GREEN

Formic Acid

CIR EXPERT PANEL MEETING
JUNE 11-12, 2012
June 11, 2012

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Manager/Lead Specialist

Subject: Re-review Document on Formic Acid.

At the March 15-16, 1995 CIR Expert Panel Meeting (54th), the Panel issued a final report with a conclusion stating that formic acid is safe when used in cosmetic formulations as a pH adjuster with a 64 ppm limit for the free acid. This final report was subsequently published in a special issue of the International Journal of Toxicology in 1997. In this report, the only reported function for formic acid in cosmetics is that of a pH adjuster. However, according to the most recent version of the International Cosmetic Ingredient Dictionary and Handbook, formic acid functions as a fragrance ingredient, preservative, and pH adjuster in cosmetic products. These 2 new functions for formic acid in cosmetics will be considered by the Expert Panel along with new data on the safety of this ingredient in cosmetics that entered the published literature since the final report was issued in 1995.

A copy of the re-review document is included along with the following: CIR report history, Literature search strategy, Ingredient Data profile, 2011 FDA frequency of use Data, and the published CIR final report on Formic Acid.

After consideration of the re-review document, the Panel should determine whether the published final report on formic acid should be re-opened. Based on the study results presented in this re-review document, it does not appear that the final safety assessment needs to be reopened; however, the impact of the new reported uses of formic acid needs to be considered. In the event that the Panel determines that the final report should be reopened, data on sodium formate could then be added. It should be noted that, although sodium formate is not reviewed in the published final report, oral reproductive and developmental toxicity data on this ingredient are included in the re-review document in the absence of these data on formic acid.

The available data on formic acid can be used to support the safety of sodium formate, a salt of formic acid, in cosmetic products. Therefore, if the Panel determines that the final report on formic acid should not be reopened, revising the original conclusion to include sodium formate in the re-review summary that will be published should be considered.
The CIR Staff notifies the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.**

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**Expert Panel Decision**

**Document for Panel Review**

**Option for Re-review**
CIR History of:

Formic Acid

At the March 15-16, 1995 CIR Expert Panel Meeting (54th), the Panel issued a final report with a conclusion stating that formic acid is safe when used in cosmetic formulations as a pH adjuster with a 64 ppm limit for the free acid. This final report was subsequently published in a special issue of the *International Journal of Toxicology* in 1997.

1st Re-review, Belsito and Marks Teams/Panel: June 11-12, 2012

A re-review document was prepared for the Panel’s review. Because the CIR final report on Formic Acid was issued more than 15 years ago, the safety of this ingredient in cosmetics is being re-considered at this meeting to determine whether the original safety assessment should be re-opened.

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Formic Acid

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Literature Search on Formic Acid

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*Data in Table: Publications found; Multidatabase = HSDB, CCRIS, ITER, IRIS, Gene-Tox, and LacMed

Searches Performed on 3/21 and 3/25-26/2012
Search Updated on

Ingredients/Search Terms (for years 1992-2012)
Formic Acid
64-18-6

Search Strings (NLM databases)
Formic Acid OR 64-18-6

SciFinder Search Terms
Formic Acid
### 2011 FDA VCRP Data

**FORMIC ACID**

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Re-review for consideration by the Cosmetic Ingredient Review Expert Panel

Formic Acid as Used in Cosmetics

June 11, 2012

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D.

This report was prepared by Wilbur Johnson, Jr., M.S., Manager/Lead Specialist.
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INTRODUCTION

At the March 15-16, 1995 CIR Expert Panel Meeting (54th), the Panel issued a final report with a conclusion stating that formic acid is safe when used in cosmetic formulations as a pH adjuster with a 64 ppm limit for the free acid. This final report was subsequently published in a special issue of the *International Journal of Toxicology* in 1997.1 Because the CIR final report on Formic Acid was issued more than 15 years ago, the safety of this ingredient in cosmetics is being re-considered at this meeting to determine whether the original safety assessment should be re-opened.

In the published final safety assessment, the only reported function for formic acid in cosmetics is that of a pH adjuster. However, according to the most recent version of the *International Cosmetic Ingredient Dictionary and Handbook*, formic acid functions as a fragrance ingredient, preservative, and pH adjuster in cosmetic products.2 The 2 new functions for formic acid in cosmetics will be considered by the Panel along with new data on the safety of this ingredient in cosmetics that entered the published literature since the final report was issued in 1995. Unpublished data included in the Organization for Economic Co-operation Development’s (OECD) Screening Information Data Set (SIDS) report on formic acid and formates that was published in 2008 and in the European Chemical Agency’s (ECHA) International Uniform Chemical Information Database (IUCLID) on formic acid, last update in 2000, are also included in the report text for the Panel’s review, in that these unpublished data (dated before and after 1995) were not available for inclusion in the published final safety assessment. Background information relating to the OECD SIDS and IUCLID data is presented below.

In 1998, the global chemical industry, through the International Council of Chemical Associations (ICCA) and in cooperation with the OECD, launched the High Production Volume (HPV) Chemicals Initiative.3 Under this program, screening-level hazard data is collected and submitted to the OECD member countries for hazard assessment. The information presented for assessment is the internationally agreed-upon SIDS, which consists of the following 6 categories: acute toxicity, repeat dose toxicity, reproductive/developmental toxicity, genetic toxicity, ecotoxicity, and environmental fate. The data set provides a sound basis for the initial hazard assessment of the chemical, which is prepared by the industry and country sponsor, and is presented at the OECD SIDS Initial Assessment Meeting (SIAM).

The OECD SIDS Initial Assessment Report on Formic Acid and Formates was presented at SIAM 26, held in Paris on April 15-18, 2008.4 The sponsor country for production of this report was the United States (U.S. Environmental Protection Agency [EPA]) and the industry sponsor was the Formates Panel of the American Chemistry Council. The industry sponsor conducted a comprehensive literature search, including all generally accepted databases, reference books, unpublished studies and data in company files. This information formed the basis for compilation of the IUCLID dossiers. IUCLID is a software application (freely downloadable tool) to capture, store, maintain, and exchange data on intrinsic and hazard properties of chemical substances.5 This software application will assist chemical companies globally in fulfilling their obligation to the European Chemicals Agency under the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) legislation.

CHEMISTRY

**Definition and Structure**

Formic acid (CAS No. 64-18-6) is an organic acid with the following formula:2

\[
\text{HCOOH}
\]

Other names for this chemical include: methanoic acid, hydrogen carboxylic acid, formylic acid, aminic acid, and acidum formicum.2

**Method of Manufacture**

Methods of production of formic acid are as follows:6 (1) treatment of sodium formate and sodium acid formate with sulfuric acid at low temperatures (vacuum distilled); (2) by acid hydrolysis of methyl formate; and (3) as a by-product in the manufacture of acetaldehyde and formaldehyde.
UV Absorption

The photodissociation dynamics of formic acid have been studied using velocity map ion imaging at the UV region. The absorption spectrum of formic acid exhibits a broad distribution and origin at 267.2 nm. The absorption cross-section increases with decreasing wavelength and peaks near 210 nm. At the longest wavelength region, the spectrum shows resolved rovibronic structures superimposed on a diffuse feature. However, the absorption spectrum shows apparent continuum at the wavelengths below 200 nm.

Photodecomposition

The photooxidation of formic acid in the presence of hydrogen peroxide was studied using a low-pressure vapor mercury lamp. A glass filter was used to eliminate light below 220 nm. The initial concentration of formic acid was 1.0 x 10^{-3} mol · L^{-1}. In this study, C_f denotes the concentration of formic acid and C_{H_2O_2} denotes the concentration of hydrogen peroxide. Photodecomposition rates for formic acid at pH 9.5 were much greater than those at pH 1.5. At pH 9.5, C_f decreased to nearly zero in the presence of 1.0 x 10^{-2} mol · L^{-1} hydrogen peroxide within 3 h. At pH 1.5, C_f was decreased by ~ 60% under the same experimental conditions. In the absence of hydrogen peroxide, formic acid did not decompose at either pH.

USE

Cosmetic

Formic acid reportedly functions as a fragrance ingredient, preservative, and pH adjuster in cosmetic products. According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2011, formic acid was being used in 36 cosmetic products. These data are summarized in Table 1.

Cosmetic products containing formic acid 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 is 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).

Noncosmetic

Formic acid is listed as a component of synthetic flavoring substances and adjuvants that are permitted by FDA for direct addition to food for human consumption (21CFR 172.515). FDA has also determined that it may be safely used as a food additive in feed and drinking water consumed by animals. 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 FDA. According to the Food Chemicals Codex, formic acid is used as a flavoring agent and preservative.

Formic acid had been used as an active ingredient in over-the-counter (OTC) drug products (i.e., 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.
**TOXICOKINETICS**

**Inhalation Studies**

Twelve male farmers (mean age = 38 ± 14 years) were exposed to formic acid (inhalation) while on the job, and had been in the farming business for 17 ± 14 years. The farmers used solutions containing 60 to 80% formic acid during silage making, which resulted in exposure to 7.3 ± 2.2 mg formic acid/m³ for 8 h. Each subject provided urine samples immediately and at 15 h and 30 h after the end of exposure. The excretion of formate was linearly related to the exposure at 15 h and 30 h after the end of exposure. Exposure resulted in an increase in renal ammoniagenesis and urinary calcium at 30 h post-exposure. It was noted that both biochemical effects may be explained by the interaction of formic acid with the oxidative metabolism of renal tubular cells, as formic acid is a known inhibitor of cytochrome oxidase.

**TOXICOLOGY**

**Acute Toxicity**

**Inhalation**

The acute inhalation 4-h LC50 value for formic acid vapor in male and female Sprague-Dawley rats was 7.4 mg/L in a study conducted in a manner comparable to the OECD TG 403 protocol. 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. 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. Dead animals had dilated and hyperemic hearts and inflated lungs. Signs consistent with respiratory tract irritation were also observed.

When Wistar rats were exposed to saturated atmospheres (44,168 ppm or ~ 83.16 mg/L) of formic acid in an inhalation hazard test, 8 of 12 rats exposed for 3 minutes died within 2 days, and 12 of 12 rats exposed for 10 minutes died after 2 days. Symptoms during exposure included ocular and nasal irritation, gasping, increased salivation, and opaque pupils. In another study, 6 of 6 Wistar rats (3 males, 3 females) exposed for 10 minutes to a saturated atmosphere of formic acid died within 2 days. Symptoms during exposure included ocular and nasal irritation, gasping, increased salivation, and opaque pupils.

Rats (number and strain not stated) were exposed for 7 h to an atmosphere enriched or saturated, at 20ºC, with 50% aqueous formic acid. There were no mortalities after 30 minutes of exposure. Lethality was noted after prolonged exposure. Exposure of rats to 25% aqueous formic acid for 3 h and to 10% aqueous formic acid (same conditions) also did not result in mortality. However, all 12 rats (males and females) died after 10 and 116 minutes of inhalation exposure to an atmosphere saturated, at 20ºC, with the volatile part of formic acid (> 98% purity). After 3 minutes of inhalation exposure, 8 of 12 rats died.

**Oral**

Male and female WISW (SPF TNO) rats (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 acute oral LD50 for formic acid in the rat was 730 mg/kg body weight. Severe clinical signs were noted at ~30 minutes post-dosing and included: hunched posture, dyspnea, bloody nose, and blood in the urine. Gross pathology revealed hyperemia of the stomach and mottled livers and kidneys.

An LD50 of 1,100 mg/kg body weight was calculated for mice. Further details were not provided.

**Dermal**

Formic acid was not evaluated for dermal toxicity in OEC’sDSIDS report on formic acid and formates due to its caustic nature (pH < 2).
Subcutaneous

An LD50 of > 300 mg/kg was reported in an acute subcutaneous toxicity study involving rabbits (number and strain not stated). Study details were not provided.

Repeated Dose Toxicity

Inhalation

In a study performed in accordance with the OECD TG 413 test protocol, rats were exposed to formic acid vapor (whole-body inhalation) at the following concentrations: 0, 0.015, 0.030, 0.062, 0.122, or 0.244 mg/L (0, 8, 16, 32, 64, or 128 ppm). The duration of exposure was 6 h/day on 5 days per week for 13 weeks. Increased absolute or relative liver weights and decreased lung weights were seen without histopathological correlation. Irritation of the upper respiratory tract was observed at 128 ppm (0.244 mg/L), and degeneration of the olfactory epithelium and squamous metaplasia of the respiratory were also observed at this concentration. The no observed adverse effects concentration (NOAEC) and the lowest observed adverse effects concentration (LOAEC) were 64 ppm (0.122 mg/L) and and 128 ppm (0.244 mg/L), respectively, based on respiratory effects. Further details were not provided.

Another 13-week inhalation toxicity study was performed using B6C3F1 mice. The same protocol (OECD TG 413) and test concentrations in the preceding study were used in this study. Decreased body weights and increased liver weights were observed in male mice at all doses. Mild degeneration of the olfactory epithelium was observed at the 2 highest concentrations. The NOAEC and LOAEC were determined to be 32 ppm (0.062 mg/L) and 64 ppm (0.122 mg/L), respectively, based on changes in the olfactory epithelium. Further details were not provided.

Dermal

Formic Acid (pH 5.5) was applied topically to shaved skin (2 cm x 2 cm site above tail area) of 8 Fischer 344/N female rats daily for 2 weeks. A control group of 8 rats was treated with saline according to the same procedure. After 2 weeks, the rats (both groups) all appeared healthy without any local side effects, such as redness or swelling, or evidence of any systemic toxicity. The total hair follicle count was lower in the test group when compared to the saline control group; however, the difference was not statistically significant.

Cytotoxicity

Formic acid was evaluated in a cytotoxicity study using cultured cell lines from photoreceptors (661W, mouse cell line) and the retinyl pigment epithelium [RPE] (ARPE-9, human cell line). When compared to ARPE-19 cells, 661W cells have the following lower antioxidant levels: 50% less glutathione, glutathione peroxidase and catalase protein, and 90% less catalase enzyme activity. Catalase and glutathione were analyzed in these 2 retinal cell lines to determine whether differences in these antioxidant systems contributed to cell-type-specific differences in cytotoxicity. Cells were exposed to 30 mM formic acid (pH 6.8) in the culture medium in the presence or absence of a catalase activity inhibitor, 3-amino-1,2,4-triazole (AT), or a glutathione synthesis inhibitor, buthionine L-sulfoximine (BSO). Catalase protein, catalase enzyme activity, glutathione, glutathione peroxidase activity, cellular ATP, and cytotoxicity were analyzed. In both cell types, formic acid treatment produced decreases in glutathione and glutathione peroxidase, and glutathione synthesis inhibition with BSO produced greater ATP depletion and cytotoxicity than formic acid exposure alone. It was concluded that treatment with formic acid produced lower toxicity in ARPE-19 cells than in 661W cells, due at least in part to the high antioxidant levels in ARPE-19 cells.

Ocular Irritation

Formic acid solutions (0.01 ml) were instilled to one eye of each male and female rat and mouse. Wistar rats (3 males, 3 females; 5 to 6 weeks old), ddY mice (3 males, 3 females; 5 to 6 weeks old) were used. Saline (control) was instilled into the other eye. Reactions in one eye were observed with a slit-lamp for one week after instillation. Formic acid (5 to 6%) induced ocular irritation. These were the minimum concentrations at which positive effects were observed.
According to the OECD’s SIDS report on formic acid and formates, formic acid is assumed to be corrosive to the eyes due to its inherent properties as a strong acid, and thus, testing was not required.\(^4\)

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.\(^21\) At 30 min 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 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.

**Skin Irritation and Sensitization**

Primary skin irritation tests (open patch tests were performed using the following species: Wistar rats (3 males, 3 females; 5 to 6 weeks old), ddY mice (3 males, 3 females; 5 to 6 weeks old), and 3 Hartley guinea pigs.\(^20\) Test solutions (1 ml/kg or 1 g/kg) were applied once, unoccluded (3 x 4 cm [rats]; 1 x 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 to 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 (same groups and strains as above). The test solution (0.01 ml) was injected intradermally at one 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 to 3%) induced skin irritation. These were the minimum concentrations at which positive effects were observed.\(^20\)

The ability to cause skin corrosion, expressed as the lowest observed effect concentration (LOEC) in rabbits, was determined for a series of carboxylic acids.\(^22\) 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 (QSM) is shown to exhibit a sound predictability. Thus, predictions are calculated for a set of 30 biologically non-tested carboxylic acids. The developed QSAR is 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.

Quantitative structure activity relationships (QSARs) were derived relating skin corrosivity data of organic acids, bases and phenols to their log(octanol/water partition coefficient), molecular volume, melting point and pK.\(^23\) Data sets were analysed using principal components analysis. Plots of the first 2 principal components of the preceding parameters, which broadly model skin permeability and cytotoxicity, for each group of chemicals showed that the analysis was able to discriminate well between corrosive and non-corrosive chemicals. It was noted that the derived QSARs should be useful for the prediction of the skin corrosivity potential of new or untested chemicals. Formic Acid (clogP\(_{ow}\) = -0.641) was classified as a corrosive material.

An in vitro skin corrosivity test on formic acid (33.9%) was performed using the Skin\(^2\) cutaneous model ZK 1300/ZK 1350, a three-dimensional human skin tissue consisting of dermal, epidermal, and corneal layers (9 x 9 cm tissue samples used).\(^24\) 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 MTT assay. This is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol- 2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The % viability of the treated skin cultures was calculated as a percentage of the untreated control values. For classification of corrosive/non-corrosive chemicals with the model ZK 1350 corrosivity assay, 80% viability was used as the cut-off value ( < 80% viability = corrosive, > 80% viability = non-corrosive). The concordance between the in vivo and in vitro corrosive or non-corrosive classification was approximately 70% for corrosives and non-corrosives combined. Formic acid (33.9%) was classified as noncorrosive.
Skin irritation studies were not available for inclusion in the OECD SIDS report on formic acid and formates.\textsuperscript{4} However, it was noted that, in agreement with the low pH (< 2), it is known that formic acid is corrosive to the skin and gastrointestinal tract in humans.

Formic acid did not induce skin sensitization in 20 guinea pigs when tested in the Buehler test (OECD TG 406 test protocol).\textsuperscript{4} 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 h or 48 h after challenge. Further details were not provided.

**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.\textsuperscript{25} 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, i.v. 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.\textsuperscript{26} 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 h, only 7 patients continued to have respiratory distress due to development of pulmonary edema, and 2 of them needed assisted ventilation. One patient died due to 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 corneo-limbo-scleral ulceration; one 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.\textsuperscript{27} 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.

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

**Inhalation**

In a study conducted in accordance with the OECD TG 413 test protocol, rats and B6C3F1 mice were exposed to formic acid vapor (whole-body inhalation) at the following concentrations: 0, 0.015, 0.030, 0.062, 0.122, or 0.244 mg/L (0, 8, 16, 32, 64, or 128 ppm).\textsuperscript{4} The duration of exposure was 6 h/day on 5 days per week for 13 weeks. Reproductive organs were examined. In rats, there were no effects on testicular or epididymal weights, sperm density and sperm motility, or estrous cycles. In mice, sperm motility values were lower at all concentrations, but no dose-response relationship was seen and the values were within the range of historical controls. There were no effects in female mice. Therefore, the NOAEC was 0.244 mg/L, the highest concentration tested.

**Oral**

Sodium formate was administered to pregnant Wistar rats via gavage (23-25/dose) at 0, 59, 236, and 945 mg/kg body weight per day during gestational days 6 to 19). The study was performed in accordance with the OECD 414 study protocol.\textsuperscript{8} The results of this study are included because oral reproductive and developmental toxicity data on formic acid were not found. There were no mortalities, clinical signs of toxicity, or body weight differences among the animals 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 group in the conception rate, the mean number of corpora lutea and implantation sites, or in the values calculated for the pre- and post-implantation losses, as well as the number of resorptions and viable fetuses.
Examination of the fetuses showed that the sex distribution was not affected, that the weight of placentae and the fetal weight were comparable between treated groups and the control group. There was one external malformation exclusively in the high-dose fetuses (1/212 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 NOAEL was 945 mg/kg body weight per day for maternal toxicity, embryotoxicity, and teratogenicity.4

In Vitro

The developmental toxicity of formic acid in whole embryo cultures in vitro was evaluated.28 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 h incubation period): 0, 0.14, 0.27, 0.54, 0.81, or 1.08 mg (0, 2.95,5.9,11.8,17.6, or 23.5 mM) formic acid/ml of culture medium. Mouse embryos were exposed to the following different concentrations of formic acid (24 h incubation period): 0, 0.27, 0.54, 0.81, 1.6 or 2.0 mg (0, 5.9, 11.8, 17.6, 34.8, or 44 mM) formic acid/ml of culture medium. The following embryo measurements were tested for concentration response using a regression model: crown-rump length (CRL), developmental score (DEVSC), head length (HL), somite number (SOM), and yolk sac diameter (YSD).

Mouse embryos cultured with formic acid showed a significant trend toward decreased YSD, CRL, HL, SOM and DEVSC. The incidence of dead embryos was elevated at the three highest formic acid concentrations, and anomalies were significantly increased at concentrations ≥ 0.54 mg formic acid/ml culture medium. The highest concentration at which embryos survived resulted in 100% malformations. Protein and DNA concentrations were reduced with increased formic acid exposure. Rat embryos cultured with formic acid showed significant reductions of YSD, CRL, HL, SOM and DEVSC. Embryolethality was increased at 1.08 mg/ml culture medium. Protein and DNA concentrations both decreased with increased formic acid concentrations.28

The effect of formic acid on embryonic development in vitro was evaluated using embryos from pregnant Sprague-Dawley rats.29 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 0.141-1.055 µl 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 pmol/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.

GENOTOXICITY

In the Ames test (OECD TG 471 protocol), formic acid did not induce gene mutations with or without metabolic activation.4 Further details were not provided. Results were also negative for formic acid (concentrations up to 500 µg/ml) in the HGPRT forward mutation test (OECD TG 476 protocol) using Chinese hamster ovary cells.

In an in vitro chromosomal aberrations test (OECD TG 473 protocol) using Chinese hamster ovary cells, formic acid induced chromosomal aberrations at concentrations of 10 to 14 mM (associated with pHs of 6.0 to 6.8), but not at lower concentrations associated with higher pH values.4 When tested using a buffer, formic acid did not induce chromosomal aberrations unless the buffering capacity exceeded, e.g., formic acid concentrations of 25 to 27.5 mM and pH values of 5.7 to 6.7). Further details were not provided. It was noted that there is evidence that formic acid may be a chromosome mutagen in mammalian cells in vitro, but, due to issues of pH and high dosage levels, the evidence is equivocal. It was concluded that genetic toxicity data (gene mutation and chromosomal aberrations) for formic acid were negative based on weight of evidence evaluation.

Formic acid was negative in the SOS-chromotest using Escherichia coli strain PQ37 with and without metabolic activation.30,31
CARCINOGENICITY

Animal

The carcinogenicity of potassium formate was evaluated in 2 studies. The results of these studies are included because oral carcinogenicity data on formic acid were not found. A combined 104-week chronic toxicity and oncogenicity rat study was performed using 50 Crl:HanWist(Glx:BRL)BR rats/sex/concentration, at concentrations of 0, 50, 400, and 2000 mg/kg body weight/day. A combined oral feed, 80-week chronic toxicity and oncogenicity study was performed using 51 Crl:CD-1 (ICR)BR mice/sex/concentration, at concentrations of 0, 50, 400, and 2000 mg/kg bw per day. The mortality patterns in mice and rats did not indicate any treatment-related effect. Also, the spectrum of tumors was generally consistent with that expected in rats or mice of these strains. There were no tumors, of an unusual nature or incidence, indicative of specific target organ carcinogenicity in the stomach or any other tissue at any concentration level (in any species or sex).

In a dermal carcinogenicity study involving mice (number and strain not stated), 8% formic acid in mineral oil was painted on the ear twice per week for 50 days. Further details were not provided. When compared to tumor promoters (croton oil and Tween 60), there were no histopathologic or histomorphometric changes. According to a remark on this study in the IUCLID database on formic acid, the method used is not acceptable and does not comply with current criteria, and documentation is inadequate; therefore, the study could not be assessed.

Human

This report consists of a more detailed explanation of positive findings from an earlier study regarding occupational risk factors for lymphoma and myeloma. This study was a large case-control study involving hundreds of occupational exposures and 19 cancer sites. There were 4,576 eligible cancer patients between 1979 and 1985, and 3,730 of these (82%) were successfully interviewed. There were 215 non-Hodgkin’s lymphoma cases interviewed out of 258 eligible cases (83% response rate). A pool of potential controls (2,357 subjects) was constituted from among all the other cancer patients, excluding lung cancer patients. Non-Hodgkin’s lymphoma is associated with exposure to copper dust, ammonia and a number of fabric and textile-related occupations and exposures. For Non-Hodgkin’s lymphoma incidences, 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 of 2.2 (95% confidence interval: 0.4 to 11.3) with respect to developing non-Hodgkin’s lymphoma was reported for formic acid (no. of non-substantially exposed cases = 2). Additionally, an odds ratio of 1.5 (95% confidence interval: 0.3 to 8.0) with respect to developing non-Hodgkin’s lymphoma was reported for formic acid (no. of substantially exposed cases = 2). The substantially exposed group comprised those who had been exposed (probable or definite exposure) and who also had more than 5 years of exposure at a high frequency and concentration. The rest was considered non-substantially exposed.

MISCELLANEOUS STUDY

A placebo-controlled clinical trial was performed in patients with common viral warts. Using a needle puncture technique, a total of 34 male and female patients (age range of most patients: 11 to 20 years) received 85% formic acid in distilled water solution on their lesion on one 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 7 types of 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.

OCCUPATIONAL EXPOSURE

The National Institute for Occupational Safety and Health (NIOSH) occupational exposure limit for formic acid is a time-weighted-average (TWA) of 5 ppm (9 mg/m³). TWA is defined as the mean exposure concentration for a conventional 8-hour workday and a 40-hour workweek.
<table>
<thead>
<tr>
<th>Exposure Type</th>
<th># of Uses</th>
<th>Conc. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Area</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Incidental Ingestion</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Incidental Inhalation - Sprays</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Incidental Inhalation - Powders</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dermal Contact</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Deodorant (underarm)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hair - Non-Coloring</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Hair-Coloring</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nail</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mucous Membrane</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Baby Products</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of Use</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leave-On</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Rinse off</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Diluted for (bath) Use</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Totals***/Conc. Range</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses

NOTE: 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.
References


Final Report on the Safety Assessment of Formic Acid

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 benz-
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; Tracer 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

<table>
<thead>
<tr>
<th>Product category</th>
<th>Number of formulations in category</th>
<th>Number of formulations containing formic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face and neck skin care (excluding shaving preparations)</td>
<td>261</td>
<td>1</td>
</tr>
<tr>
<td>Foot powders and sprays</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td><strong>1995 Total</strong></td>
<td><strong>263</strong></td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>


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

Absorption, 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 14C-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 urinary excretion of ammonia decreased as urinary 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 ± 2.2 mg Formic Acid/m³ 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-
associated 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 epithel-
Table 2. Incidence of histopathologic findings in B6C3F₁ mice and F344/N rats in 2-week inhalation study of Formic Acid

<table>
<thead>
<tr>
<th>Histopathologic finding</th>
<th>Exposure concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td>Rats</td>
</tr>
<tr>
<td>Nose</td>
<td></td>
</tr>
<tr>
<td>Respiratory epithelium</td>
<td></td>
</tr>
<tr>
<td>Squamous metaplasia</td>
<td>1 3 0</td>
</tr>
<tr>
<td>Inflammation</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Necrosis</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Olfactory epithelium</td>
<td></td>
</tr>
<tr>
<td>Degeneration</td>
<td>---</td>
</tr>
<tr>
<td>Necrosis</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Larynx</td>
<td></td>
</tr>
<tr>
<td>Squamous metaplasia</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Inflammation</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Necrosis</td>
<td>---</td>
</tr>
<tr>
<td>Pharynx</td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>---</td>
</tr>
</tbody>
</table>

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

a Lesions were moderate to marked in appearance.

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 CO₂. 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/10T1/2 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 significant (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.
FORMIC ACID

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 CO₂. 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 non-exposed 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.

REFERENCES


FORMIC ACID


