FINAL REPORT ON THE SAFETY ASSESSMENT OF FORMIC ACID[1]

Formic Acid is a simple organic acid used as a pH adjustor in cosmetic products. It is a common metabolic intermediate that can be oxidized to carbon dioxide. The available data suggest that Formic Acid is an ocular and skin irritant and can be especially irritating to lung tissue. Both positive and negative results were noted in various mutagenicity studies (acidic experimental conditions were indicated in most cases of positive mutagenicity). In cosmetic formulations, Formic Acid is expected to be used at low concentrations and neutralized into various formate salts. Thus, the free Formic Acid level is expected to be very low. Using data from an inhalation toxicity study in which 64 ppm was found to be nonirritating, it was extrapolated that such a level of free Formic Acid in a cosmetic formulation should not produce adverse effects. Accordingly, it was concluded that Formic Acid is safe for use in cosmetics as a pH adjustor with a limit of 64 ppm for the free acid.

Formic Acid is used in cosmetics as a pH adjustor. The following is a summary of data available to Cosmetic Ingredient Review (CIR) concerning the chemistry, cosmetic use, toxicity, and mutagenicity of this compound.

CHEMISTRY

Chemical and Physical Properties

Formic Acid (CAS No. 64-18-6) is an organic acid that conforms to the formula in Figure 1 (Wenninger and McEwen, 1995a).

Other names for this ingredient include Methanoic Acid, Aminic Acid, Formylic Acid, and Hydrogen Carboxylic Acid (RTECS, 1993; Sax, 1979). Formic Acid has a molecular weight of 46.03 and is a colorless, highly corrosive liquid with a pungent odor. It is a strong reducing agent. It has a boiling point of 100.5°C and a melting point of 8.4°C and is miscible with water, alcohol, ether, and glycerin and soluble in ben-

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel.

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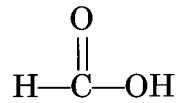

Figure 1. Formula for Formic Acid.

zene, toluene, and especially acetone (Wagner, 1980). Its specific gravity is approximately 1.20. It can react as an acid and an aldehyde. At temperatures greater than 69°C, vapor and liquid forms of Formic Acid are flammable (RTECS, 1993; Budavari, 1989; National Academy of Sciences, 1996; Sax, 1979; Wagner, 1980).

Formic Acid was first observed in 1670 by S. Fisher in products resulting from the distillation of red ants. It is found in some unripened fruit; in the venom of ants, wasps, and bees; and in mammalian muscle tissue, sweat, and urine (National Toxicology Program, 1992; Smolin and Wong, 1982; Tracor Jitco, Inc., 1974). Formic Acid is produced in forest fires and is found in tobacco smoke (Sakuma et al., 1983).

Methods of Production

Formic Acid is produced by heating carbon monoxide and sodium hydroxide under pressure and then treating the resulting sodium formate with sulfuric acid (Budavari, 1989). No information is available on impurities.

Analytical Methods

Formic Acid can be detected by gas chromatography (Barchan et al., 1986).

USE

Cosmetic

Formic Acid is used as a pH adjustor in cosmetic formulations (Wenninger and McEwen, 1995b). The product formulation data that were submitted to the Food and Drug Administration (FDA) in 1995 indicated that Formic Acid was contained in two cosmetic product formulations, as shown in Table 1 (FDA, 1995).

Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992a); however, product formulation data submitted to the FDA in 1984 indicated that Formic Acid was used at concentrations of 1% or less in hair conditioners, and 0.1% or less in noncoloring shampoos (FDA, 1984).

Table 1. Frequency of use of formic acid

Product category	Number of formulations in category	Number of formulations containing formic acid
Face and neck skin care (excluding shaving preparations)	261	1
Foot powders and sprays	32	1
1995 Total		***2***

Source. FDA (1995).

International

Formic Acid is restricted to a maximum authorized concentration of 0.5% for the acid in cosmetics by the European Economic Community (EEC, 1993).

Noncosmetic

The FDA has declared that a pediculicide drug product containing Formic Acid would not be generally recognized as safe and effective and would be misbranded (Federal Register, 1992b).

GENERAL BIOLOGY

Abosrption, Distribution, Metabolism, and Excretion

General

Formic Acid is a common metabolic intermediate. It can be metabolically oxidized to carbon dioxide (Eells et al., 1981, 1983; Martin-Amat et al., 1978). Formic Acid oxidation *in vivo* occurs in the liver and erythrocytes primarily via the folate-dependent pathway (Plaut et al., 1950; Stedman and Welsch, 1989; Tephley, 1991). Mice and rats metabolize Formic Acid more rapidly than do monkeys and humans (McMartin et al., 1977). The differences in the rate of Formic Acid oxidation between species seem to depend on hepatic tetrahydrofolate concentrations. Mice, having greater tetrahydrofolate concentrations (42.9 nmol/g liver) than do monkeys (7.4 nmol/g liver), can oxidize Formic Acid at a rate of 300 mg/kg/h compared with the maximum rate in monkeys of 40 mg/kg/h (Johlin et al., 1987). Researchers estimate human hepatic tetrahydrofolate concentrations to be 6.5 nmol/g liver and the Formic Acid oxidation rate to be comparable to that of monkeys. Pigs have the lowest levels of the folate (3.3 nmol/g liver). The Formic Acid half-life in blood is 12 min in rats and guinea pigs, 67 and 77 min in

cats and dogs, and 55 min in humans (Restani and Galli, 1991); however, in two separate cases of human methanol poisoning in which 0.7 g and 1.3 g of methanol/kg body weight were estimated to have been ingested, the blood half-life of Formic Acid during dialysis was calculated to be between 1 and 2 h (McMartin et al., 1980). Shahanigian et al. (1984) reported the half-life of Formic Acid in cases of human methanol poisoning to be as long as 20 h.

Rabbits

The ear vein of fifteen male New Zealand rabbits (3070 ±220 g) was injected with 1 mL of a solution containing 100 mg Formic Acid/kg body weight. The Formic Acid was adjusted to pH 7.4 with a 0.01 M phosphate buffer. A total of five injections were administered with 24 h between doses; the fifth dose contained ^{14}C-Fromate. Three control animals were injected with buffer alone. The animals received feed and water ad libitum and were killed 1, 2, and 20 h after the last dose. Blood samples were drawn and urine collected from the bladder. In addition, organs were examined both for radioactivity and chemical determination of Formic Acid. Peak concentrations of Formic Acid were measured 1 h after the fifth dosage in the blood (0.7 ±0.4 μmol/g), heart (0.8 ±0.3), liver (1.5 ±0.5), kidney (1.7 ±0.7), and urine (44 ±22). At all times, the urine contained the highest concentration. The maximum concentration in the brain (1.3 ±0.6 μmol/g) was reached 2 h after the final dosing. At each of the three times and in all tested organs and fluids, the amount of Formic Acid determined radiochemically was less than that found chemically. Calcium deposits were detected in all examined organs of the injected animals and were not found in controls (Liesivuori et al., 1987). The researchers noted that the maximum concentration detected in the organs was roughly equivalent to the 1 mmol Ki needed for inhibition of mitochondrial cytochrome oxidase by Formic Acid (see section on biologic activity of this report for references on mitochondrial inhibition).

In another study, Formic Acid (300 mg/kg) was administered by gastric intubation to four male New Zealand rabbits (body weight: 3420 ± 140 g). The urinary pH in these samples was 6.89 ±0.48 and decreased linearly during the 30-h observation period despite the fact that the bulk of the dose (700 ±288 mmol/mol creatinine) was excreted 7 to 12 h after the gavage (±is the standard deviation). Urinary Formic Acid levels decreased to 56 ± 15 mmol/mol creatinine 30 h after exposure (Liesivuori and Savolainen, 1987).

Humans

Nineteen workers exposed to methanol vapor and four workers exposed to Formic Acid vapor (5 females and 18 males, 38 ±10 years of age)

with approximately 8 years in their current occupation took part in a clinical study. Urine samples were collected on the morning of the fifth day of a work week and analyzed by gas chromatography (Liesivuori and Savolainen, 1987). The uninary excretion of ammonia decreased as uninary Formic Acid increased (the values were corrected for creatinine concentration). The mean urinary ammonia concentration was 2.4 mol/mol creatinine in the five workers with the lowest Formic Acid concentration (27 mmol/mol creatinine) compared with an ammonia concentration of 1.9 mol/mol creatinine in those five with the highest Formic Acid concentration (101 mmol/mol creatinine). The urinary calcium concentration increased linearly as the Formic Acid concentration increased.

In a similar study, Liesivuori et al. (1992) reported that the urinary ammonia content increased with postexposure time. The urinary ammonia concentration increased with increasing urinary Formic Acid levels in 12 male farmers exposed to 7.3 $\pm$2.2 mg Formic Acid/m^3 for 8 h during silage making. Immediately after exposure, the mean Formic Acid concentration was 31 mmol/mol creatinine with an ammonia concentration of 1.5 mmol/mol creatinine, which was similar to the levels in nine nonexposed controls who had urinary Formic Acid and ammonia concentrations of 26 and 1.4 mmol/mol creatinine, respectively. At 30 h postexposure, the mean Formic Acid concentration in workers was 104 mmol/mol creatinine and the ammonia concentration was 2.3 mmol/mol creatinine. No change occurred in urine pH, whereas urine calcium levels increased with prolonged postexposure time.

Biological Activity

Formic Acid is identified as a protoplasmic poison, a class that produces its effect either by forming salts with proteins or by binding or inhibiting calcium or other organic ions necessary for tissue viability and function (Jalenko, 1974).

Formic Acid is an inhibitor of the cytochrome–oxidase complex at the terminus of the respiratory chain in mitochondria (Erecin'ska and Wilson, 1980; Moody, 1991; Nicholls, 1976). The inhibitory action of Formic Acid increases with decreasing pH; the acid is permeable through the inner mitochondrial membrane only as an undissociated acid (Nicholls, 1976). This action can lead to acidosis in monkeys and humans (McMartin et al., 1980; Liesivuori and Savolainen, 1991). Metabolic acidosis is characterized by an increase in the excretion of calcium, ammonia, and protons (Liesivuori and Savolainen, 1991). Martin-Amat et al. (1978) demonstrated that ocular toxicity can be induced without onset of acidosis. Monkeys intravenously infused with methanol such that blood formate levels were equivalent to those asso-

ciated with methanol-poisoning developed optic disc edema despite interruption of metabolic acidosis by maintaining normal blood pH.

Metabolic acidosis and edema of the optic disc have been observed in humans following ingestion of methanol (McMartin et al., 1980) (for more details, see section on case reports in the "Clinical Assessment of Safety" of this report).

DNA Synthesis

Stedman and Welsch (1989) reported that 1 mM Formic Acid attenuated the inhibition of DNA synthesis by 2-methoxyacetic acid (2-MAA) in CD-1 mouse embryos.

Metabolic Cooperation

At concentrations of up to 300 μg/mL, Formic Acid did not affect the metabolic cooperation between cocultured mutant HGPRT– and wild type HGPRT+ Chinese hamster V79 lung fibroblasts (Malcolm et al., 1985).

ANIMAL TOXICOLOGY

Short-Term

Inhalation

In an NTP study (1992), groups of five male and five female Fischer 344/N rats and B6C3F1 mice were given Formic Acid by inhalation exposure for 6 h/day for 12 days (five days/week for 2 weeks). The exposure concentrations were 31, 62.5, 125, 250, or 500 ppm of Formic Acid (95% pure). All animals were individually caged. Feed was available ad libitum except during exposure periods. One female and three male rats of the 500-ppm exposure group died on day 10 of exposure. All mice exposed to 500 ppm died during the first week of the study; a female mouse of the 250-ppm group became moribund and was killed on day 4. The deaths occurring after dosing were attributed to swelling of the nasal mucosa, which impaired respiration. The surviving animals were killed at the end of the 2 weeks and necropsy was performed. No microscopic lesions were found in either rats or mice of the control or 31-ppm exposure groups, and no significant findings were found in mice dosed with 62.5 ppm. Table 2 summarizes the findings from the other exposure groups.

Lesions were noted in the upper respiratory tract of rats dosed at concentrations of 62.5 ppm or greater; lesions in the respiratory and olfactory epithelium in the anterior and mid portion of the nasal mucosa were found at air concentrations of 125 ppm or greater; squamous metaplasia and necrosis of the respiratory and olfactory epithe-

Table 2. Incidence of histopathologic findings in B6C3F$_1$ mice and F344/N rats in 2-week inhalation study of Formic Acid

	Exposure concentration (ppm)															
	62.5				125				250				500			
	Rats		Mice		Rats		Mice		Rats		Mice		Rats		Mice	
Histopathologic finding	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Nose																
Respiratory epithelium																
Squamous metaplasia	4	3	0	2	5	5	3	3	5	5[a]	4	4	5	5[a]	1	0
Inflammation	0	0	0	0	3	4	2	2	5	5	4	5	5[a]	5[a]	5	5
Necrosis	0	0	0	0	0	0	0	0	5	3	0	2	5	5[a]	4	5
Olfactory epithelium																
Degeneration	—	—	0	0	—	—	0	0	—	—	3	2	—	—	1	0
Necrosis	0	0	0	0	1	1	0	0	2	4	0	1	5	5[a]	3	5
Larynx																
Squamous metaplasia	0	0	0	0	0	0	0	0	0	0	0	0	1	1	5	1
Inflammation	0	0	0	0	0	0	0	0	0	1	0	0	2	1	3	3
Necrosis	—	—	—	0	—	—	—	0	—	—	—	0	—	—	—	5
Pharynx																
Necrosis	—	—	0	0	—	—	0	0	—	—	0	0	—	—	3	2

Notes. M = male, F = female. Five animals of each sex and species were used.

[a] Lesions were moderate to marked in appearance.

Source. NTP (1992).

lium were present in all rats but were most severe in those of the 500-ppm group. At 500 ppm, squamous metaplasia of the larynx occurred in one male and one female rat. In mice, lesions were limited to the nasal passages except for mice of the 500-ppm group; these mice had lesions in the larynx, pharynx, and trachea. At 500 ppm, the most severe lesions were in the cranial section of the nose and consisted of necrosis of the respiratory epithelium and an accumulation of inflammatory cells in the mucosa and lumen of the nasal cavity.

Subchronic

Inhalation

In a 13-wk NTP study (1992), groups of 10 rats and mice of each sex were exposed to Formic Acid vapor at target concentrations of 8, 16, 32, 64, and 128 ppm for 6 h/day, 5 days/wk. Ten additional male and female rats per group were included for clinical pathology studies, which were performed on days 3 and 23. At the end of the study, necropsy was performed on all animals.

All rats survived to the end of the study. Male rats exposed to 16, 32, and 64 ppm Formic Acid had significantly greater body weight gains compared with control animals. No unusual gross lesions were noted at necropsy. In the 128-ppm exposure group, 9 of 10 males and 5 of 10 females showed minimal degeneration of the olfactory epithelium. Also at this dosage, 9 of 10 male rats and 6 of 10 female rats had minimal to mild squamous metaplasia of the respiratory epithelium in which the pseudostratified, ciliated columnar cells were replaced by a flattened, nonciliated epithelium. Sperm motility was lower in the exposed groups, but the values remained within the historical range for controls. No effects of exposure to sperm density or testicular or epididymal weights and no changes in the length of the estrous cycle were observed. One male and one female mouse of the 128-ppm exposure group died before the end of the study. Gross and microscopic lesions were limited to minimal degeneration of the olfactory epithelium of the nose in 2 of 10 female mice of the 64-ppm exposure group and 2 of 10 male mice and 5 of 10 female mice in the 128-ppm exposure group.

Based on the NTP findings, the no-observed-adverse-effect-level (NOAEL) for microscopic lesions in rats and mice was 31 ppm from the 2-wk study and 64 ppm from the 13-wk study. The researchers postulated that the lack of systemic effects in either the 2-wk or 13-wk study may be attributed to the ability of rodents to metabolize Formic Acid to CO_2. No explanation was given as to why the 13-wk NOAEL is higher than the 2-wk value.

MUTAGENICITY

Bacteria

The mutagenicity of Formic Acid at concentrations between 0.0050% and 0.0075% was tested in strains B/Sd-4/1,3,4,5 and B/Sd-4/3,4 of *Escherichia coli*. The bacteria were exposed for 3 hours (Demerec et al., 1951). The reverse mutation rate for streptomycin dependence was 18.1 to 44.0 per 10^8 in the exposed groups and 2.7 to 15.3 mutants/10^8 in the control group. The incidence rate of mutations was not dose dependent.

In an NTP study (1992), buffered solutions of Formic Acid at doses of up to 3.33 mg/plate were found not to be mutagenic in *Salmonella typhimurium* strains TA100, TA 1535, TA97, and TA98 both with and without S9 mix (S9: enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley or Syrian hamster liver).

Mammalian Cell Lines

Formic Acid at concentrations of up to 1000 μg/mL did not either transform or initiate transformation of C3H/10$T_{1/2}$ CI 8 mouse embryo fibroblast cells. At the 500-μg/mL concentration, 70% of the cells survived compared with controls; at 1000 μg/mL, 2% survived (Ragan and Boreiko, 1981).

In a Sister Chromatid Exchange (SCE) assay using Chinese hamster V79 cells, neither 1-h to 3-h nor 8-h exposures to Formic Acid (up to 2.0 mM) induced any statistically significant effect, either with or without S9 addition (prepared from Aroclor 1254-induced male Wistar rats) (Basler et al., 1985).

The effects of pH on the clastogenicity of Formic Acid was assayed in Chinese hamster ovary (CHO) K1 cells. The dosage and conditions at which chromosomal aberrations occurred with statistical significance were as follows: at initial pH 6.1, in the absence of S9 mixture, 12 mM Formic Acid induced aberrations such as chromatid gaps, breaks and exchanges, and chromosomal exchanges in 15.9% of the 113 cells scored. No significant effect was noted at 10 mM. With S9 mixture, 10 mM Formic Acid induced aberrations in 20.5% of the 200 cells scored, with the majority of damage being chromatid breaks and exchanges. No effect was noted at 8 mM (S9 was derived from the livers of rats pretreated with phenobarbital and 5,6-benzoflavone). When the medium was neutralized to pH 6.4 or 7.2 after the addition of either 12 or 14 mM Formic Acid, no significant clastogenic effects were observed. In cells grown in F12 medium containing sodium carbonate as a buffer, a clastogenic effect was observed in 10.5% of 200 CHO-K1 cells after exposure to 27.5 mM Formic Acid in the absence of S9 mixture. Upon

addition of that concentration of Formic Acid, the pH dropped to 5.7. Under these conditions, exposure to 25 mM Formic Acid did not have a statistically significant effect (less than 0.5% of cells had aberrations). When F12 medium containing the buffer HEPES was used after adjustment to pH 8.5, 12.0% of the 200 cells scored had a combination of chromatid gaps, breaks, or exchanges when exposed to 25 mM Formic Acid (initial pH upon acid addition was 6.7). The next-greater dose tested, 20 mM, did not have any effect. Formic Acid was nonclastogenic, because the effects could be eliminated by either neutralization of the medium or enhancement of its buffering ability (Morita et al., 1990).

A 48-h treatment of 10 mM Formic Acid induced signigicant ($P < 0.01$) SCE in cultured human lymphocytes (Sipi et al., 1992). The researchers, in reference to the Morita publication (1990), noted that the pH of the media was its lowest, 6.53, following addition of the 10 mM Formic Acid and represented a change of 1.04 pH units compared with control values; however, as other tested agents induced SCEs without lowering the pH, the researchers postulated that the effect of Formic Acid may be related to altered culture conditions but could not be assigned to lower pH alone.

Other

Stumm-Tegethoff (1969) tested for sex-linked lethals in three broods produced by male *Drosophila melanogaster* after the males had been exposed for 24 h to 0.1% Formic Acid vapor. In the 3048 chromosomes tested, sex-linked lethals were found in 1.31%, a value statistically significant from the 0.15% found in 2584 control chromosomes. In a larval feeding experiment, 0.1% Formic Acid in the media induced mutations in 1.11% of the chromosomes tested versus 0.15% for historical controls. When the pH of the media was stabilized to 7.5, however, the 0.1% Formic Acid induced mutations in 0.38% of the 544 chromosomes tested, which was not significant compared with the control mutation rate.

CLINICAL ASSESSMENT OF SAFETY

In Vitro Dermal Sensitization

A total loss of epidermal structure was observed in frozen sections of skin from two atopic dermatitis patients after incubation with 1 M Formic Acid (Gehring, 1990). In addition, the optical loss of nuclei was also greater in the dermatitic skin than in the skin of 10 healthy controls.

SUMMARY

Formic Acid is an organic acid that was reported in 1993 to be used as a pH adjustor in four cosmetic formulations. It is a common metabolic intermediate and can be further oxidized via a folate-dependent pathway to CO_2. Humans and primates are less efficient at metabolizing Formic Acid than are mice and rats. Formic Acid is an inhibitor of mitochondrial cytochrome oxidase, and this inhibition may lead to metabolic acidosis. Formic Acid also may be toxic to the eyes without onset of acidosis.

Lowered ammonia levels and increased calcium levels were found in the urine of humans with the highest formate levels after 1 wk of occupational exposure; however, urinary ammonia levels did increase with prolonged postexposure time and were higher in workers than in nonexposed controls.

In a 2-wk inhalation study, one of five female and three of five male rats and all five mice exposed to 500 ppm Formic Acid vapor died. Histopathologic lesions were found in rats and mice exposed to 62.5 ppm or higher. In the 13-wk inhalation study, no significant effects were observed in mice or rats exposed to 64 ppm or less.

In an NTP study, no mutations were found in *S. typhimurium* after exposure to buffered solutions. Formic Acid at concentrations of up to 1000 μg/mL did not transform or initiate transformation of mouse embryo fibroblast cells. Concentrations of 2.0 mM Formic Acid did not induce SCEs in CHO cells. The clastogenic effects of Formic Acid on CHO cells and the ability of Formic Acid to induce mutations in *Drosophila* were attenuated by controlling medium pH; however, 10 mM Formic Acid did induce significant SCEs in cultured human lymphocytes. The researchers did not attribute the effect to acidification of the media.

DISCUSSION

The CIR Expert Panel recognized that, although Formic Acid may be a dermal or ocular irritant, its use as a pH adjustor in cosmetic formulations dictates that most of the acid is neutralized into various formate salts. Furthermore, the concentration of Formic Acid used depends on the alkaline content of the formulations. In any case, the concentration of free Formic Acid is expected to be low, and systemic toxicity is not expected to be a relevant issue. The safety of Formic Acid as a pH adjustor, therefore, should not be based on the concentration use, but on the amount of free Formic Acid that remains after neutralizing the formulation. The Panel decided that a safety evaluation can be made

with the available data on the risks associated with exposure to low levels of Formic Acid.

In reviewing the data, the Panel elected to limit the concentration of free Formic Acid that may be present in formulation to 64 ppm or less. This value was the NOAEL determined by the 13-wk inhalation study conducted by the NTP (1992). Several considerations led the Panel to set its limits based on the results of this study. Foremost, it was acknowledged that the respiratory system is more sensitive and responsive to irritancy and toxicity than is the dermal system. The Panel was confident that because 64 ppm Formic Acid did not irritate the lungs of mice and rats, neither would that concentration in a product applied dermally adversely affect the skin. Second, it was noted that the design of an inhalation study is such that there is exposure of the test substance to the body surfaces and to the eye, and no adverse effects were found.

CONCLUSION

The CIR Expert Panel concludes that Formic Acid is safe when used in cosmetic formulations as a pH adjustor with a 64-ppm limit for the free acid.

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