ppm.)

Table 1: Concentrations of formic acid in commercial yogurts

Author	**Formic acid concentration**	**Formic acid concentration in ppm**
(Robinson, 2002)	40 µg/ml	40
(Marsili et al., 1981)	40 µg/g	40
(Rasic and Kurmann, 1978)	19.5 mg/100 ml	195
(Wei et al., 2001)	290 mg/L	290
(Izco et al., 2002)	30.9 mg/100g	390
(Fernandez-Garcia and McGregor, 1994)	717 µg/g	717
(Ligor et al., 2008)	70-210 mg/100g	700-2100

Formic acid concentrations reported in various cheeses are presented in Table 2. Organic acids like formic acid contribute to the flavor of most aged cheeses and the concentration of formic acid increases with age (ripening time). Formic acid concentrations of up to 2960 ppm have been reported in cheese (Zeppa et al., 2001).

Table 2: Concentrations of formic acid in commercial cheeses

Author	**Type of cheese**	**Formic acid conc.**	**Formic acid conc. in ppm**
(Buffa et al., 2004)	Goat cheese	3.6-12.6 mg/kg	4-13
(Marsili et al., 1981)	Cottage Cheese	<40 µg/ml	<40
(Izco et al., 2002)	Parmesan	9.6 mg/100 g	96
(Izco et al., 2002)	Farmers Cheese	12.0 mg/100 g	120
(Izco et al., 2002)	Blue Cheese	12.2 mg/100 g	122
(Bergamini et al., 2010)	Sheep cheese	25.7 ± 9.6 mg/100 g	161-353
(Andic et al., 2010)	Kashar Cheese	Up to 272.3 ± 27.1 mg/kg	245-299
(Mullin and Emmons, 1997)	Cheddar	0.28-0.50 mg/g	280-500
(Marsili et al., 1981)	Sharp Cheddar	420 ± 40 µg/ml	380-460
(Izco et al., 2002)	Cheddar	39.4 mg/100 g	394
(Marsili et al., 1981)	Blue Cheese	420 ± 20 µg/ml	400-440
(Califano and Bevilacqua, 2000)	Gouda	500-1000 mg/kg	500-1000
(Izco et al., 2002)	Roncal	57.3 mg/100 g	573
(Murtaza et al., 2011)	Cheddar cheese	700-1150 ppm	700-1150
(Shin et al., 2011)	Emmental	0.8 g/kg	800
(Akalin et al., 2002)	White Cheese	850-950 µg/ml	850-950
(Califano, 1999)	Mozarella	1000-1700 mg/kg	1000-1700
(Zeppa et al., 2001)	Ossolano	2.96 g/kg	2960

Laboratory analyses show that adding formate to the starter culture does not increase the final concentration measured at the end of the fermentation (Arioli et al., 2015). Enzymatic determination of formic acid concentration (Boehringer Mannheim/R-Biopharm Formic acid UV-method) at the end of acidification revealed a higher concentration of formate in the control samples (35 mg/L) compared to the samples in which sodium formate was added (26 mg/L). These results support the hypothesis that the exogenous formic acid added to milk is being quickly used by the cultures, limiting the accumulation of endogenous formate produced by *S. thermophilus* during growth in milk, as shown in Figure 7.

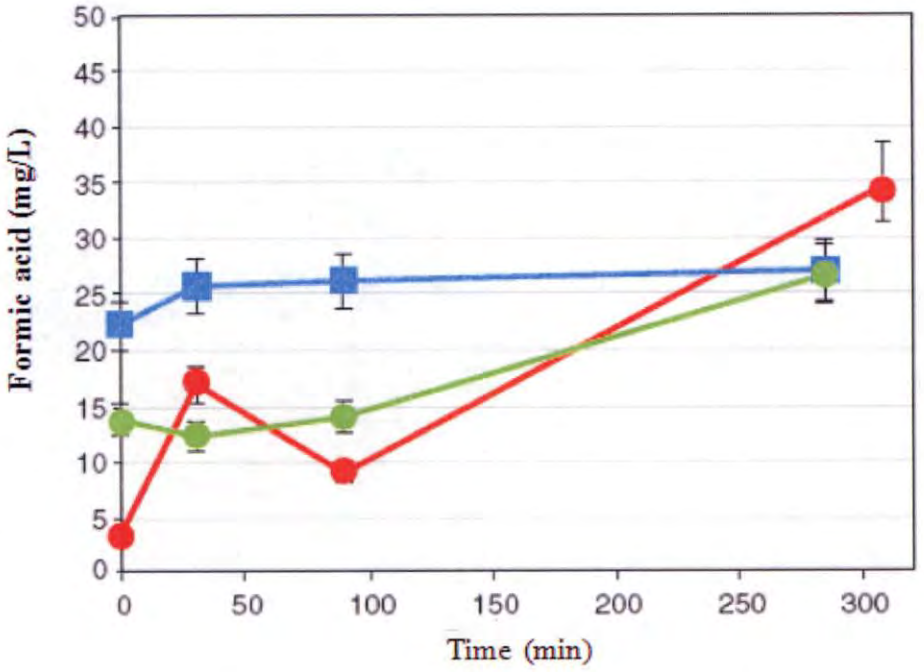


Figure 7. Quantity of formic acid during fermentation of the starter culture Y078 in high-quality fresh pasteurized milk. Control, 0 mg/L (●), addition of sodium formate at 10 mg/L (●) and 20 mg/L (■) (Arioli et al., 2015).

In another test, the impact of 10 mg/L sodium formate added to three different milk preparations on the acidification curves of *S. thermophilus* ST115 was tested (Figure 8), clearly showing reduced variability when sodium formate was added.

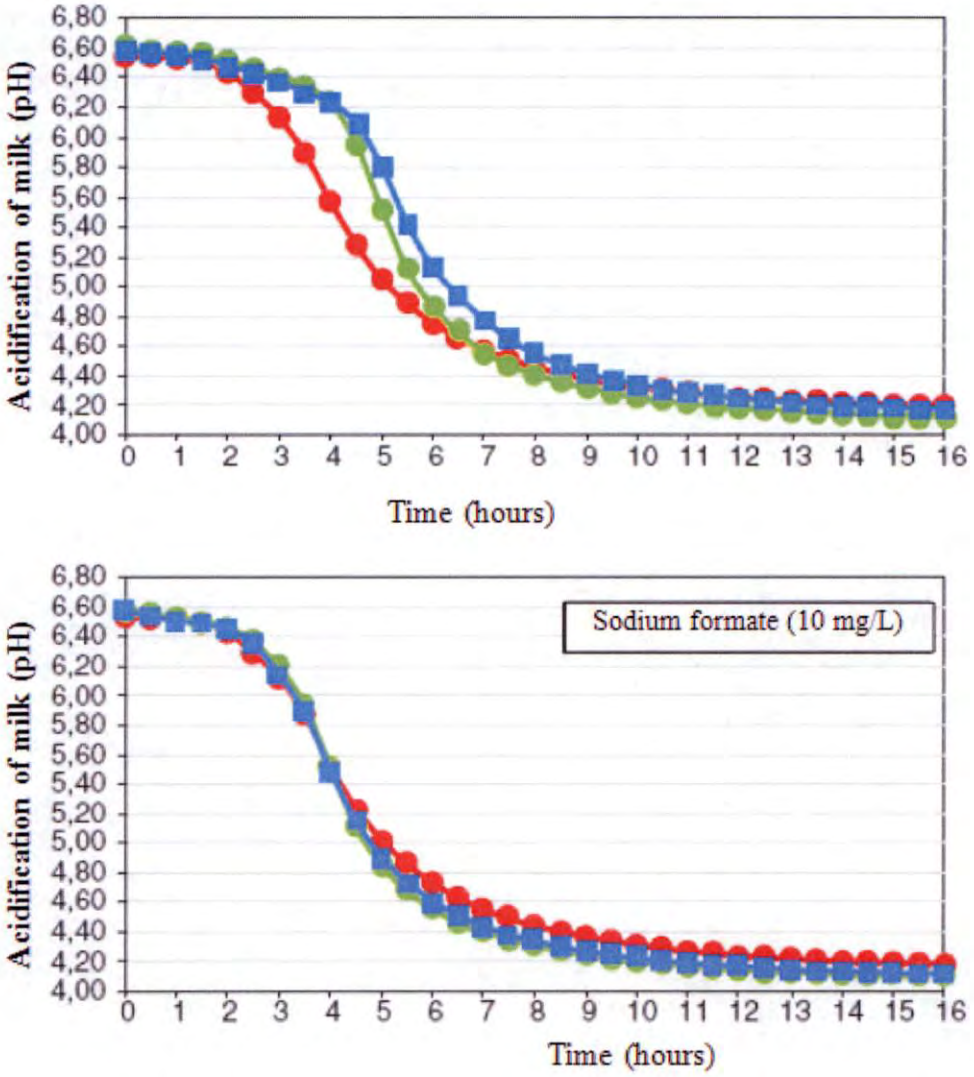


Figure 8. Acidification curves in reconstituted skim milk (●), pasteurised milk for dairy use (●) and high-quality fresh pasteurised milk (■) of starter culture *S. thermophilus* ST115, with no sodium formate added (top figure) and with 10 g/L sodium formate added (bottom figure). The experiment was conducted at 42°C (Arioli et al., 2015).

Since the final concentration of formate is not increased by the addition of up to 13.24 mg/kg of formate (20 mg/kg sodium formate) to the milk before fermentation (see Fig. 7), the total formate intake by consumers through yogurt or cheese consumption will not increase compared to a situation when formate is not added.

In a worst case scenario, it is assumed that all added formate ends up in the cheese, none is lost in the whey, nor is it metabolized. Using the daily per capita cheese consumption of 45g/day (Bentley, 2012), the additional intake of formate from cheese is 6.0 mg/day or 0.1 mg/kg bw (equal to 6.3 mg/day of formic acid):

- With annual cheese consumption estimated at 36 pounds, this calculates out to 16.33 kg/year or 0.045 kg cheese/day or 45 g cheese/day.
- It takes 10 kg of milk to make 1 kg of cheese. Formate is added to that milk at up to 13.24 mg/kg (20 mg/kg sodium formate), resulting in 132.4 mg/kg formate in 1 kg of cheese
- The potential additional daily intake of formate from cheese would be 6.0 mg based on a daily consumption of 45 g of cheese and a formate concentration in cheese of 132.4 mg/kg or 0.1 mg formate/kg bw or 0.105 mg formic acid/kg bw.

The additional intake of formate from yogurt assuming a worst case scenario here as well, where all the sodium formate used in the culture remains in the yogurt and the mean daily consumption of yogurt is 15 g, the additional daily intake would be 0.188 mg/day (equal to 0.198 mg/day of formic acid):

- The annual consumption of yogurt is 11.5 pounds or 5.215 kg/year.
- The daily consumption of yogurt 15 grams (0.0142 kg).
- The potential additional daily intake of formate from yogurt, would be 0.188 mg based on a daily consumption of yogurt of 15 g and a formate concentration in yogurt of 0.188mg/60 mg/kg or 0.0031 mg formate/kg bw or 0.0033 formic acid/kg bw.

The total amount of formic acid consumed per day from cheese and yogurt assuming a worst case scenario would 0.108 mg formic acid/kg/bw, significantly lower than the upper limit of the acceptable daily intake (ADI) level of 0 - 3 mg/kg/bw, when used as a food preservative or food flavor ingredient, established by The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1998).

9 Safety Testing

9.1 Animal studies

Acute toxicity studies

Oral

Formic Acid

Male and female WISW (SPF TNO) rats (ages not stated; 5/sex/dose) were administered 501, 631, 794, and 1,000 mg formic acid (undiluted) /kg body weight by gavage according to the OECD TG 401 protocol (OECD, 2011). The test substance was administered at a dose volume of 0.41 to 0.82 ml/kg. The animals were observed daily for 14 days post administration. The acute oral LD_{50} was reported to be 730 mg/kg bw (calculated to be 714 mg formate/ kg bw). The only effect reported was a dose-related decrease in body weight gain (EPA, 2014).

The acute toxicity of 1000-1200 mg/kg formic acid was tested in 55 mice (neither sex nor strain were reported) and LD_{50} determined to be 1100 mg/kg formic acid (1076 mg/kg when calculating for formate) (Malorny, 1969).

In an acute oral toxicity study of formic acid in rats (number and strain not stated), an LD_{50} of 1830 mg/kg body weight (1790 mg formate/kg bw) was reported. Study details were not included (Katz and Guest, 1994; EPA, 2014).

Sodium Formate

The acute oral toxicity of sodium formate was evaluated in a study involving 45 mice (ages, sex and strain not reported). An LD_{50} of 7410 mg formate/kg bw was reported. Additional study details were not included (EPA, 2014).

Table 3. Acute oral toxicity of formic acid and sodium formate in mice and rats

Substance	**Species**	**Sex**	**Route**	**LD_{50} (mg/kg bw) as formate**	**Reference**
Formic acid	White mouse	NR, 55 animals	Oral	1076 (calculated from 1100 mg formic acid/kg bw)	(Malorny, 1969)
Formic acid	Rat	5m, 5 f	Oral	714 (calculated from 730 mg formic acid/kg bw)	(EPA, 2014)
Formic acid	Rat			1790 (calculated from 1830 mg formic acid/kg bw)	(EPA, 2014)
Na-Formate	Mouse	NR, 45 animals	Oral	7410 (calculated from 11200 mg Na-formate/kg bw)	(EPA, 2014)

9.2 Repeated Dose Toxicity

Oral

Sodium Formate

Six Wistar rats (sex not stated) received sodium formate in drinking water at a concentration of 1% continuously for 1.5 years. The authors reported that the mean intake of sodium formate was 274 mg/animal or 185 mg formic acid/animal. A control (unspecified) group of animals was also included in the study. Toxicity was not reported in any of the animals tested. Additional details relating to this study were not available (Malorny 1969).

9.3 Human studies

It was noted by SCOGS in 1976 that *"Formic acid is a natural constituent of many foods", "is a metabolite in normal intermediary metabolism, and is a precursor in the biosynthesis of several body constituents. Formate is an intermediate in normal human metabolism and is normally present at low levels in the body. The tolerance of the body "to large amounts is relatively high"* and *"In men is reported 8 mg of formic acid/kg per day orally for a period of four weeks"* (FDA Code of Federal Regulation, 1976 (SCOGS) 186.1756; FDA Code of Federal Regulation, 1976 (SCOGS) 186.1316; Jelleff Carr, 1976).

10 Safety Assessment

Katz et al. 1994 report that formate is a normal constituent of intermediate metabolism and a precursor of many amino acids and purines. Thus formate may ultimately be incorporated into nucleic acids, proteins, lipids, and carbohydrates. Some formic acid is eliminated unchanged or as sodium formate. Low level systemic exposure is not likely to result in adverse effects (Katz et al, 1994). Gosselin et al., (Gosselin et al., 1976) referenced in the National Institutes of Health Toxicology Data Network, (TOXNET, 2003), the entry for formic acid and salts, lists for sodium formate: *"sodium formate appears to have a low toxicity (10 g by mouth without ill effects in man)"*(Gosselin et al., 1976). Sodium formate is dissoluted into Na+ and formate ($HCOO^-$) so it is appropriate also to discuss the safety of formic acid (OECD, 2011).

11 Regulatory Status of Sodium Formate

11.1 USA

Sodium Formate
The primary FDA clearance for sodium formate, as such, is 21 C.F.R. § 186.1756, which affirms the GRAS status of sodium formate for use in paper and paperboard food contact materials at levels not to exceed good manufacturing practice. Sodium formate is simply the sodium salt of formic acid, so clearances for formic acid are applicable to sodium formate as well (FDA Code of Federal Regulation, 1976 (SCOGS) 186.1756).

Formic Acid
Formic acid, used at GMP levels, is cleared under 21 C.F.R. § 172.515, the food additive regulation for flavoring substances and adjuvants (FDA 21CFR172.515; FDA 21CFR573.480).

The US FDA has also determined that it may be safely used as a food additive in feed at levels not to exceed 2.25% of silage on a dry weight basis, or 0.45% of direct cut silage consumed by animals, and at a level of 1.2% of complete feed for swine. (FDA 21CFR573.480).

11.2 Australia and New Zealand

Sodium formate is listed under Australian/New Zealand Food Standards Code, STANDARD 1.3.3, Processing Aids clause 18, Permitted microbial nutrients and microbial nutrient adjuncts (Australian New Zealand Food Standard Code 1.3.3, 2015). The processing aids listed in the Table 18 may be used as microbial nutrients or microbial nutrient adjuncts in the course of manufacture of any food.

11.3 JECFA

Formic acid has been evaluated by International Programme on Chemical Safety, WHO: Safety Evaluation of Certain Food Additives and Contaminants (JECFA, 1998). WHO Food Additives series 40 concludes in Table 1:

> *"Formic acid is produced endogenously and it is a normal component of intermediate metabolism. No safety concern based on current levels."*

In 1996 at its 46th meeting, JECFA re-evaluated and recommended the ADI for formic acid of 0 - 3 mg/kg body weight was still an acceptable level. In the Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives the functional class of Formic acid INS 236 was preservative and flavoring agent, FEMA 2487 (JECFA, 2003).

Formic acid was registered under the General Standards for Food Additives (GSFA) provisions of the Food and Agriculture Organization of the United Nations (FAO) as a food preservative in sauces and similar products to a maximum of 200 mg/kg and flavoured drinks to a maximum 100 mg/kg (Codex 2011). However, according to the Codex Commission, July 2014, 46 session on food additives meeting, information which the commission had requested earlier from members as well as observers on the commercial use of formic acid as an additive was not provided. Therefore, due to the lack of support for this substance, and not a safety issue, formic acid was removed from the list (Codex, 2014).

11.4 European Union

Until 1995, formic acid (E236) and sodium formate (E237) were both on the EU list of food additives (preservatives). The EU made specific purity criteria for preservatives for use in foods in Directive 76/463 of 4 May 1976, second amendment of Directive 65/66. The use of formic acid and sodium formate as additives was removed from the additive legislation published in 1995 because no information of use as a food additive was reported. The use as a processing aid was not within scope of this food additive directive. There are no regulatory restriction for the use of both formic acid and sodium formate as processing aids in the EU (European Commission, DG 1333/2008).

Formic acid is approved as an EU flavoring substance.
The European Food Safety Authority (EFSA) Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) evaluated formic acid and published their opinion that formic acid that *"intake is below threshold"* and with *"no safety concern"* as a flavouring substance (EFSA (AFC), 2008).

European Commission's expert group for technical advice on organic production authorized the use sodium formate for production of silage for organic farming and processing in 2011(European Commission, DG (EGTOP), 2011). The EFSA Panel on Additives and Products or Substances Used in Animal Feed (FEEDAP) has, after an obligatory reevaluation in 2015, concluded that sodium formate and formic acid are considered safe feed additives for all species or categories of animals, for all feeding stuffs at 10,000 ppm without a time limit (EFSA FEEDAP, 2015).

11.5 France

1990: Following a petition from a culture manufacturer the French Commission on Food Technology (CTA) and the French Superior Council of Public Health (CSHPF) issued the following opinions:

CTA opinion 21/11/1990:

"The Commission acknowledges the technological need for sodium formate addition in lactic acid bacteria preparations, knowing that formate is a natural metabolite of lactic acid bacteria and that this addition following the conditions of use proposed by the petitioner, do not increase significantly the level of formate naturally present in the finished food products. This use appears to be justified within the limit of 5% in a frozen culture concentrate." (Revue De L'Industrie Agro - Alimentaire 1991).

1996: A manufacture requested amended conditions of use and labelling exemption in France.

Labelling exemption:

In a letter dated 3 September 1996, the French administration clarified that (Zylbermann, 1996), in absence of any specific regulation on microbial cultures, the French regulation on the labelling of foodstuff applies (French decree n°84-1147 of 7th December 1984 now Code de la Consommation). Following the requirements of this regulation, when restoring a component that may be lost during the production process, it is not required to label the component if the restoration does not exceed the amount naturally present in the product.

11.6 Denmark

1990: Following a petition from a culture manufacturer The Danish Veterinary and Food Administration issued the below permission (as quoted):

"The Agency has evaluated this application and finds, that the use of formic acid must be considered as a processing aid to an additive. In the [Danish] Positive List, p 136 (dated October 1988), processing aids to additives are divided into two groups, the purpose of which are, respectively, to obtain a technological function in the additive itself, or to disperse dilute, or activate the additive, or the like.
The function of formic acid is, as described in your letter, similar to both types (cell survival and formation of nucleotides, respectively).The Agency has estimated that the main use is the technological function. Since formic acid, accordingly to the Positive List (Danish list of approved food additive, now repealed), *is a permitted processing aids to an additive, the use is legal."*

2007: Following a petition from a culture manufacturer The Danish Veterinary and Food Administration issued the below permission:

Revision of permission to use formic acid/formate in cultures 29/10/2007

In its letter dated 13 July 2007, the manufacture has requested a revision of the permission to use formic acid/formate for bacterial cultures, dating from 1990.

Background

The request for a revised permission reflects the fact that the development in the technology in the field of bacterial cultures has made it possible to produce cultures with a higher activity (more concentrated) than before. It is therefore possible to inoculate a smaller amount (volume) of bacterial cultures to the milk, i.e. down to 0.0025%. In the light of the use of cultures with a higher activity, which are added to milk in smaller amounts than before, the manufacture wishes to increase the permitted usage of formic acid in bacterial cultures from 5% to 20% formic acid or the equivalent of 30% sodium formate.

Decision (as quoted)
"The Danish Veterinary and Food Administration grants the wish of the manufacture that bacterial cultures designated for use in dairies may contain up to 20% formic acid in order to obtain optimal conditions for the cultures. Likewise, the wish that formic acid may be replaced by the equivalent amount of sodium formate, corresponding to up to 30% of the culture product, is granted."

12 Conclusion

It may be concluded from a critical evaluation of the available information on sodium formate summarized above, that the proposed uses of sodium formate up to 20 ppm are safe and suitable based on its non-toxigenicity and non-pathogenicity, its safe common use in food, product specific studies and lack of reported adverse effects in clinical studies.

It may be further concluded that these proposed uses of sodium formate are GRAS based on scientific procedures, supplemented by a history of safe use in foods, and consistent with provisions for GRAS substances in 21 CFR 170.30.

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14 Appendix

14.1 Product Descriptions

14.2 Certificates of Analysis

14.3 Expert Panel Report

14.4 Expert Panelist Curriculum Vitae

JOST CHEMICAL CO. PRODUCT SHEET

NAME AND CODE

Sodium Formate Purified Granular

Code 2728

CHEMICAL FORMULA

$CHNaO_2$ Mol. Wt. 68.01

CAS NUMBER

141-53-7

DESCRIPTION

White fine crystal

CHEMICAL SPECIFICATION

TESTS	SPECIFICATIONS
Identification	Passes
Description	Crystal powder
Color	White
Arsenic (As)	3 ppm maximum
Lead (Pb)	10 ppm maximum
Copper & Zinc	50 ppm maximum
Zinc	25 ppm maximum
Loss on Drying	2.0% maximum
Assay	98.0% minimum
Microbial Test Results	
Aerobic Plate Count	1000 cfu / gram maximum
Yeast and Mold Count	100 cfu / gram maximum
Total Coliforms	Negative

CONTAINERS

110 lb. /50 kg fiber drums; 25 kilogram packs EU only

STORAGE

Store in a clean, dry warehouse in the original unopened containers.

REVISION DATE

04/08/14

8150 LACKLAND, ST. LOUIS, MO 63114 TEL. 314-428-4300 FAX 314-428-4366
www.jostchemical.com

JOST CHEMICAL CO.
8150 LACKLAND ST. LOUIS, MO 63114 TEL. 314-428-4300 FAX 314-428-4366
www.jostchemical.com

1985 2015
JOST CHEMICAL
30 YEARS

CERTIFICATE OF ANALYSIS

Product Name:	Sodium Formate, Purified Granular
Date:	Wednesday, November 18, 2015
Lot Number:	27285010
Date of Manufacture:	Monday, November 16, 2015

	SPECIFICATIONS	ANALYSIS
Description:	Crystalline Powder	Pass
Color:	White	Pass
Identification:	Conforms	Conforms
LOD:	2.0% Maximum	0.00 %
Assay:	98.0% Minimum	99.2 %
Arsenic:	3 ppm Maximum	0.10 ppm
Lead:	10 ppm Maximum	0.01 ppm
Zinc:	25 ppm Maximum	0.27 ppm
Copper and Zinc:	50 ppm Maximum	0.35 ppm

Microbial Test Results

Aerobic Plate Count:	1000 cfu / gram Maximum	< 1000 cfu / gram
Yeast and Mold Count:	100 cfu / gram Maximum	< 100 cfu / gram
Total Coliforms:	Negative	Negative

(b) (6)

JOST CHEMICAL CO. / QUALITY DEPARTMENT

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1985 2015
JOST CHEMICAL
30 YEARS

CERTIFICATE OF ANALYSIS

Product Name:	Sodium Formate, Purified Granular
Date:	Tuesday, November 17, 2015
Lot Number:	27285009
Date of Manufacture:	Tuesday, November 10, 2015

	SPECIFICATIONS	ANALYSIS
Description:	Crystalline Powder	Pass
Color:	White	Pass
Identification:	Conforms	Conforms
LOD:	2.0% Maximum	0.22 %
Assay:	98.0% Minimum	99.1 %
Arsenic:	3 ppm Maximum	0.10 ppm
Lead:	10 ppm Maximum	0.01 ppm
Zinc:	25 ppm Maximum	0.93 ppm
Copper and Zinc:	50 ppm Maximum	1.03 ppm

Microbial Test Results

Aerobic Plate Count:	1000 cfu / gram Maximum	< 1000 cfu / gram
Yeast and Mold Count:	100 cfu / gram Maximum	< 100 cfu / gram
Total Coliforms:	Negative	Negative

(b) (6)

JOST CHEMICAL CO. / QUALITY DEPARTMENT

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www.jostchemical.com

1985 2015
JOST CHEMICAL
30 YEARS

CERTIFICATE OF ANALYSIS

Product Name:	Sodium Formate, Purified Granular
Date:	Monday, November 23, 2015
Lot Number:	27285011
Date of Manufacture:	Wednesday, November 18, 2015

	SPECIFICATIONS	ANALYSIS
Description:	Crystalline Powder	Pass
Color:	White	Pass
Identification:	Conforms	Conforms
LOD:	2.0% Maximum	0.07 %
Assay:	98.0% Minimum	99.2 %
Arsenic:	3 ppm Maximum	0.10 ppm
Lead:	10 ppm Maximum	0.01 ppm
Zinc:	25 ppm Maximum	0.71 ppm
Copper and Zinc:	50 ppm Maximum	0.81 ppm

Microbial Test Results

Aerobic Plate Count:	1000 cfu / gram Maximum	< 1000 cfu / gram
Yeast and Mold Count:	100 cfu / gram Maximum	< 100 cfu / gram
Total Coliforms:	Negative	Negative

(b) (6)

JOST CHEMICAL CO. / QUALITY DEPARTMENT

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CERTIFICATE OF ANALYSIS

Product Name:	Sodium Formate, Purified Granular
Date:	Thursday, November 19, 2015
Lot Number:	27285010
Date of Manufacture:	Monday, November 16, 2015

	SPECIFICATIONS	ANALYSIS
Description:	Crystalline Powder	Pass
Color:	White	Pass
Identification:	Conforms	Conforms
LOD:	2.0% Maximum	0.00 %
Assay:	98.0% Minimum	99.2 %
Arsenic:	3 ppm Maximum	0.10 ppm
Lead:	10 ppm Maximum	0.01 ppm
Zinc:	25 ppm Maximum	0.27 ppm
Copper and Zinc:	50 ppm Maximum	0.35 ppm

Microbial Test Results

Aerobic Plate Count:	1000 cfu / gram Maximum	< 1000 cfu / gram
Yeast and Mold Count:	100 cfu / gram Maximum	< 100 cfu / gram
Total Coliforms:	Negative	Negative

(b) (6)

JOST CHEMICAL CO. / QUALITY DEPARTMENT

Professor Emeritus
Pharmacology & Toxicology
VCU School of Medicine

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Expert Panel Report on the Generally Recognized as Safe Status of the Use of Sodium Formate in Industrial Production of Microbial Food Cultures

Introduction

The International Food Additives Council (IFAC) and the European Food and Feed Cultures Association (EFFCA) propose to utilize sodium formate in the industrial production of microbial food cultures. This proposed use is to support the symbiotic growth of streptococcus, lactobacillus, lactococcus, and leuconostoc species in fermented dairy and soy products, where the level initially added does not exceed 20 ppm, and the final concentration after fermentation is not increased over the naturally-occurring formate concentration in the fermented product when formate is not added.

In making this determination, IFAC and EFFCA critically reviewed (1) the safe history of use of sodium formate; and (2) the safety of use in clinical trials.

IFAC and EFFCA convened an Expert Panel ("The Panel") of independent scientist, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients and foods, to conduct an independent, critical and comprehensive evaluation of the available information on the safety of sodium formate and to determine whether the proposed use of sodium formate in industrial production of microbial food cultures is safe, and is Generally Recognized as Safe (GRAS) based on scientific procedures. The members of the Expert Panel included Professor Joseph F. Borzelleca, Ph. D. (Virginia Commonwealth University Scholl of Medicine), and Professor Michael W. Pariza (University of Wisconsin – Madison). *Curricula vitae* of the members of the Expert Panel are included in Appendix A.

The Panel, independently and collectively, critically evaluated a supporting GRAS dossier (**GRAS Dossier, Sodium Formate Use in the Industrial Production of Microbial Food Cultures; April 29, 2016)** submitted by IFAC and EFFCA which included a description of sodium formate; details of the manufacturing process and product specifications; history of use; intended use and use level; exposure; safety testing; safety assessment; bibliography and appendix. The Panel also considered other materials deemed appropriate or necessary.

Following its independent and collective critical evaluation of the available information, The Panel unanimously concluded, "the use presented in the dossier of sodium formate produced consistent with cGMP and meeting appropriate food grade specifications presented in the dossier, are safe and "Generally Recognized as Safe" ("GRAS") based on scientific procedures corroborated by a history of safe use.

A summary of the basis for the conclusions of The Panel is presented below.

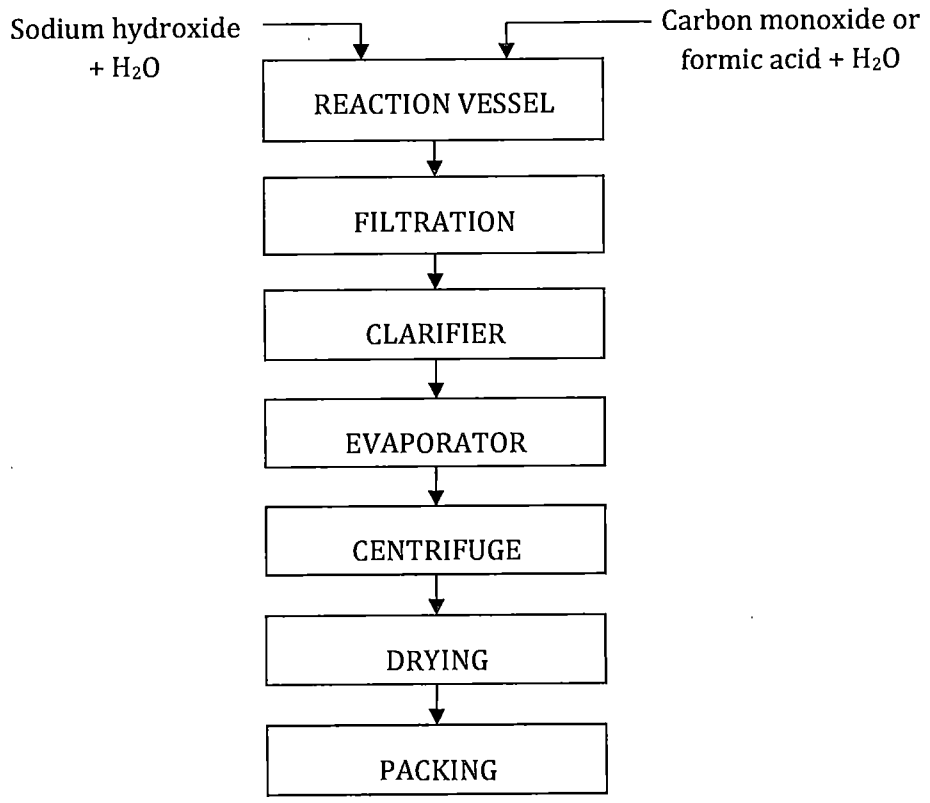
Description of Sodium Formate

Sodium formate is the sodium salt of formic acid. It is a white crystalline powder that does not have flammable or explosive properties. It is completely soluble in water.

Sodium formate is used to restore the naturally produced metabolite, formate, lost during industrial microbial food culture production, as sodium formate is much less hazardous and user-friendlier than formic acid. Sodium formate can be used as an intermediate in the production of formic acid.

Manufacturing Process

Sodium formate is manufactured in accordance with the U. S. Food and Drug Administration's current Good Manufacturing Practices guidelines in an FDA regulated and inspected facility. A summary of the manufacturing process is presented below.



Batch analyses demonstrate reproducibility of the manufacturing process (compliance with specifications)

History of Use

Sodium formate has a history of safe use from the culture industry for at least 20 years under self-GRAS assessments in the manufacturing of starter cultures. The U.S. FDA affirms sodium formate as GRAS as an indirect food substance as a component of paper and paperboard for food packaging. It has been approved for use in Australia and New Zealand under their food Standard Code for use as a microbial culture nutrient/adjunct in the manufacture of any food since 2005. It has been deemed safe by the European Food Safety Authority (EFSA), for all animal species at the use level proposed for food flavorings, with no restrictions for use.

Intended Use/Use Level

The use of sodium formate is limited to the production of fermented dairy and soy products where addition of sodium formate supports the symbiotic growth of streptococcus, lactobacillus and leuconostoc microbial food cultures. Depending on the species and physiological activity, the microbial food culture with added sodium formate is added to the milk so that the level of formate is less than or equal to 20 ppm in the milk.

Exposure

Variable concentrations of naturally occurring formic acid are found in milk, yogurt and cheese. Concentrations found in yogurts ranged from 40 to 2100 ppm and in cheeses, the concentrations ranged greatly, up to 2960 ppm in some cheeses.

It has been shown that adding formate to the starter culture does not increase the final concentration of formic acid measured at the end of the fermentation. It is believed that the formic acid produced from the added sodium formate added to the milk is being quickly used by the cultures, thus limiting the accumulation of endogenous formate produced by the cultures during their growth in the milk. Since the final concentration of formate is not increased by the addition of sodium formate, up to 20 mg/kg, to the milk before fermentation, the total intake by consumers through yogurt or cheese consumption will not increase compared to the situation where sodium formate is not added.

However, in a worst case scenario, where it is assumed that all added formate ends up in the cheese or yogurt, and none is lost in the whey, nor is it metabolized, it can be calculated that the additional intake of formic acid consumed per day from cheese and yogurt, would be 0.108 mg formic acid/kg/bw. This is significantly lower than the upper limit of acceptable daily intake (ADI) level of 0-3 mg/kg/bw, when used as a food preservative or food flavor ingredient, established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1998.

Safety Testing

Regulatory Status of Sodium Formate

Under the U.S. FDA 21 CFR section 186.1756, sodium formate is affirmed GRAS for use in paper and paperboard food contact material. Sodium formate is simply the sodium salt of formic acid, so clearances for formic acid are applicable to sodium formate as well (FDA Code of Federal Regulation, 1976 (SCOGS) 186.1756). It is also listed under the Australia and New Zealand Food Standards Code, Standard 1.3.3, Processing Aids clause 18, as a permitted microbial nutrient and nutrient adjunct (2015). Sodium formate was also on the EU list of food additives in May 1976(preservatives) (EU Directive 76/463, second amendment of Directive 65/66). However in 1995, because no information on the use as a food additive was reported for sodium formate, it was removed from the additive legislation. The use as a processing aid was not within the scope of this food additive directive and there are currently no regulatory restrictions for the use of sodium formate as a processing aid in the EU (European Commission, DG 1333/2008). A technical need for the addition of sodium formate in lactic acid bacteria preparations was acknowledged by the French Food Technology Committee (CTA – Comité Du Technologie Alimentaire) in 1990.

Regulatory Status of Formic Acid

The U.S. FDA has determined that formic acid may be safely used at GMP levels under 21 CFR section 172.515 as a food additive for flavoring substances and adjuvants. In 1996, JECFA re-evaluated and recommended the ADI for formic acid of 0 – 3 mg/kg body weight was still an acceptable level and it has been evaluated by the International Programme on Chemical Safety, where it was concluded that *"Formic acid is produced endogenously and it is a normal component of intermediate metabolism. No safety concern based on current levels."* (JECFA, 1998). Formic acid was also registered under the General Standards for Food Additives (GSFA) provisions of the Food and Agriculture Organization of the United Nations (FAO) as a food preservative in sauces and similar products. However in July 2014, the Codex Commission removed formic acid from the list due to the lack of support for this substance, and not because of safety concerns. Formic acid was also on the EU list of food additives in May 1976(preservatives) (EU Directive 76/463, second amendment of Directive 65/66). However in 1995, because no information of the use as a food additive was reported for formic acid, it was removed from the additive legislation. The use as a processing aid was not within the scope of this food additive directive and there are currently no regulatory restrictions for the use of formic acid as a processing aid in the EU (European Commission, DG 1333/2008). Formic acid is approved as a EU Flavoring substance. The European Food Authority (EFSA) Panel on Food Additives, Flavorings, Processing Aids and Materials in contact with Food (AFC) determined that formic acid "intake is below threshold" and with "no safety concern" as a flavoring substance (EFSA (AFC), 2008). The Danish Veterinary and Food Administration reviewed the use of formic acid in 1988 and concluded, "the use of formic acid must be considered as a processing aid to an additive." They go on to state that "Since formic acid, accordingly to the Positive List, is a permitted processing aids to an additive, the use is legal." Note, however, the Danish list of approved food additives has been repealed. In 2007, The Danish Veterinary and Food Administration again issued permission to use formic acid/formate in cultures dating from 1990 (19/10/2007).

Animal Studies

A significant number of animal studies of both sodium formate and formic acid were critically evaluated and tabulated in the dossier. In one study, the acute toxicity of 1000-1200 mg/kg formic acid was tested in 55 mice and LD_{50} determined to be 1100 mg/kg formic acid (1076 mg/kg when calculating for formate) (Malorney, 1969). In another study, 10 rats were administered various doses, with a maximum dosage of 1,000 mg formic acid, undiluted/kg body weight and the animals were observed daily for 14 days post administration. The acute oral LD_{50} in this study was reported to be 730 mg/kg bw (calculated to be 714 mg formate/ kg bw) (EPA, 2014). An acute oral toxicity study of formic acid in rats (number and strain not stated), an LD_{50} of 1830 mg/kg body weight (1790 mg formate/kg bw) was reported (Katz et al, 1994; EPA, 2014), and in another acute oral toxicity study, sodium formate was evaluated involving 45 mice (ages, sex and strain not reported). An LD_{50} of 7410 mg formate/kg bw was reported (EPA, 2014). Lastly, a study where six rats received sodium formate in drinking water at a concentration of 1% continuously for 1.5 years, it was reported that the mean intake of sodium formate was 274 mg/animal or 185 mg formic acid/animal. A control (unspecified) group of animals was also included in the study. Toxicity was not reported in any of the animals tested (Malorney, 1969). It can be concluded from these studies that sodium formate is well tolerated at high levels and there was no toxicity observed over 1.5 years in a repeated dosing study.

Human Studies

As noted in the 1976 U.S. FDA SCOGS report on formic acid, "Formic acid is a natural constituent of many foods", "is a metabolite in normal intermediary metabolism, and is a precursor in the biosynthesis of several body constituents. Formate is an intermediate in normal human metabolism and normally present at low levels in the body." It also states that "the tolerance of the body to large amounts is relatively high" as it reported daily oral intake of up to 8 mg of formic acid/kg for a period of four weeks was tolerated in men.

Safety Assessment

Low-level systemic exposure to formic acid is not likely to result in adverse effects (Katz et al, 1994). Formic acid is a normal constituent of intermediate metabolism and a precursor of many amino acids and purines. It may also be incorporated into nucleic acids, proteins, lipids, and carbohydrates. It is eliminated, unchanged or as sodium formate. The National Institutes of Health Toxicology Data Network (TOXNET, 2003) as referenced in Gosselin et al., 1976, lists sodium formate under the entry for formic acid and salts as such: "*sodium formate appears to have a low toxicity (10 g by mouth without ill effects in man.*"

Human exposure will not be increased by the addition of sodium formate to the milk before fermentation as the sodium formate is being used quickly by the cultures, limiting the accumulation of endogenous formate produced by the cultures during their growth in the milk.

Conclusion

We, the members of the Expert Panel, have individually and collectively critically evaluated the information summarized above and other information deemed appropriate and conclude that sodium formate, produced consistent with cGMP and meeting appropriate food grade specifications presented in the dossier, is safe (i.e., meets the standard of reasonable certainty of no harm) and suitable for use in the industrial production of microbial food cultures summarized in the dossier.

We, the members of the Expert Panel, have individually and collectively critically evaluated the information summarized above and other information deemed appropriate and conclude that sodium formate, produced consistent with cGMP and meeting appropriate food grade specifications presented in the dossier, is Generally Recognized As Safe (GRAS) based on scientific procedures and corroborated by a history of safe use for use in the industrial production of microbial food cultures summarized in the dossier .

It is our opinion that other experts qualified to assess the safety of food and food ingredients would concur with these conclusions.

By (b) (6)

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22 June 2016
Date

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25 June 2016
Date

Pages 000053-000097 of Curriculum Vitae removed in accordance with the Privacy Act of 1974.

SUBMISSION END