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EVALUATION OF THE HEALTH ASPECTS OF FORMIC ACID, SODIUM FORMATE, AND ETHYL FORMATE AS FOOD INGREDIENTS

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NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

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I. INTRODUCTION

This report concerns the health aspects of using formic acid, sodium formate, and ethyl formate as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1973.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of January 28, 1977 (42 FR 5425 and 5426) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information and views on the health aspects of using formic acid, sodium formate, and ethyl formate as food ingredients. The Select Committee received no requests for such a hearing on formic acid, sodium formate and ethyl formate.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Federal Regulations (2) [21 CFR 170.3] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Regulations also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

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*The document (PB-228 558/3) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Select Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Select Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Select Committee, there are insufficient data upon which to base a conclusion. The Select Committee, aware that biological testing is dynamic, bases its conclusions on information now available; it cannot anticipate the results of experiments not yet conducted or those of tests that may be reconducted, using new technologies. These conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on formic acid, sodium formate, and ethyl formate and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Formic acid, or methanoic acid, is the first member of the homologous series identified as fatty acids with the general formula RCOOH (3). Formic acid was obtained first from the red ant; its common name is derived from the family name for ants, Formicidae (4). This substance also occurs naturally in bees and wasps, and is presumed to be responsible for the "sting" of these insects. Formic acid in the free acid state has been reported as a constituent of honey, plant nettles, unripe grapes, peaches, raspberries, strawberries, mace or nutmeg oils, bitter orange, coffee, rums, wines, mineral waters, milk, and cheese (5-8).

Formic acid is used in the food industry as a flavoring adjunct, animal feed additive, brewing antiseptic, and as a food preservative in certain European countries (6, 7,9). Natural levels reported in some common foods and beverages are shown in Table I.

Ethyl formate, an ester of formic acid with the formula $HCOOC_2H_5$, has been reported as a natural constituent in certain plant oils, fruits (apples, pears, and oranges), honey, wines, and distilled liquors (7). In the food

TABLE I

Natural Formic Acid Content Reported for Some Foods and Beverages

Food	Amount formic acid (mg/100g)	Ref.
Fruits	2-4	10
Fruit juices	3-10	11
Fruit syrups	65-163	12
Honey	2-200	13
Wines	0.1-34	14, 15
Coffee, roasted	135-220	16
Coffee, extracts	200-770	16
Milk (evap.)	3-4	17
Cheese	2-30	18, 19

industry, ethyl formate is used as a flavoring in candy, chewing gum, ice cream, baked goods, meat products, frozen dairy desserts, and essences (5, 20).

Statements concerning the antimicrobial effects of formic acid were reported in German Current Food Additives legislation in 1969 (9), by von Oettingen (20), in a report of the Joint FAO/WHO Expert Committee on Food Additives (21), and by Berard et al. (22). The use of formates as fumigants has been described by the NAS/NRC Food Protection Committee (5), von Oettingen (20), and Vincent and Lindgren (23).

Table II lists specifications provided in the Food Chemicals Codex (24) for formic acid and ethyl formate; sodium formate is not listed. Formic acid and sodium formate are cited as generally recognized as safe (GRAS) in the Federal Regulations (2) as substances migrating to food from paper and paperboard products [21 CFR 182.90]. Formic acid is also separately regulated as a synthetic flavoring substance or adjuvant [21 CFR 172.515].

Ethyl formate is cited as general recognized as safe (GRAS) in the Federal Regulations (2) as a substance that may be used as a multiple purpose GRAS food substance when used as a fumigant for cashew nuts with a residue tolerance of 0.0015 percent [21 CFR 182.1295] and is separately regulated as a synthetic flavoring substance or adjuvant [21 CFR 172.515].

This report concerns the evaluation of formic acid and sodium formate only as ingredients of paper and paperboard food packaging materials, and ethyl formate as a multiple purpose food substance.

TABLE II

Specifications for Formic Acid and Ethyl Formate (24)

Specification	Formic acid HCOOH	Ethyl formate $HCOOC_2H_5$
Assay	≮85.0% HCOOH	≮95.0% $HCOOC_2H_5$
Free acid (as formic acid)	-------	≯0.1%
Acetic acid	≯0.4%	------
Arsenic (as As), ppm	≯3	------
Heavy metals as lead, ppm	≯10	------
Sulfate, ppm	≯40	------

III. CONSUMER EXPOSURE DATA

An NRC subcommittee (25) surveyed manufacturers in 1970 concerning the the level of addition of GRAS substances to foods and estimated the possible average daily intakes of formic acid and ethyl formate. No reports of food uses for sodium formate were received by the NRC subcommittee in its survey. Based on information supplied by those manufacturers who reported adding a GRAS substance to at least one food in a category, weighted means were calculated for the usual and maximal addition of the substance to foods in the category. Weighted means of the usual level of addition of formic acid and ethyl formate are given in Table III. It may be assumed that the uses reported are essentially those of synthetic flavoring substances or adjuvants, inasmuch as the amount of formic acid (as well as sodium formate) used in paper and paperboard products and the amount of ethyl formate used as a fumigant for cashews would not have been reported and would be comparatively small. It is to be noted that these weighted means do not express the highest percentage of these substances added by any manufacturer; they do not indicate that all foods in a category contain added formic acid and/or ethyl formate; and they do not necessarily coincide with the levels added by any one manufacturer.

The National Research Council subcommittee (25) has estimated possible average daily intakes of formic acid and ethyl formate for various age groups from data collected by the Market Research Corporation of America on the mean frequency of eating foods by food category, data on mean portion size of foods in those categories from the U.S. Department of Agriculture, and the assumption that all food products within a category contain formic acid and/or ethyl formate at the levels shown in Table III. Such an assumption is likely to lead to overestimates of intake. The NRC subcommittee has recognized that in most cases its calculations of possible intakes are

TABLE III

Level of Addition of Ethyl Formate and Formic Acid for Flavoring Purposes to Food by Food Category (25)

Food category	Ethyl formate Weighted mean percent	Formic acid Weighted mean percent
Baked goods, baking mixes	0.03	<0.01
Frozen dairy desserts, mixes	0.01	<0.01
Meat products	<0.01	
Soft candy	0.02	<0.01
Gelatins, puddings, fillings	0.01	<0.01
Beverages, nonalcoholic	<0.01	<0.01
Hard candy	0.01	<0.01
Chewing gum	0.01	

Blanks in the table mean that the substance is not added to the foods indicated. Level of addition of ethyl formate and formic acid is the weighted mean of the levels reported by manufacturers as their usual addition to one or more products in a food category. For discussion of weighted mean see Section X and Exhibit 50 of reference 25.

TABLE IV

Possible Average Daily Intake of Added Formic Acid and Ethyl Formate as Flavoring Substances by Age Group (25)

Substance	0-5 mo		6-11 mo		12-23 mo		2-65+ yr	
	mg	mg/kg	mg	mg/kg	mg	mg/kg	mg	mg/kg
Ethyl formate	4	0.28	10	1.25	21	1.91	48	0.80
Formic acid	0.01	<0.01	0.09	0.01	0.18	0.02	0.43	<0.01

Calculated intake, mg/kg body weight, was based on an average weight of 60 kg for an adult (26) and the following estimated weights of infants by age groups: 0-5 mo, 5 kg; 6-11 mo, 8 kg; and 12-23 mo, 11 kg (27)

overstated, often by considerable margins.* Because of factors detailed in Section XI of the subcommittee's report, it was stated that the possible average estimated total dietary intakes are likely to be much higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which the substances had been added at the maximum levels (25).

Estimates of the possible average daily per capita intake of each of the substances can also be made from the total quantity used in foods as given in Table V. It is apparent that the per capita consumption (0.3 mg per day) of ethyl formate calculated on this basis is much less than the estimate of 48 mg per day for individuals over two years of age (Table IV). The Select Committee believes that the estimate in Table V is the more realistic.

TABLE V

Quantity of Formic Acid and Ethyl Formate Added Annually to Foods and Per Capita Daily "Intake" Calculated Therefrom (25)

Substance	Relative quantities added[a] 1970/1960	Total quantity added (1970)[b] kg	Per capita daily "intake"[c] mg
Ethyl formate	1.00	22,000	0.3
Formic acid	----	97	<0.1

[a] Based only on the reports from those respondents to the National Research Council (NRC) survey who submitted information for both 1960 and 1970.

[b] Total usage is based on the sum of kilograms used in foods supplied by NRC and the Flavor and Extract Manufacturers' Association (FEMA) recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.

[c] Based on 1970 total consumption and a U.S. population of 205 million.

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (25). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."

The Joint FAO/WHO Expert Committee on Food Additives has proposed conditional acceptable daily intake levels (ADI) of 0 up to 5 mg per kg body weight for formic acid and ethyl formate, calculated as total formic acid from all food additive sources (21, 28).

IV. BIOLOGICAL STUDIES

Absorption, metabolism and excretion

Formic acid, ethyl formate, and sodium formate are absorbed from the gastrointestinal tract of man (20, 29, 30) and dogs (31). Formic acid and ethyl formate are absorbed through the respiratory tract of man (32), rats (33), guinea pigs (34), cats (35), and rabbits (35). Formic acid is absorbed through the intact skin and from the urinary bladder of the dog (20, 31, 36). However, the data reported by Smyth et al. (33) would suggest that little, if any, formic acid is absorbed through the skin of rabbits. A human subject receiving 4.44 grams of formic acid orally (about 6.3 mg per kg) had a blood level, expressed as sodium formate, of 11.8 mg per dl 10 minutes following ingestion (29).

In a review of work on the toxicity of formic acid and its esters, von Oettigen (20) states that in the intact animal, formic acid is oxidized to carbon dioxide and water. The extent of this oxidation may be influenced by dose (small doses, 100 mg per kg, are completely oxidized; larger doses, 20 g per kg, are partly excreted unchanged), period of oral administration, amount and nature of intestinal contents, the concentration of solution used, the rate of intravenous injection and species of animal.

The biological half-life of formic acid in various species has been reported by Malorny (29, 36), as shown in Table VI. Vitamin E deficiency

TABLE VI

Biological Half-life of Formic Acid in Various Species (29, 36)

Species	Route of administration	Biological half-life (minutes)
Rat	oral	12
Guinea pig	i.v.	22
Rabbit	i.v.	32
Cat	i.v.	67
Dog	oral	77
Man	oral	45-46

results in altered patterns of biotransformation and distribution after injection of labeled sodium formate (37-39). Various workers have reported that in animals and humans folic acid (40-43), and vitamin B_{12} (43, 44), deficiency result in an increase in the excretion of unchanged formic acid. Malorny (36) found that addition of folic acid results in an acceleration of formic acid oxidation. Oro and Rappoport (45) reported that the oxidation of formic acid to carbon dioxide and water involves a catalase-hydrogen peroxide complex with no dehydrogenases. The enzymes responsible for the formation of hydrogen peroxide include xanthine oxidase, uricase, monoamine oxidase and D-amino acid oxidase. Palese and Tephly (46) conclude that formate is oxidized normally in rats through the one-carbon pool, but in folate deficiency, the catalase-peroxidative system serves as an alternative pathway. There are several reports (20, 29, 36, 47), that oxidation of formic acid occurs in the liver, intestinal mucosa, spleen, kidneys, lungs, and erythrocytes.

Sperling et al. (48) injected ^{14}C-labeled sodium formate intraperitoneally into large (400-537 g) Osborne-Mendel albino rats. Eighty percent of the injected dose (0.07 to 0.10 millicurie) was excreted and the formate was distributed in all body tissues. The highest concentration of ^{14}C sodium formate was found in fat from testes, lungs, spleen, heart, and kidneys; and the lowest concentrations in depot fat and spinal cord. The greatest amounts of ^{14}C formate were found in tissue proteins in the stomach, spleen, kidneys, testes, and liver.

Rabbits have been found to metabolize formic acid parenterally administered almost quantitatively; alkalosis causes the urinary excretion of greater amounts of formic acid (20, 49, 50). In the dog, Lund (31) reported that orally administered sodium formate is oxidized almost completely, and that unchanged sodium formate is absorbed through the bladder wall. Von Oettigen (20) and Malorney (29) have reported that formic acid ingested orally as sodium formate is oxidized by humans. Gley and Courtois (6) stated that formic acid is a normal constituent of human urine, and that 13 to 120 mg are excreted per day.

According to reports by Annison and White (51) and Gley and Courtois (6), the role of formic acid in intermediary metabolism is well established. It is a precursor of serine, methionine, cysteine, and purines, and it is incorporated into RNA, DNA, proteins (including milk proteins), lipids, and carbohydrates (5, 51-53).

Biochemical, physiological, and pharmacological effects

Formic acid has been reported to inhibit lysozyme, ribonuclease, trypsin, and catalase (resulting in methemoglobinemia)(20, 54). Gastrointestinal activity is stimulated by formic acid. The central nervous system appears to be sensitive to the action of formate. Whereas low doses (0.46 g to 1.25 g per kg) intravenously in the rabbit may cause depression of the central nervous system, larger doses (ca. 4 g per kg) may cause convulsions, then death. In myocardial tissue, the nature and magnitude of the response

have been reported to be a function of the dose: low doses may stimulate and larger doses depress the myocardial contraction rate and amplitude. Formic acid is more toxic than formaldehyde or methanol to the myocardium. Intravenously administered formic acid causes vasoconstriction and an increase in blood pressure (except at high doses); and sodium formate elicits vasodilatation. In addition, formic acid exerts a diuretic effect, but large doses are nephrotoxic; rabbits were the most sensitive of all species studied (20).

Malorny (36) in studies with the cat reported that folic acid antagonists inhibit the oxidation of formic acid, resulting in the excretion of large amounts of unchanged formic acid.

Short-term studies

A summary of the available acute toxicity data on formic acid, ethyl formate, and sodium formate is presented in Table VII. Sporn et al. (55) have reported that the toxicity of formic acid by intraperitoneal injection in mice is less than that of salicylic or boric acid, but greater than benzoic acid. Amdur (34) exposed guinea pigs (7 to 16 per group) to formic acid vapors (0.34 to 42.5 ppm) alone and with sodium chloride aerosol for one hour. She concluded that formic acid is a more potent respiratory irritant than formaldehyde. Lund (49) found that two rabbits (3.15 and 3.30 kg) tolerated subcutaneous doses of 317 and 303 mg per kg without adverse effects. In other work Lund (31) reported that a male dog tolerated a single subcutaneous dose of 200 mg per kg, and that another dog tolerated 100 mg per kg injected into the bladder without adverse effects.

Sheep were reported by Neumark (59) to tolerate formic acid at a level of 150 mg per kg administered orally without adverse effects. He also reported that formic acid caused anorexia in sheep because of a local irritant effect on the nerve endings in the gastric mucosa.

Human intoxication due to formic acid was reviewed by Karunakaran and Pillai (60), and von Oettingen (20). The signs and symptoms from intentional or accidental overdoses (about 50 g or more) include salivation, vomiting, burning sensation in the mouth and pharynx, bloody vomitus, diarrhea, severe pain, rapid and soft and then slow pulse and cold and clammy skin, blood pressure drop and shock, respiratory distress and cyanosis, albuminuria, hematuria, and anuria. Death may be the result of uremia, circulatory failure, or pneumonia. The ingestion of massive quantities of formic acid may lead to such pathological changes as swollen and necrotic areas of the tongue, palate, pharynx, esophagus, larynx, trachea, stomach and intestine; hyperemic and hemorrhagic kidneys, as well as hemosiderin deposits in the liver.

Smyth et al. (33) reported that rabbits tolerated 20 mg of ethyl formate per kg body weight applied to the skin under an impervious film girdle; however,

TABLE VII

Acute Toxicity

Substance	Animal	Route	Dosage, mg/kg body wt	Measurement	Ref.
Formic acid	Mice	p. o.	1100	LD_{50}	36
	Mice	i. p.	145	LD_{50}	36
	Mice	i. p.	940	LD_{50}	55
	Rats	p. o.	1830	LD_{50}	55
	Rabbits	p. o.	4000+	MLD	20
	Rabbits	i. v.	239	MLD	56
Ethyl formate	Rats	p. o.	1850	LD_{50}	57
	Guinea pigs	p. o.	1110	LD_{50}	57
Sodium formate	Mice	p. o.	11200	LD_{50}	36
	Mice	i. v.	807	LD_{50}	36
	Dogs	p. o.	4000	MLD	58
	Dogs	i. v.	3000	MLD	58
	Man	p. o.	1000	MLD	58

ethyl formate produced a severe corneal burn in the eye of the rabbits. It was nontoxic when applied topically to the skin. Rabbits and guinea pigs, when exposed to atmospheres containing up to 130 mg per liter of ethyl formate, exhibited depression of central nervous system activity and pneumonia (35). The intravenous administration of ethyl formate to rabbits elicited conflicting results, i.e., 28 mg per kg administered as the undiluted ester caused an increase in respiration but no effects on the central nervous system, while 250 mg per kg administered as a 5 percent solution did not elicit any adverse effect (20).

Long-term studies

In work by Sporn et al. (55), young white rats (about 40 g body weight, 8 per group) received formic acid in their diet at levels of 0.5 percent or 1.0 percent (2.5 g per kg per day) and two levels of casein (11.8 percent and 18.2 percent) for five to six weeks. Controls received an 18.2 percent casein ration. Formic acid at both levels appeared to cause a lower weight gain. Similar results were obtained when formic acid was added to the drinking water at levels of 0.5 percent or 1.0 percent for six weeks. In both series, treated animals showed smaller weight livers, kidneys, adrenals (except for 1 percent in the diet), and spleens (except both 1 percent dietary and drinking water levels). Sollmann (58) fed rats (six per group) the following levels of formic acid in their drinking water: 8.2, 10.25, 90, 160, 360 mg per kg body weight daily. The exposure period was 2 to 27 weeks. Food consumption and growth were inhibited by formic acid at the highest level; but no adverse effects were seen with the lower doses. There were no fatalities reported.

Hagan et al. (61) fed Osborne-Mendel rats (10 males, 10 females per level) diets containing ethyl formate at levels of 1000, 2500, and 10,000 ppm (100, 250, and 1000 mg per kg per day) for 17 weeks. No observable adverse effects were reported.

Male and female Wistar rats were given 150 to 200 mg per kg body weight of calcium formate daily in drinking water (at level of 0.2 percent) for their life span (36). No deaths or toxic signs attributable to calcium formate were noted through five successive generations. There were no effects on fertility, pregnancy, or fetal development. Doubling the level in water to 0.45 percent for two years did not produce adverse effects. Malorny (36) exposed Wistar rats to sodium formate (1 percent in drinking water equal to 730 mg per kg body weight) for one and a half years. No adverse effects were reported.

The daily oral administration of 0.5 g of formic acid (about 8 mg per kg) to men by Lebbin [cited in Sollmann (58)], for four weeks failed to produce any adverse effect.

Miscellaneous effects

Von Oettigen (20) noted that formic acid, at concentrations as low as 32 mg per liter of air, is corrosive to skin and mucous membranes.

Special studies

Mutagenesis: Although Freese et al. (62) reported that formic acid (at levels of 0.046 and 0.46 percent) did not inactivate or mutate transforming DNA at a significant rate, Demerec et al. (63) reported formic acid (at concentrations of from 0.005 to 0.007 percent) to be moderately mutagenic in Escherichia coli, and Stumm-Tegethoff (64) reported it to be mutagenic for Drosophila germ cells. However, ethyl formate was found to exhibit no mutagenic activity in in vitro plate and suspension tests with Saccharomyces cerevisiae, D4, and Salmonella typhimurium TA-1535, TA-1537, and TA-1538 at concentrations up to 5 percent, with or without activation by mouse, rat, or monkey liver homogenates (65). The Select Committee is not aware of any mutagenic studies on formic acid, sodium formate, or ethyl formate in mammals.

Teratogenesis: Malorny (36) reported that the injection of sodium formate into chicken eggs (5, 10, 20 mg per egg) did not produce malformations. The Select Committee is not aware of other teratogenicity studies.

Carcinogenesis: Frei and Stephens (66) observed no significant histologic changes when formic acid, at a concentration of 8 percent in water, was painted twice each week on the ears of Swiss mice which were examined on days 2, 5, 10, 20 and 50 after treatment. The Select Committee is not aware of studies of carcinogenesis involving oral administration of formic acid, sodium formate, or ethyl formate.

V. OPINION

Formic acid is a natural constituent of many foods. It is a metabolite in normal intermediary metabolism, and is a precursor in the biosynthesis of several body constituents. The tolerance of the body to large amounts is relatively high. For example, 160 mg of formic acid per kg of body weight orally was tolerated by rats; men reportedly tolerated 8 mg of formic acid per kg per day orally for a period of four weeks; and no adverse effects were reported in rats that received 730 mg of sodium formate per kg in their diet for one and a half years. Average daily intake of ethyl formate and formic acid is about 1 mg per kg or less as formic acid. Although formic acid appears to be moderately mutagenic in E. coli and Drosophila, ethyl formate is not mutagenic toward strain D4 of Saccharomyces cerevisiae or to three strains of Salmonella typhimurium. No adverse effects attributable to formate

were found in five successive generations of rats given up to 200 mg of calcium formate per kg of body weight daily.

Based on these considerations, the Select Committee concludes that:

There is no evidence in the available information on formic acid and sodium formate that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used as ingredients of paper and paperboard food packaging materials, or as they might reasonably be expected to be used for such purposes in the future.

There is no evidence in the available information on ethyl formate that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current and in the manner now practiced or that might reasonably be expected in the future.

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15. Supplementary Notes

16. Abstracts

This report, by a group of qualified scientists designated the Select Committee on GRAS Substances (SCOGS), provides an independent evaluation on the safety of Formic Acid, Sodium Formate and Ethyl Formate in food at their present or projected levels of use.

17. Key Words and Document Analysis. 17a. Descriptors

17b. Identifiers/Open-Ended Terms

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Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents

WHO FOOD ADDITIVES SERIES NO. 5

The evaluations contained in this publication were prepared by the Joint FAO/WHO Expert Committee on Food Additives which met in Geneva, 25 June - 4 July 19731

World Health Organization
Geneva
1974

1 Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives, Wld Hlth Org. techn. Rep. Ser., 1974, No. 539; FAO Nutrition Meetings Report Series, 1974, No. 53.

FORMIC ACID

Explanation

Formic acid has been evaluated for acceptable daily intake by the Joint FAO/WHO Expert Committee on Food Additives (see Annex 1, Refs No. 6 and No. 9) in 1961 and 1964. The previously published monographs are reproduced in their entirety below.

BIOLOGICAL DATA

BIOCHEMICAL ASPECTS

Formate is an intermediate in normal metabolism. It takes part in the metabolism of one-carbon compounds and its carbon may appear in methyl groups undergoing transmethylation. It is eventually oxidized to carbon dioxide (Williams, 1959). When formate is administered it could also be expected to enter one-carbon metabolism. However, there is a species difference in the extent of this metabolism, for in rabbits no administered formate is excreted, whereas in dogs about half the administered formate is excreted unchanged in the urine (Croner & Seligmann, 1907). Its metabolism in human beings is probably somewhere between that in dogs and that in rabbits, judging from the relative amounts of formate excreted by man, dogs and rabbits receiving methanol (Lund, 1948a; Lund, 1948b).

Formic acid (or formate) is apparently more toxic than other fatty acids, possibly owing to its enzyme-inhibiting activity (Bleyer et al., 1933). However, no cumulative toxic effects are known.

TOXICOLOGICAL STUDIES

Special studies

No data are available.

Acute toxicity

Exact LD50 values are not available. In dogs, sodium formate in oral doses of 4000 mg/kg and i.v. doses of 3000 mg/kg bw produced toxic effects such as methaemoglobinaemia and heart congestion (Fleig, 1907). About 50 mg/kg in 10% aqueous solution given orally to dogs or 6 mg/kg given s.c. to rabbits produced methaemoglobinaemia which lasted about 10 days (Croner & Seligmann, 1907). This slow disappearance may be due to the inhibition of catalase by formic acid (Lück, 1957). 4.6 mg/kg i.v. given to six dogs produced no ill effect and 13.8 mg/kg only slight hypertension (Erra, 1958).

Short-term studies

Dog

0.5 g of formic acid daily in the food has been tolerated by dogs without effect (Dick, 1909).

Long-term studies

No data are available.

OBSERVATIONS IN MAN

2-4 g of sodium formate daily did not produce toxic manifestations in human subjects, even if they were suffering from

kidney disease. It has been stated that a daily intake of 2-4 g for therapeutic purposes could be tolerated for months without untoward effects (Rost, 1917).

Comments:

An evaluation may be made on the basis of the available biochemical studies on man and on the knowledge of its role in normal metabolism.

EVALUATION

Estimate of acceptable daily intake for man

0-3 mg/kg bw.

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See Also:
Toxicological Abbreviations
Formic acid (ICSC)
Formic acid (FAO Nutrition Meetings Report Series 38a)
FORMIC ACID (JECFA Evaluation)