Article

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Safety Assessment of Formic Acid and Sodium Formate as Used in Cosmetics

Wilbur Johnson Jr[1], Bart Heldreth[2], Wilma F. Bergfeld[3], Donald V. Belsito[3], Ronald A. Hill[3], Curtis D. Klaassen[3], Daniel C. Liebler[3], James G. Marks Jr[3], Ronald C. Shank[3], Thomas J. Slaga[3], Paul W. Snyder[3], and F. Alan Andersen[4]

Abstract

Formic acid functions as a fragrance ingredient, preservative, and pH adjuster in cosmetic products, whereas sodium formate functions as a preservative. Because of its acidic properties, formic acid is a dermal and ocular irritant. However, when used as a pH adjuster in cosmetic formulations, formic acid will be neutralized to yield formate salts, for example, sodium formate, thus minimizing safety concerns. Formic acid and sodium formate have been used at concentrations up to 0.2% and 0.34%, respectively, with hair care products accounting for the highest use concentrations of both ingredients. The low use concentrations of these ingredients in leave-on products and uses in rinse-off products minimize concerns relating to skin/ocular irritation or respiratory irritation potential. The Cosmetic Ingredient Review Expert Panel concluded that formic acid and sodium formate are safe in the present practices of use and concentration in cosmetics, when formulated to be nonirritating.

Keywords

formic acid, sodium formate, safety, cosmetics

Introduction

In 1997, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a final report with the conclusion that formic acid is safe when used in cosmetic formulations as a pH adjuster with a 64 ppm limit for the free acid.[1] At the time of publication, the only reported function of formic acid in cosmetics was that of a pH adjuster. Currently, the *International Cosmetic Ingredient Dictionary and Handbook* reports that formic acid functions as a fragrance ingredient, preservative, and pH adjuster in cosmetic products (Figure 1).[2] In June 2012, the Panel agreed to reopen the CIR final safety assessment on formic acid to address any safety concerns that may be associated with the new functions of this ingredient and to add sodium formate, which is also being used as a preservative in cosmetic products. This safety assessment presents information on the preservative and other functions of formic acid and the preservative function of sodium formate in cosmetics, new data on the safety of formic acid, and the available safety test data on sodium formate. Information on the role of formic acid in normal metabolism and additional information relating to the safety of formic acid in cosmetic products can be found in the 1997 final report.

Chemistry

Definition and Structure

Formic acid (CAS No. 64-18-6), the simplest carboxylic acid, having just 1 carbon, is a volatile (vapor pressure is 42.71 hPa), weak (pKa 3.7) organic acid.[2,7] Sodium formate (CAS No. 141-53-7) is the sodium salt of formic acid.

Chemical and Physical Properties

Formic acid. Formic acid is a colorless to yellow, pungent liquid (molecular weight = 46.03 g/mol), and the following $\log K_{ow}$ value has been reported for formic acid at 23°C and pH = 7: −2.1.[3] Formic acid melts at 4°C and boils at 100.2°C (1,013 hPa). The density of formic acid is 1.2195 and it is miscible in water.[4]

Sodium formate. Sodium formate is a white, colorless powder with a molecular weight of 69.02 g/mol; it melts at 253°C, has a density of 1.968 g/mL, and is highly soluble in water. Formate anion has a $\log K_{ow}$ of −4.27.[4]

[1] Cosmetic Ingredient Review Scientific Analyst/Writer, Cosmetic Ingredient Review, Washington, DC, USA
[2] Cosmetic Ingredient Review Chemist, Cosmetic Ingredient Review, Washington, DC, USA
[3] Cosmetic Ingredient Review Expert Panel Member, Cosmetic Ingredient Review, Washington, DC, USA
[4] Former Director, Cosmetic Ingredient Review, Washington, DC, USA

Corresponding Author:
Lillian J. Gill, Cosmetic Ingredient Review, Suite 1200, 1620 L Street, NW, Washington, DC 20036, USA.
Email: cirinfo@cir-safety.org

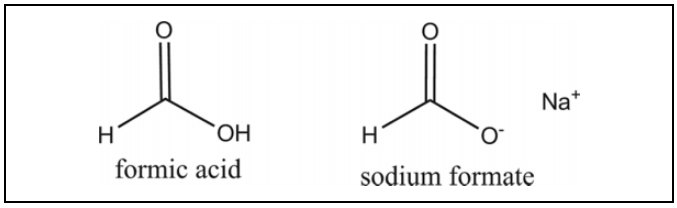

Figure 1. Structures of formic acid and sodium formate.

Method of Manufacture

Formic acid. The primary method of formic acid manufacture is via acid hydrolysis of methyl formate. Some other methods of production of formic acid are as follows[5]: (1) treatment of sodium formate and sodium acid formate with sulfuric acid at low temperatures (vacuum distilled) and (2) as a by-product in the manufacture of formaldehyde and acetaldehyde.

Sodium formate. Sodium formate is a by-product in the synthesis of polyols such as pentaerythritol. However, it is also produced directly from the catalyzed reaction of sodium hydroxide and carbon monoxide.[4]

Composition/Impurities

Formic acid. The specifications for technical grade formic acid are as follows: acetic acid (<0.8% weight), chlorides (20 ppm), heavy metals (<5 ppm), iron (3 ppm), and sulfates (10 ppm). Except for the absence of acetic acid, commercial grade formic acid has the same specifications.[3]

Ultraviolet Absorption

The absorption spectrum of formic acid ranges from ≤200 nm to 267.2 nm, with an absorption maximum at approximately 210 nm.[6]

Use

Cosmetic

Formic acid functions as a fragrance ingredient, preservative, and pH adjuster in cosmetic products.[2] Sodium formate also functions as a preservative in cosmetic products.

The safety of formic acid and sodium formate in this safety assessment is evaluated based on the data received from the US Food and Drug Administration (FDA) and the cosmetic industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported under the cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by industry in response to surveys conducted by the Personal Care Products Council (Council) on the maximum reported use concentrations, by product category. According to information supplied to the FDA VCRP in 2013, formic acid and sodium formate were being used in 31 and 9 cosmetic products, respectively.[7] These data are summarized in Table 1. Results from a survey of ingredient use concentrations provided by the Council (also included in Table 1) in 2012 indicate that formic acid and sodium formate were being used at concentrations up to 0.2% and 0.34%, respectively, with hair care products accounting for the highest use concentrations of both ingredients.[8]

Cosmetic products containing formic acid or sodium formate may be applied to the skin and hair or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Formic acid and its sodium salt are included on the list of preservatives allowed in cosmetic products marketed in the European Union, with a maximum use concentration of 0.5% (expressed as acid).[9]

Formic acid is used in products that are sprayed (reported maximum use concentration = 0.2% in an aerosol hair spray). Because formic acid is used in products that are sprayed, it could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared with pump sprays.[10,11] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[12,13]

Noncosmetic

Formic acid. Formic acid is listed as a component of synthetic flavoring substances and adjuvants that are permitted by the FDA for direct addition to food for human consumption.[14] The FDA has also determined that it may be safely used as a food additive in feed and drinking water consumed by animals.[15] Formic acid, as a constituent of paper and paperboard used for food packaging, is included on the list of indirect food substances affirmed as generally recognized as safe (GRAS) by the FDA.[16] According to the Food Chemicals Codex, formic acid is used as a flavoring agent and preservative.[17]

Formic acid had been used as an active ingredient in over-the-counter drug products (ie, pediculicide drug products). However, FDA has determined that there are inadequate data to establish general recognition of safety and effectiveness of this ingredient for use in pediculicide drug products.[18]

The safety of formic acid as a food flavor ingredient for the consumer has been assessed by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives, who proposed an acceptable daily intake value of 0.3 mg/kg. The European Food Safety Authority Panel on Additives and Products or Substances Used in Animal Feed concluded that formic acid is considered safe for all animal species at the use level proposed for food flavorings.[19]

Table 1. Frequency and Concentration of Use According to Duration and Type of Exposure.[7,8,a,b]

	Formic acid		Sodium formate	
	Number of uses	Conc (%)	Number of uses	Conc (%)
Totals/conc range	31	0.003-0.2	9	0.0005-0.34
Duration of use				
Leave on	9	0.2	NR	NR
Rinse off	21	0.003-0.08	NR	0.0005-0.34
Diluted for (bath) use	1	NR	NR	NR
Exposure type				
Eye area	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR
Incidental inhalation—sprays	NR	0.2	NR	NR
Incidental inhalation—powders	NR	NR	NR	NR
Dermal contact	4	0.006-0.02	NR	0.0005
Deodorant (underarm)	NR	NR	NR	NR
Hair—noncoloring	27	0.003-0.2	9	0.2
Hair—coloring	NR	0.03	NR	0.34
Nail	NR	NR	NR	NR
Mucous membrane	4	0.006-0.02	NR	NR
Baby products	NR	NR	NR	NR

Abbreviations: Conc, concentration; NR, not reported.
[a]Totals = rinse-off + leave-on product uses.
[b]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not be equal to sum total uses.

Sodium formate. Sodium formate is classified by the FDA as an indirect food substance affirmed as GRAS and is listed as a component of adhesives that may be used as components of articles intended for use in packaging, transporting, or holding food for human consumption.[20,21]

Toxicokinetics

Formic acid is a common metabolic intermediate and can be metabolically oxidized to carbon dioxide.[1] Formic acid oxidation in vivo occurs in the liver and erythrocytes, primarily via the folate-dependent pathway. Mice and rats metabolize formic acid more rapidly than do monkeys and humans. It was noted that the differences in the rate of formic acid oxidation between species seem to depend mainly on hepatic tetrahydrofolate concentrations. Additionally, according to another reference, rodents have high tetrahydrofolate and 10-formyl tetrafolate levels, which allow them to rapidly metabolize formate to CO_2.[22] The formic acid half-life in human blood is approximately 55 minutes.[1]

Oral

Formic acid

Animal. Four male New Zealand rabbits received 5 oral doses (gavage) of formic acid (adjusted to pH 7.4; 300 mg/kg body weight/day) on 5 consecutive days.[3] The fifth dose was administered as ^{14}C-radiolabeled formate (specific activity = 58 mCi/mmol). The clinical signs observed were described as very deep respiration during the first 12 hours postdosing. The urinary excretion time course of ^{14}C-radiolabeled formate was described as exponential, and 4.5% of the administered dose was excreted within 40 hours postdosing. For chemically determined formic acid, urinary excretion was more rapid. Results relating to toxicity are included in the Repeated Dose Toxicity section (Oral studies) of this report.

Human. In a study involving 16 participants (ages not stated), formic acid (2 g) was ingested.[4] The urinary excretion of formate, measured in 24-hour urine samples, under normal background conditions was ~13 mg/24 h. In 3 additional experiments (the same participants), formic acid was ingested as a 0.4% aqueous solution, and the total urinary excretion of formic acid was 3.81% of the dose within 24 hours. In another experiment involving the same 16 participants, plasma formate levels were examined following ingestion of 1,000 and 2,000 mg formic acid. Formic acid was rapidly absorbed and reached peak levels within 10 to 30 minutes. Overall, it was concluded that formic acid was rapidly absorbed.

Sodium formate

Animal. Six Wistar rats (sex not stated) received sodium formate in drinking water continuously for 1.5 years.[4] Sodium formate was administered at a concentration of 1% (equal to 274 or 185 mg/animal calculated as formic acid). Urinary excretion of formic acid at the end of 1.5 years was ~13.8% of the administered dose in 24-hour urine. Results relating to toxicity in this study are included in the section on Repeated Dose Toxicity (Oral studies). Results relating to carcinogenicity are included in the Carcinogenicity section of the report.

In a study involving dogs (number and breed not stated), sodium formate was administered, with meat, at a dose of 5 g/d for 12 days.[4] Approximately 30% to 40% of the administered dose was excreted in 24-hour urine. Additional details were not included.

Human. In an oral feeding study involving 16 participants (age not stated), the following doses of sodium formate were ingested: 1,480, 2,960, and 4,400 mg (equivalent to 1, 2, or 3 g of formic acid).[4] Within 24 hours, 2.1% of the 1,480 mg dose was excreted as formate in the urine. At higher doses, there was a trend toward increased excretion as formate. Urinary excretion was described as rapid, considering that 65% and 84% of the formic acid excreted appeared in the urine within the first 6 hours after ingestion of 1,480 and 2,960 mg, respectively. Concentrations of formic acid had returned to control levels in urine samples at 12 hours after dosing with 1,480 and 2,960 mg sodium formate. It was noted that both the urine volume and pH were increased following ingestion of sodium formate.

In another study involving the same 16 participants, plasma formate levels were examined following ingestion of 2,960 and 4,400 mg sodium formate (equivalent to 2,000 and 3,000 mg formic acid). Formate was rapidly absorbed and reached peak levels within 10 to 30 minutes. The blood pH value remained largely unchanged. Plasma levels were examined in 2 participants dosed with 2,960 and 4,400 mg sodium formate, respectively. The plasma $t_{1/2}$ values were calculated to be 45 and 46 minutes, respectively. Overall, it was concluded that sodium formate was rapidly absorbed and rapidly eliminated.

Parenteral

Formic acid. Fifteen male New Zealand rabbits received 5 intravenous (IV; into ear vein) doses of formic acid (adjusted to pH 7.4; 100 mg/kg body weight/day) on 5 consecutive days.[3] The fifth dose was administered as ^{14}C-radiolabeled formate (specific activity = 58 mCi/mmol). A control group (treatment details not given) was also included in the study. The animals were killed at 1, 2, and 20 hours after administration of the fifth dose. Tissues were prepared for light and electron microscopy. Formic acid distributed rapidly after IV injection. Peak levels were observed at 1 hour postinjection in all tissues, except brain; a rapid decrease in tissue concentrations was noted within 20 hours. The radiolabel measurements were always associated with higher tissue concentrations of formic acid, when compared to chemically determined formic acid concentrations. The authors interpreted the difference between the chemically determined concentrations and the higher radiolabel to reflect an accumulation of formic acid. However, the decline within 20 hours after dosing was rapid and accumulation was regarded to be unlikely. Negative controls, which could have provided background levels, were not included in the study. Histopathological findings are included in the Repeated Dose Toxicity (Parenteral) section of this report.

Sodium formate. Groups of 4 normal and NEUT2 homozygous mice (between 3 and 10 months old; number not stated) were injected intraperitoneally (IP) with [^{14}C] sodium formate at a dose of 5 mg/kg (≈2 μmol; specific activity ≈ 0.06 μCi/μmol) or 100 mg/kg (≈44 μmol; specific activity ≈ 0.002 μCi/μmol).[23] NEUT2 homozygous mice are deficient in cytosolic 10-formyltetrahydrofolate dehydrogenase. The test substance was administered at a dose volume of 100 μL/30 g body weight. Expired air from individual mice was bubbled through methanol:ethanolamine (2:1, vol/vol) to trap $^{14}CO_2$. The counting efficiency for ^{14}C was >85%. Both normal and NEUT2 homozygous mice oxidized 52.6% ± 1.7% and 27.6% ± 2.5% of the low sodium formate dose (≈2 μmol) to $^{14}CO_2$, respectively, over the 60-minute time course. The oxidation of sodium formate was rapid in normal mice; however, NEUT2 homozygous mice had a much diminished response. At the high sodium formate dose (≈44 μmol), rapid oxidation of sodium formate to CO_2 occurred at identical rates in normal and NEUT2 homozygous mice. Normal and NEUT2 homozygous mice oxidized 65.5% ± 2.9% and 66.0% ± 1.2% of the high dose to $^{14}CO_2$. Therefore, a difference in the rate of sodium formate oxidation between normal and NEUT2 homozygous mice was observed only after the administration of the low dose (5 mg/kg) of sodium formate in this study.

Ex Vivo Study

Formic acid. The transfer of formic acid across the placenta was studied using a dual perfusion procedure involving a single placental lobule ex vivo.[24] Immediately after elective cesarean sections, term placentas were obtained from healthy mothers with uncomplicated pregnancies. For each placenta, a vein/artery pair supplying a clearly identifiable cotyledon was chosen for cannulation, and maternal and fetal circulations were established within 30 minutes of delivery. After a 1-hour control period, formic acid (2 mM) was introduced into the maternal circulation with (n = 4) or without folate (1 μM; n = 4) and was allowed to equilibrate for 3 hours. At the end of each perfusion, the lobule was isolated; perfused and unperfused tissue from the same placenta was homogenized and then centrifuged. The supernatant was removed and analyzed for formic acid using gas chromatography–flame ionization. The area under the curve was calculated using the trapezoidal rule. Formic acid transferred rapidly from the maternal to the fetal circulation, and transfer was not altered with the addition of folate. When compared to the control period, there was a significant decrease in human chorionic gonadotrtopin (hCG) secretion ($P = 0.03$) after the addition of formic acid. The decrease in hCG secretion was mitigated after the addition of folic acid to the perfusate. The authors concluded that formic acid rapidly transfers across the placenta and, thus, has the potential to be toxic to the developing fetus. They also concluded that formic acid decreases hCG secretion in the placenta, which may alter steroidogenesis and differentiation of the cytotrophoblasts and that this adverse effect can be mitigated by folate.

Toxicology

Acute Toxicity

Inhalation

Formic acid. The acute inhalation 4-hour median lethal dose (LC_{50}) for formic acid vapor in male and female Sprague

Dawley rats (ages not stated) was 7.4 mg/L in a study conducted in a manner comparable to the Organisation for Economic Co-Operation Development (OECD) TG 403 protocol.[22] The animals (10 rats per sex per concentration) were exposed to formic acid at analytical concentrations of 2.82, 6.6, 8.08, 10.6, and 14.7 mg/L in a whole-body inhalation chamber (volume = 200 L). This was followed by a 14-day observation period. None of the animals dosed with 2.82 mg/L died. Mortality increased rapidly between concentrations of 6.6 and 8 mg/L, and 100% mortality occurred at concentrations ≥10.6 mg/L. Clinical signs in all treated groups included closed eyelids, discharge and corrosion of the nose and eye, salivation, corneal opacity, loss of pain reflex, dyspnea, noisy breathing, apathy, hunched posture, unsteady gait, and decreased body weight. Among these are clinical signs associated with respiratory tract irritation. Animals that died had dilated and hyperemic hearts and inflated lungs.

Eight-week-old Wistar rats (males and females; 3 per sex) were exposed for 10 minutes to saturated atmospheres (83.16 mg/L) of formic acid in cylindrical glass tubes. Each glass tube contained 3 rats. All animals died overnight. Clinical signs observed during exposure included ocular and nasal irritation, gasping, increased salivation, and opaque pupils.[22]

Groups of 6 or 12 Sprague Dawley rats (males and females, 7-10 weeks old) were exposed to formic acid while restrained in exposure tubes.[3] The exposure groups were as follows: 10% formic acid (19.5 mg/L of air, 7-hour exposure) for 12 rats, 25% formic acid (19.9 or 21.5 mg/L) for a group of 12 rats (3-hour exposure) and for a group of 6 rats (7-hour exposure), and 50% formic acid (no data on mg/L of air) for 3 groups of 12 rats (0.5-hour, 1-hour, and 3-hour exposures, respectively) and for a group of 6 rats (7-hour exposure). Exposure concentrations were not measured but were calculated from the air flow and the amount of formic acid released during a given experiment. Additional details were not provided. Exposures were followed by a 14-day observation period. One of the 6 rats exposed to 25% formic acid for 7 hours died, but there were no deaths in the 10% formic acid exposure group (12 rats, 7-hour exposure). Deaths due to 50% formic acid exposure were as follows: 1 of 12 rats (after 1 hour), 2 of 12 rats (after 3 hours), and 5 of 6 rats (after 7 hours). These data indicate a concentration-related increase in mortalities.

Clinical signs observed in the 50% formic acid exposure group included corrosion of the nose and eyes, corneal opacity, loss of pain reflex, dyspnea, respiration sounds, flatulence, trembling, and unsteady gait. Except for corrosion of the eyes, flatulence, trembling, and unsteady gait, the preceding signs were also observed after exposure to 25% formic acid. None of the signs described was observed in the 10% formic acid exposure group. Gross pathology findings reported for the 50% formic acid exposure included heart dilatation and hyperemia and inflated lungs in animals that died. There were no gross pathology findings in animals exposed to either of the 3 concentrations, which were killed at the end of the observation period.[3]

The acute inhalation toxicity of formic acid was studied using 3 groups of 12 Wistar rats (6 males, 6 females/group; ages not stated).[3] The 3 groups were exposed (nose only) to a dose defined as a saturated atmosphere at 20°C for 3, 10, and 116 minutes, respectively. Exposure was followed by a 14-day observation period, after which surviving animals were killed. The mortality incidence was 75% after 3 minutes of exposure, and all remaining animals had died after a 10-minute exposure period. Most deaths occurred within 28 hours after exposure. The clinical signs reported included blood in urine, dyspnea, respiration sounds, unsteady gait, trembling, loss of pain reflex, corrosion of the nose, and corneal opacity. Gross pathology findings, only in animals that died, were as follows: dark red to black areas and blood in lungs, brown-colored trachea (3 rats), severely distended stomach (in rats exposed for ≥10 minutes), blood in urinary bladder (2 females), and markedly reddened intestinal tract.

Sodium formate. The acute inhalation toxicity of sodium formate was evaluated using groups of Sprague Dawley rats (9-10 weeks old; 5 males, 5 females/group).[4] The solid test material was milled to a fine powder that was aerosolized. The animals were exposed to the aerosol in a 100-L plexiglass exposure chamber. The flow rate was 35 L/min, and this was considered to have provided the maximum level of dust practically attainable, given the equipment that was being used. The dust concentration in the air was determined gravimetrically to be 0.67 mg/L (nominal concentration based on material loss = 10 mg/L), and the dust had a mass mean aerodynamic diameter (MMAD) of 5.4 ± 2.4 μm. The aerosol was considered respirable, and the animals were exposed for 4 hours (chamber concentration of test material = 0.5-0.86 mg/L). The animals were singly housed during exposure and doubly housed during the 14-day observation period. Surviving animals were killed at the end of the observation period and submitted for gross necropsy. None of the animals died during exposure or during the 14-day observation period. Adverse clinical signs, which were described as minimal, included decreased activity, lacrimation and nasal discharge, and slight transient reduction in body weight gain. There were no treatment-related findings at gross necropsy. The acute inhalation LC_{50} was >0.67 mg/L.

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/kg body weight formic acid (undiluted) via oral gavage according to the OECD TG 401 protocol. The test substance was administered at a dose volume of 0.41 to 0.82 mL/kg, followed by a 14-day observation period. The acute oral LD_{50} for formic acid in the rat was 730 mg/kg body weight.[22] Body weight gain decreased in a dose-related manner. Severe clinical signs were noted at ~30 minutes postdosing and included hunched posture, dyspnea, bloody nose, and blood in the urine. Except for 1 animal, these symptoms subsided and were not observed at the end of the observation period. Gross pathology revealed hyperemia of the stomach and mottled livers and kidneys. Discoloration of the kidneys and pancreas were also observed.

An LD_{50} of 1,830 mg/kg body weight was reported for rats (number and strain not stated) in an acute oral toxicity study of formic acid. Study details were not included.[25]

Sodium formate. The acute oral toxicity of sodium formate was evaluated in a study involving 45 mice (ages and strain not stated). An LD_{50} of 7,410 mg/kg body weight was reported. Additional study details were not included.[25]

Dermal

Sodium formate. The acute dermal toxicity of sodium formate (in 0.5% carboxymethylcellulose) was evaluated using Wistar rats (8-14 weeks old; 5 males, 5 females).[4] The test material (dose = 2,000 mg/kg body weight) was applied, under a semi-occlusive dressing, to clipped dorsal skin for 24 hours. Removal of the dressing was followed by a 14-day observation period. Application sites were examined for skin reactions at 30 to 60 minutes after removal of the dressing. Necropsy with gross pathology examination was performed at the end of the observation period. None of the animals died, and there were no treatment-related changes in body weight gain. At gross pathological examination, there was no evidence of systemic or local signs of toxicity or organ toxicity. It was concluded that the LD_{50} was >2,000 mg/kg body weight.

Parenteral

Formic acid. An LD_{50} of >300 mg/kg was reported for formic acid in an acute subcutaneous (SC) toxicity study involving rabbits (number and strain not stated).[26] Study details were not provided.

Sodium formate. In an acute IV toxicity study involving 50 mice (strain not stated), an LD_{50} of $\sim$807 mg/kg body weight was reported.[4]

Free radical generation in Fischer male rats with acute sodium formate (2 g/kg body weight, injected IP) poisoning was studied.[27] Spin trapping and electron spin resonance spectroscopy was used to detect free radical formation in Fischer male rats. This technique was used with α-(4-pyridyl-1-oxide)-*N*-*t*-butylnitrone, which reacts with free radical metabolites to form radical adducts. Such radical adducts were detected both in bile and urine, and the free radical concentration in the bile was $\sim$1.2 μM.

Repeated Dose Toxicity

According to the OECD's Screening Information Data Set report on formic acid and formates, repeated dose toxicity studies on these chemicals must be interpreted with caution because rodents have high tetrahydrofolate and 10-formyltetrafolate dehydrogenase levels, which allow them to rapidly metabolize formate to CO_2.[22] The authors also noted that humans have much lower levels of this coenzyme and enzyme and, therefore, might be more sensitive to formate exposures.

Inhalation

Formic acid. Ten male Wistar rats were exposed (inhalation) to formic acid at a concentration of 0.037 mg/L, 6 h/d for 3 to 8 days.[3] A concurrent vehicle control group was also included in the study. There was no evidence of clinical symptoms in animals tested. When compared to the control group, the glutathione concentration was decreased in the kidneys ($P < 0.05$) on days 3 and 8 of exposure and in the liver ($P < 0.05$) only on day 3. There were no treatment-related effects on cerebral superoxide dismutase activity, and the same was true for the following liver microsomal enzyme activities: cytochrome P450, cytochrome C reductase, and *p*-nitrophenol glucuronide transferase. Liver ethoxycoumarin deethylase activity was increased ($P < 0.05$) on day 8. Kidney cytochrome P450 activity was decreased ($P < 0.05$) on days 3 and 8, and kidney ethoxycoumarin deethylase activity was decreased ($P < 0.05$) on day 3.

Oral

Formic acid. In a toxicokinetic study, 4 male New Zealand rabbits received 5 oral doses (gavage) of formic acid (300 mg/kg body weight/day) on 5 consecutive days.[3] The fifth dose was administered as ^{14}C-radiolabeled formate (specific activity = 58 mCi/mmol). The clinical signs observed were described as very deep respiration during the first 12 hours postdosing. Results relating to toxicokinetics (oral studies) are included in the Toxicokinetics section.

Sodium formate. Six Wistar rats (sex not stated) received sodium formate in drinking water continuously for 1.5 years.[25] Sodium formate was administered at a concentration of 1% (equal to 274 mg/animal formate or 185 mg/animal calculated as formic acid). A control (unspecified) group of animals was also included in the study. Toxicity was not observed in any of the animals tested. Additional details relating to this study were not available. Results relating to urinary excretion of the administered dose are included in the section on Toxicokinetics (Oral studies). Results relating to carcinogenicity are included in the Carcinogenicity section.

Dermal

Formic acid and sodium formate. Formic acid (pH 5.5) was applied topically to shaved skin (2×2 cm^2 site above the tail area; volume not stated) of 8 Fischer 344/N female rats daily for 2 weeks.[28] Sodium formate was applied to another group of 8 rats according to the same procedure. A control group of 8 rats was treated with saline. After 2 weeks, the rats treated with formic acid, sodium formate, or saline appeared healthy and without evidence of systemic toxicity. The total hair follicle count was lower in the test groups when compared to the saline control group; however, the difference was not statistically significant. Results relating to skin irritation are included in the Skin Irritation and Sensitization section.

Parenteral

Formic acid. In a toxicokinetic study, 15 male New Zealand rabbits received 5 IV (into ear vein) doses of formic acid (adjusted to pH 7.4; 100 mg/kg body weight/day) on 5 consecutive days.[3] The fifth dose was administered as ^{14}C-radiolabeled formate (specific activity = 58 mCi/mmol; no further details). The animals were killed at 1, 2, and 20

hours after administration of the fifth dose. Tissues were prepared for light and electron microscopy. Calcium deposits were observed in the kidneys (cortex), liver, heart (endocardium), and brain. However, electron microscopy did not reveal changes in the subcellular structures (ie, mitochondria, endoplasmic reticulum, or lysosomes) after dosing with formic acid for 5 days.

Ocular Irritation

Formic acid. Formic acid solutions (0.01 mL) were instilled into 1 eye of each male and female rat or mouse. Wistar rats (3 males, 3 females; 5-6 weeks old) and ddY mice (3 males, 3 females; 5-6 weeks old) were used.[29] Saline (control) was instilled into the other eye. Reactions in 1 eye were observed with a slit lamp for 1 week after instillation (frequency of observations not stated). Formic acid, 5% to 6% (pH < 2), induced ocular irritation, and these were the minimum concentrations at which positive effects were observed.

Sodium formate. The ocular irritation potential of sodium formate was evaluated using 6 New Zealand white rabbits (3 males, 3 females; at least 8 weeks old).[4] The test material (0.1 mL, powder) was instilled into the left eye (lower conjunctival sac) of each animal. The right eye served as the control. Reactions were scored at 1, 24, 48, and 72 hours and 7, 10, 14, and 17 days postinstillation. Moderate to severe conjunctival irritation was observed in all 6 rabbits, and conjunctival necrosis was observed in 4 of the 6 rabbits. All reactions had cleared by day 17.

Skin Irritation and Sensitization

Formic acid. Primary skin irritation tests (open patch tests) were performed using the following species: Wistar rats (3 males, 3 females; 5-6 weeks old), ddY mice (3 males, 3 females; 5-6 weeks old), and 3 Hartley guinea pigs.[29] Test solutions (1 mL/kg or 1 g/kg) were applied once, unoccluded (3 × 4 cm [rats]; 1 × 2 cm [mice]) to shaved skin of the back. For guinea pigs (and rats for comparison), test solutions (0.01 mL) were applied as 4 occluded circles (each 1.5 cm in diameter) on shaved skin of the back. Distilled water served as the control. Inflammatory reactions were observed for 1 week after application. Formic acid (10%-12%) induced skin irritation. These were the minimum concentrations at which positive effects were observed.

An intradermal test was performed using mice, rats, and guinea pigs (the same groups and strains as above). The test solution (0.01 mL) was injected intradermally at 1 spot on shaved skin of the backs of rats and mice. Hartley guinea pigs (and rats for comparison) were injected intradermally with the test solution, 0.01 mL into 4 spots on shaved skin of the back. Saline served as the control. Skin reactions were observed for 1 week after application. Formic acid (2%-3%) induced skin irritation. These were the minimum concentrations at which positive effects were observed.[29]

The ability to cause skin corrosion, expressed as the lowest observed effect concentration (LOEC) in rabbits, was determined for a series of carboxylic acids.[30] By means of partial least squares analysis, these values are related to a multivariate set of chemical descriptor variables. The developed multivariate quantitative structure–activity relationship was shown to exhibit predictability. Thus, predictions were calculated for a set of 30 biologically nontested carboxylic acids. The developed quantitative structure–activity relationship (QSAR) was introduced and discussed from a multivariate and statistical experimental design perspective. Formic acid ($\log P = -0.54$) was predicted to have an LOEC of 2.3 M.

The QSARs were derived relating the skin corrosivity data of organic acids, bases, and phenols to their log(octanol/water partition coefficient), molecular volume, melting point, and pK plots.[31] Because the $\log P_{ow}$ values were calculated using the CHEMICALC system, they were referred to as $\text{clog}P_{ow}$ values. Data sets were evaluated using principal components analysis. Plots of the first 2 principal components of each parameter, which broadly model skin permeability and cytotoxicity, for each group of chemicals showed that the analysis was able to discriminate well between corrosive and noncorrosive chemicals. It was noted that the derived QSARs should be useful for the prediction of the skin corrosivity potential of new or untested chemicals. The authors noted that acids with lower $\text{clog}P_{ow}$ values, larger molecular volumes, or higher melting points (all features associated with lower skin permeability) were less likely to be found in corrosive areas of the plots, unless they are particularly acidic. Short-chain aliphatic carboxylic acids, such as formic acid (weak acid), was classified as corrosive by virtue of its relatively high skin permeability ($\text{clog}P_{ow} = -0.641$).

An in vitro skin corrosivity test on formic acid (33.9%) was performed using the Skin2 cutaneous model ZK 1300/ZK 1350, a 3-dimensional human skin tissue consisting of dermal, epidermal, and corneal layers (9 × 9 mm tissue samples used).[32] Formic acid (15 μL) was dispensed onto glass coverslips. The epidermal side of the skin cultures was then placed on the test material for an exposure time of 10 seconds. Distilled water alone served as the untreated control. The effect of formic acid on cell viability was assessed using the 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. This is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide by mitochondrial succinate dehydrogenase. The percentage viability of the treated skin cultures was calculated as a percentage of the untreated control values. For classification of corrosive/noncorrosive chemicals with the model ZK 1350 corrosivity assay, 80% viability was used as the cutoff value (<80% viability = corrosive; >80% viability = noncorrosive). The concordance between the in vivo and in vitro corrosive or noncorrosive classification was approximately 70% for corrosive and noncorrosive combined. Formic acid (33.9%) was classified as noncorrosive.

The skin sensitization potential of formic acid (0.5 mL under occlusive patch) was evaluated in the Buehler test

(OECD TG 406 test protocol) using twenty 6-week-old guinea pigs.[3] Ten guinea pigs served as controls. Formic acid was tested at concentrations of 7.5% and 2% during induction and challenge phases, respectively. There were no skin reactions in test or control animals at 24 or 48 hours after challenge. In a pretest (details not included), the minimum irritant concentration of formic acid was determined to be 5% and the maximum nonirritant concentration was determined to be 2%.

Sodium formate. The skin irritation potential of sodium formate (in physiological saline) was evaluated using 4 rabbits (3 males, 1 female; ages and strain not stated).[4] The test material was applied to 4 abraded sites per animal (left and right, front and back) under an occlusive patch that remained in place for 24 hours. Reactions were scored at 72 hours after patch removal. Skin irritation was not observed in any of the animals.

Formic acid and sodium formate. Two groups of 8 female Fischer 344/N rats were treated with formic acid (pH 5.5) and sodium formate, respectively. During a 2-week daily application period, each test substance (volume not stated) was applied topically to a 2 × 2 cm^2 area of skin above the tail area.[28] A control group of 8 rats was treated with saline according to the same procedure. Neither redness nor swelling at the application site was observed in test or control groups. Results relating to repeated dose toxicity (dermal) are included in that section.

Case Reports

Systemic toxicity developed in a 3-year-old girl who was exposed to 90% concentrated formic acid while playing near a leather-tanning workroom.[33] The child was burned over 35% of her total body surface area. She presented with profound metabolic acidosis and a serum formate level of 400 μg/mL. The child was successfully treated with hemodialysis, IV bicarbonate, and supportive measures.

Forty-two passengers (24 males and 18 females; mean age = 32 years) acquired formic acid burns following a tanker and bus collision.[34] In the first 24 hours, all 42 patients had respiratory symptoms (cough, chest tightness, and breathlessness) induced by inhaling the formic acid fumes (85% formic acid). After 24 hours, only 7 patients continued to have respiratory distress attributable to the development of pulmonary edema, and 2 of them needed assisted ventilation. One patient died of respiratory failure as a result of severe pulmonary edema. The skin burns were superficial in 30 (71.43%) and deep in 12 (28.57%) patients. Corneal epithelial defects healed in 50 (60.97%) eyes within 1 week of treatment. Two patients developed progressive corneolimboscleral ulceration; 1 patient underwent conjunctivo-tenoplasty, and another needed the application of a glued on, rigid gas permeable contact lens to the ulcerating corneal stroma.

A 39-year-old male sustained an accidental chemical injury while transporting 98% formic acid.[35] The chemical was accidentally sprayed in the face, resulting in a 3% total body surface area burn that was superficial and second degree in depth. Dyspnea was also reported initially and at 2 weeks after discharge from the hospital. Spirometry results 2 weeks after the injury revealed an improvement in vital capacity, forced expiratory volume, and forced expiratory function, all consistent with improved pulmonary function.

A man was accidentally splashed with 80% formic acid solution in both eyes and the face while at work. Both eyes were flushed with water within 10 seconds and irrigation was continued.[36] At 30 minutes after the accident, the eyes were irritated and chemotic and the corneal surface appeared irregular with debris. Vision was limited to counting fingers at 0.5 m. Treatment of both eyes with an antibiotic followed, and on the following day, vision had improved to 3 m, while chemosis, subconjunctival hemorrhaging, and limbal swelling were visible. The high stromal penetrability of formic acid resulted in acid penetration through the right cornea, leading to extensive stromal scarring and endothelial damage. In vivo confocal microscopy of the central cornea 8 months following the injury revealed a normal-appearing epithelium bilaterally. One year after the accident, dendrites or sprouting subbasal nerves were visible in the right cornea and long, parallel subbasal nerves were observed in the left cornea.

Reproductive and Developmental Toxicity

Oral

Sodium formate. A single oral dose of sodium formate (750 mg/kg body weight) was administered, by gavage, to a group of 14 CD-1 mice on day 8 of gestation.[37] The administered dose yielded a formate concentration of 1.05 mM in the plasma and the decidual swellings contained 2 mmol/kg. The plasma concentration of formate reached a peak at approximately 8 hours. Another group of 14 mice served as the untreated control group. The dams were killed on day 10 or day 18 of gestation, and the fetuses were examined for neural defects. Any evidence of maternal toxicity was not reported in this study. When the test and control groups were compared, the incidence of neural defects was not found to be treatment related. Therefore, it was concluded that sodium formate had no effect on the incidence of neural tube defects.

Sodium formate was administered to pregnant Wistar rats via gavage at 0 (24 rats), 59 (25 rats), 236 (23 rats), and 945 (24 rats) mg/kg body weight per day during gestational days 6 to 19. The animals were 70 to 84 days old at gestational day 0. The study was performed in accordance with the OECD 414 study protocol.[22] There were no mortalities, clinical signs of toxicity, or body weight differences among the groups. The mean gravid uterus weight of the treated animals was not influenced by the treatment, and there were no findings in the dams at necropsy. There were no substance-related and/or biologically-significant differences among the test groups in the conception rate, the mean number of corpora lutea and implantation sites, or in the values calculated for the pre- and postimplantation losses, as well as the number of resorptions and viable fetuses.

Examination of the fetuses showed that the sex distribution was not affected and that the weight of placentae and the fetal weight were comparable between the treated groups and the control group. There was 1 external malformation exclusively in the high-dose fetuses (1 of 212 fetuses), but this was within the historical control range. There were no external variations in any of the groups. Two soft tissue variations (uni- or bilateral dilatation of the renal pelvis with or without dilated ureter) were detected in each group, including the controls, without any dose-dependent relationship. No skeletal variations were seen in treated animals. The observed pattern of skeletal variations was not different from that seen in the historical controls, and the incidence was not dose related and did not suggest a treatment-related effect. The No-observed-adverse-effect-level (NOAEL) was 945 mg/kg body weight per day, the highest dose tested, for maternal toxicity, embryotoxicity, and teratogenicity.[22]

The developmental toxicity of sodium formate was evaluated in Himalayan rabbits (13-21 weeks old; groups of 25) in accordance with the OECD TG 414 protocol.[22] The test substance was administered as an aqueous solution (by gavage; dose volume = 10 mL/kg) at doses of 100, 300, and 1,000 mg/kg body weight on gestation days 6 to 28. A third group served as the untreated control. Neither mortalities nor clinical signs were observed in any of the groups. The following non-statistically significant increases (all within the historical control range) in the following parameters were reported: postimplantation losses of 13.0% and 13.9% at doses of 300 and 1,000 mg/kg body weight, respectively, compared to 7.3% in controls, and the total incidence of external, skeletal, and soft tissue malformations was 6.7% at 1,000 mg/kg body weight/day compared to 3.8% in controls. The incidence of total variations (external, skeletal, and soft tissue) was 66.1% to 67.2% in the treated groups compared to 58.0% in controls. The NOAEL for maternal toxicity and reproductive effects was 1,000 mg/kg body weight/day.

In Vitro

Formic acid. The effect of formic acid on embryonic development in vitro was evaluated using embryos from pregnant Sprague Dawley rats.[38] Rat embryos (approximately 10 somites) were explanted during the afternoon of day 10 of pregnancy and cultured in rat serum. Formic acid (in water) was added to the cultured embryos at concentrations ranging from 0.141 to 1.055 µL formic acid per mL of serum (3.74-27.96 µmol formic acid per mL of serum). The no-effect concentration for formic acid was 3.74 µmol/mL. The pH of this serum at the end of the culture period was 7.28 compared to 7.38 for serum from the controls. The next highest level tested (18.66 µmol/mL) had lowered the pH to 6.94 at the end of the culture period. This concentration of formic acid was associated with severe reductions in all parameters of growth and development, including inhibition of yolk sac blood vessel development.

Formic acid and sodium formate. The developmental toxicity of formic acid in whole embryo cultures in vitro was evaluated.[39] Embryos were obtained from pregnant CD-1 mice (Cr1: CD-1 [ICR] BR strain) and pregnant Sprague Dawley rats (Cr1: CD [SD] BR strain). Embryos were explanted on the morning of day 8 (mice) or the afternoon of day 9 (rats) of gestation. Rat embryos with an intact visceral yolk sac, ectoplacental cone, and amnion were pooled in culture medium and exposed to formic acid at the following concentrations (48-hour incubation period): 0, 0.14, 0.27, 0.54, 0.81, or 1.08 mg formic acid/mL of culture medium (0, 2.95, 5.9, 11.8, 17.6, or 23.5 mM formic acid). Rat embryo cultures were also exposed to sodium formate at the following concentrations: 0, 0.2, 0.4, 0.8, 1.2, 1.6, or 2.0 mg formic acid/mL of culture medium (0, 2.95, 5.9, 11.8, 17.7, 23.5, or 29.4 mM sodium formate). Mouse embryos were exposed to the following concentrations of formic acid (24-hour incubation period): 0, 0.27, 0.54, 0.81, 1.6 or 2.0 mg formic acid/mL of culture medium (0, 5.9, 11.8, 17.6, 34.8, or 44 mM formic acid). Mouse embryo cultures were also exposed to sodium formate at the following concentrations: 0, 0.4, 0.8, 1.6, 2.0, or 3.0 mg formic acid/mL of culture medium (0, 5.9, 11.8, 23.5, 29.4, or 44.1 mM formic acid). Crown–rump length, developmental score, head length, somite number, and yolk sac diameter were tested for concentration response using a regression model.

The exposure of rat and mouse embryos to formic acid or sodium formate for 24 hours resulted in a trend toward reduced growth and development. Furthermore, an increase in the number of abnormalities was observed at higher concentrations of exposure. A trend toward reduced growth and development with increasing concentrations was observed in rat embryos exposed for 48 hours to either formic acid or sodium formate. Both embryolethality and the incidence of abnormal embryos were also increased at the higher concentrations of exposure. The exposure-related anomalies observed in rat and mouse embryos exposed to formic acid or sodium formate were primarily open anterior and posterior neuropores (with less frequent incidence of rotational defects), tail anomalies, enlarged pericardium, and delayed heart development. The authors noted that the results of this study indicate that formic acid and sodium formate were embryotoxic and dysmorphogenic in a concentration-dependent manner in rat and mouse embryo cultures.[39]

Genotoxicity

Bacterial Assays

Formic acid. The genotoxicity of formic acid was evaluated in the Ames test (OECD TG 471 protocol) at doses up to 3,333 µg/plate, using the following *Salmonella typhimurium* strains with and without metabolic activation: TA97, TA98, TA100, and TA1535.[3] The highest dose was limited due to bacteriotoxicity. Formic acid was not genotoxic with or without metabolic activation.

In the SOS chromotest, the genotoxicity of formic acid was evaluated at concentrations up to 100 mM using *Escherichia coli* strain PQ37 with and without metabolic activation.[40,41]

The SOS chromotest is a colorimetric bacterial genotoxicity assay. Formic acid was nongenotoxic both with and without metabolic activation.

Sodium formate. The genotoxicity of sodium formate (51.5% aqueous solution) was evaluated in the Ames test at doses up to 5,000 μg/plate (with and without metabolic activation), using the following *S typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538. Results were negative, with and without metabolic activation, in all strains.[25]

Mammalian Assays

Formic acid. In the hypoxanthine guanine phosphoribosyl transferase (HGPRT) forward mutation test (OECD TG 476 protocol) using Chinese hamster ovary cells, formic acid was evaluated at concentrations ranging from 0.5 to 500 μg/mL with or without metabolic activation.[3] Ethyl methane sulfonate and methylcholanthrene served as positive controls. The negative controls were untreated cultures and Ham F12 culture medium. Formic acid did not induce forward mutations with or without metabolic activation.

In Vivo Study

Sodium formate. Studies were performed to evaluate DNA and hemoglobin adduct formation in groups of male Kunming mice (8-10 mice/group) dosed orally with sodium formate.[3] In the first experiment (dose–response study), groups received the following single oral doses of ^{14}C-sodium formate: 0.01, 0.1, 1, 10, and 100 mg/kg body weight. The animals were killed at 6 hours postdosing, and DNA was obtained from the liver (every 2 mice) and kidneys (every 4 mice). Hemoglobin was isolated from blood samples (from every 2 mice). Measurement of radioactivity was performed using accelerator mass spectrometry and liquid scintillation counting. The binding of ^{14}C-formate to DNA and hemoglobin was observed. Both DNA and hemoglobin adduct formation were linearly correlated ($r > 0.998$) with dose in the log/log plot over the entire dose range. The binding of ^{14}C-formate to liver DNA was slightly higher when compared to ^{14}C-formate binding to kidney DNA. DNA binding was ~100-fold higher than hemoglobin adduct formation.

In the second experiment (time course study), groups received a single dose of 100 mg/kg body weight. The animals were killed according to the following schedule: 2, 6, 24, 72, and 120 hours postdosing. The hemoglobin adducts peaked at 2 hours postdosing (~8 adducts/10^6 amino acid residues) and then rapidly decreased to ~2 adducts/10^6 amino acid residues between 2 and 6 hours postdosing. A plateau of ~12 adducts/10^6 amino acid residues was reached at 24 to 120 hours postdosing. Liver DNA adduct formation increased to ~8 adducts/10^4 nucleotides at 24 hours postdosing, having decreased to ~3 adducts/10^4 nucleotides at 72 hours. Formate–DNA adduct formation was ~100-fold higher than that of 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline and nicotine. Based on results from the 2 experiments, it was concluded that dose-dependent DNA and hemoglobin adduct formation was observed in mice after single oral doses of formic acid over the entire range of doses tested (0.01-100 mg/kg body weight).[3]

Inhibition of DNA Synthesis

CD-1 mouse embryos (from Crl: CD-1 ICR BR(CD1)) were cultured for 6 hours, in serum-free or serum-containing medium, in the presence of 2-methoxyacetic acid (MAA).[42] The rate of DNA synthesis (in disintegrations per minute [dpm]/μg DNA) was determined following exposure of the embryos to [^{3}H]thymidine during the final hour of culture. In serum-containing medium, 2-MAA (25-100 mM) inhibited [^{3}H]thymidine incorporation in a concentration-related fashion. The presence of serum had a profound impact on the amount of 2-MAA needed to inhibit [^{3}H]thymidine incorporation, considering that 25 mM 2-MAA was required to reduce DNA labeling by approximately 50%. In contrast, in serum-free medium, 50% inhibition was achieved with only 5 mM 2-MAA. When sodium formate (1 mM) was added concomitantly with 2-MAA (5 mM) to serum-free medium, complete protection against the inhibitory effect of 2-MAA on [^{3}H]thymidine incorporation into DNA (ie, DNA synthesis) was observed. Values for the incorporation of [^{3}H]thymidine into DNA by mouse embryos (serum-free medium) were as follows: control cultures (859 ± 120 dpm/μg DNA), 5 mM 2-MAA (375 ± 36 dpm/μg DNA), and 1 mM sodium formate + 5 mM 2-MAA (763 ± 55 dpm/μg DNA). Sodium formate alone had no effect on [^{3}H]thymidine incorporation into DNA.

Carcinogenicity

Inhalation

Formic acid. A large case–control study involving hundreds of occupational exposures and 19 hospitals was conducted to examine risk factors for lymphoma and myeloma.[43] Of the 4,576 eligible patients with cancer between 1979 and 1985, 3,730 (82%) were successfully interviewed. There were 215 non-Hodgkin lymphoma cases interviewed out of 258 (83% response rate) eligible cases. A pool of potential controls (2,357 participants) was constituted from among all the other patients with cancer, excluding patients with lung cancer. Non-Hodgkin lymphoma is associated with exposure to copper dust and ammonia and a number of fabric and textile-related occupations and exposures. For Non-Hodgkin lymphoma incidence, the following substances were studied: bronze dust, copper dust, alkali and caustic solutions, ammonia, hydrogen chloride, plastics pyrolysis products, fur dust, cotton dust, plastic dust, formic acid, and fluorocarbons. An odds ratio (OR) of 2.2 (95% confidence interval [CI]: 0.4-11.3) with respect to developing non-Hodgkin lymphoma was reported for formic acid (number of nonsubstantially exposed cases = 2). Additionally, an OR of 1.5 (95% CI: 0.3-8.0) with respect to developing non-Hodgkin lymphoma was reported for formic acid

(number of substantially exposed cases = 2). Thus, none of the ORs calculated for formic acid exposure was statistically significant. The substantially exposed group comprised those who had been exposed (probable or definite exposure) to formic acid at a high frequency and concentration for more than 5 years. Those not meeting these criteria were considered nonsubstantially exposed.

Oral

Sodium formate. Six Wistar rats received sodium formate at a concentration of 1% in drinking water continuously for 1.5 years. The authors defined the 1% concentration as equal to 274 mg/animal formate or 185 mg/animal calculated as formic acid. Neoplasia was not observed in any of the animals tested. Additional study details were not included.[25]

Dermal

Formic acid. An initiation–promotion study was performed using Swiss mice (30-60 mice; 6-10 weeks old), and the induction of epidermal tumors was evaluated.[3,26] The initiation protocol involved pretreatment of both ears with 1.5% dimethyl benzanthracene. In the promotion phase of the study, both ears were painted with a brush dipped in an 8% solution of formic acid in distilled water twice per week for 20 weeks. The dose of formic acid applied was not stated. Control mice were treated with distilled water. Hyperplasia was measured as the number of nuclei per standard length of a perpendicular cross-section of the epidermis on days 2, 5, 10, 20, and 50 of treatment. Neither hyperplasia nor epidermal thickness was increased on days 2 through 50 of treatment. Furthermore, inflammation (number of inflammatory cells) was not increased on days 2, 5, and 10, the only days on which this end point was evaluated. When compared to tumor promoters (croton oil and Tween 60), neither histopathologic or histomorphometric changes were observed.

Occupational Exposure

The National Institute for Occupational Safety and Health occupational exposure limit for formic acid is a time-weighted average (TWA) of 5 ppm (9 mg/m3).[44] The TWA is defined as the exposure concentration averaged (mean) over a conventional 8-hour workday, assuming a 40-hour workweek.

Other Studies

Formic Acid

A placebo-controlled clinical trial was performed in patients with common viral warts.[45] Using a needle puncture technique, a total of 34 male and female patients (age range of most patients: 11-20 years) received 85% formic acid in distilled water on their lesion on 1 side of the body and distilled water (placebo) on the other side of the body. The solution was administered every other day and follow-up occurred every 2 weeks for up to 3 months. Complete disappearance of warts during the follow-up period was reported for 91% of the patients tested with formic acid. Complete disappearance of warts was reported for 10% of the patients treated with distilled water (placebo). The following side effects were observed following treatment with formic acid: mild pain upon puncture, pigmentary changes, bulla and ulcerations after injections, bleeding and hemorrhagic crusts, and mild atrophic scars. A total of 3.27% of the patients had no side effects.

Summary

Formic acid functions as a fragrance ingredient, preservative, and pH adjuster in cosmetic products. Sodium formate also functions as a preservative in cosmetic products. According to the information supplied to the FDA by industry as part of the VCRP in 2013, formic acid and sodium formate were being used in 31 and 9 cosmetic products, respectively. Results from a survey of ingredient use concentrations provided by the Council (also included in Table 1) in 2012 indicate that formic acid and sodium formate were being used at concentrations up to 0.2% and 0.34%, respectively, with hair care products accounting for the highest use concentrations of both ingredients.

Formic acid is a common metabolic intermediate and can be metabolically oxidized to carbon dioxide. Formic acid oxidation in vivo occurs in the liver and erythrocytes, primarily via the folate-dependent pathway. Study results indicate that formic acid was rapidly absorbed in humans dosed orally, and the urinary excretion of formate was described as exponential in rabbits dosed orally with formic acid. Following oral dosing of rats with sodium formate, the urinary excretion of formic acid was ~13.8% of the administered dose in 24-hour urine. In dogs, ~30% to 40% of the administered oral dose of sodium formate was excreted in 24-hour urine. Following ingestion of sodium formate in humans, 2.1% of the administered dose was excreted in the urine within 24 hours. In rabbits dosed IV, formic acid distributed rapidly and a rapid decrease in tissue concentrations was observed within 24 hours. After IP dosing of mice with sodium formate, the oxidation of sodium formate in expired air was rapid. In an ex vivo study using a single human placental lobule, formic acid transferred rapidly from maternal to fetal circulation.

In acute inhalation toxicity studies involving rats, an acute inhalation 4-hour LC_{50} value of 7.4 mg/L was reported for formic acid in 1 study (respiratory tract irritation; dose-related increase in mortality) and a concentration-related (10%-50% formic range) increase in mortalities was observed in another study in which rats were exposed for up to 7 hours. Gross pathology findings at the 50% exposure level included heart dilatation and hyperemia and inflated lungs in animals that died. In another study, the mortality incidence was 75% after 3 minutes of exposure to a saturated atmosphere of formic acid. The exposure of rats to aerosolized sodium formate (dust contained 0.67 mg/L; MMAD = 5.24 $\pm$ 2.4 μm) for 4 hours did not cause death, and there were no treatment-related findings at necropsy.

Oral LD_{50} values of 1,830 and 7,410 mg/kg body weight have been reported for formic acid (rats) and sodium formate (mice), respectively. In another study involving rats, an acute dermal LD_{50} of >2,000 mg/kg body weight was reported. An acute SC LD_{50} of >300 mg/kg body weight in rabbits and an acute IV LD_{50} ~807 mg/kg body weight in mice have been reported.

In a repeated dose inhalation toxicity study, there was no evidence of clinical signs in rats exposed to 0.037 mg/L formic acid. The only clinical sign observed in rabbits that received repeated oral doses of formic acid (300 mg/kg body weight) was very deep respiration during the first 12 hours postdosing. Toxicity was not observed in rats that received repeated oral doses of sodium formate (274 mg/animal formate). Following repeated dermal applications of formic acid or sodium formate to the skin of rats, there was also no evidence of systemic toxicity. Repeated IV dosing of rabbits with formic acid (100 mg/kg body weight) resulted in calcium deposits in the kidneys, liver, heart, and brain. However, electron microscopy did not reveal changes in cellular substructures.

Formic acid was an ocular irritant at concentrations of 5% to 6% in rabbits, and ocular irritation, chemosis, and subconjunctival hemorrhaging were observed in a participant accidentally splashed with 80% formic acid. Transient ocular irritation (moderate to severe) was observed in rabbits after instillation of sodium formate. Skin irritation was observed in guinea pigs tested (no occlusion) with 10% and 12% formic acid and in guinea pigs injected intradermally with 2% to 3% formic acid. In a sensitization study pretest, 5% formic acid was the minimum irritant concentration and 2% formic acid was the maximum nonirritating concentration in guinea pigs. In the sensitization study (occlusive patches), no reactions were observed when formic acid was tested at concentrations of 7.5% and 2% during induction and challenge phases, respectively. Sodium formate was not irritating to the skin of rats or rabbits (under occlusion). Accidental exposure to concentrated formic acid induced adverse effects in case reports.

Neither reproductive nor developmental effects were observed in pregnant rats dosed orally with sodium formate on gestation days 6 to 19, and the NOAEL was 945 mg/kg body weight per day (highest dose) for maternal toxicity, embryotoxicity, and teratogenicity. The NOAEL for maternal toxicity and reproductive effects in rabbits was 1,000 mg/kg body weight per day (highest dose), after dosing on gestation days 6 to 28. A single oral dose of sodium formate (750 mg/kg body weight) on gestation day 8 had no effect on the incidence of neural tube defects in mice. Both formic acid and sodium formate were embryotoxic in rat and mouse embryo cultures.

Formic acid was not genotoxic in *E coli* strain PQ37 (up to 100 mM) or *S typhimurium* strains TA97, TA98, TA100, and TA1535 (up to 3,333 μg/plate) with or without metabolic activation. The same was true for formic acid (up to 500 μg/mL) in Chinese hamster ovary cells. Sodium formate (up to 5,000 μg/plate) was not genotoxic in *S typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. In an in vivo study, groups of mice were dosed orally with sodium formate (up to 100 mg/kg body weight). Both DNA and hemoglobin adduct formation were linearly correlated with dose in the log/log plot over the entire dose range. Sodium formate alone had no effect on [^{3}H]thymidine incorporation into the DNA of mouse embryos.

Neoplasia was not observed in rats that received 1% sodium formate in the drinking water continuously for 1.5 years. In an initiation–promotion study using Swiss mice, the application of 8% formic acid to the ears for 20 weeks did not cause an increase in hyperplasia or epidermal thickness. In a case–control study that involved interviews with 215 non-Hodgkin lymphoma cases, an OR of 2.2 (95% CI: 0.4-11.3) with respect to developing non-Hodgkin lymphoma was reported for formic acid (number of nonsubstantially exposed cases = 2). Additionally, an OR of 1.5 (95% CI: 0.3-8.0) with respect to developing non-Hodgkin lymphoma was reported for formic acid (number of substantially exposed cases = 2). Thus, none of the ORs calculated for formic acid exposure was statistically significant.

A placebo-controlled clinical trial was performed using 34 patients with common viral warts. Treatment with formic acid (85% in distilled water) for up to 3 months resulted in complete disappearance of the warts in 91% of the patients.

Discussion

The Panel noted that formic acid is a dermal and ocular irritant because of its acidic properties. Concerns relating to the safe use of formic acid as a preservative or fragrance ingredient would depend primarily on the concentration of free formic acid in the formulation. However, when used as a pH adjuster in cosmetic formulations, most of the acid will be neutralized to yield formate salts. Neutralized formic acid would be present predominantly as sodium formate, which has little, if any, potential to cause adverse local or systemic health effects. Thus, the safety of formic acid as a pH adjuster depends primarily on the amount of free formic acid that remains after using it to neutralize the formulation, rather than simply on its concentration of use. The highest reported use concentration of formic acid in cosmetic products applied directly to the skin is 0.02%, and the highest reported use concentration in leave-on products (noncoloring hair products) is 0.2%. It should be noted that the concentration of free formic acid depends on the content of alkaline ingredients in the formulations. Generally, the concentrations of free formic acid are expected to be low because of neutralization by alkaline ingredients in formulations. Again, systemic toxicity is not expected to be a relevant issue. The remaining uses of formic acid are mainly in rinse-off products, and these uses would also pose minimal concerns relating to irritation potential in product formulations.

The Panel discussed the issue of incidental inhalation exposure from aerosol hair sprays. Formic acid is used in products that are sprayed (reported maximum use concentration = 0.2% in an aerosol hair spray). Acute inhalation toxicity data on formic acid are available, indicating that this ingredient causes respiratory irritation. However, the Panel considered pertinent

data indicating that incidental inhalation exposures to these ingredients in aerosol hair sprays would not cause adverse health effects, including data characterizing the potential for formic acid to cause acute oral toxicity, systemic toxicity when administered repeatedly to the skin of rats, or promote tumor formation when applied repeatedly to the skin of mice. The Panel noted that 95% to 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Conclusion

The CIR Expert Panel concluded that formic acid and sodium formate are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment, when formulated to be nonirritating.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, Washington.

Author Contributions

Wilbur Johnson contributed to conception and design, contributed to acquisition, analysis, and interpretation, and drafted the manuscript. Bart Heldreth contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted the manuscript, and critically revised the manuscript. Lillian J. Gill, F. Alan Andersen, Wilma F. Bergfeld, Donald V. Belsito, Ronald A. Hill, Curtis D. Klaassen, Daniel C. Liebler, James G. Marks, Ronald C. Shank, Thomas J. Slaga, and Paul W. Snyder contributed to conception and design, contributed to analysis and interpretation, and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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