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Final Report on the Safety Assessment of Maleic Acid[1]

Maleic Acid is a dicarboxylic acid that functions as a fragrance ingredient and pH adjuster in cosmetics—it is used in a few cosmetic product formulations at low concentrations. Maleic Acid is commonly used in research studies to induce Fanconi syndrome in rats and dogs in an attempt to study the mechanism of this disease. One such study found decreased glomerular filtration rate in rats given 9.0 mmol/kg, but not with 1.5 mmol/kg, Maleic Acid intraperitoneally. Preincubation with 0.75 mmol/L of Maleic Acid reduced sperm penetration of golden hamster eggs to zero. Maleic Acid failed to induce any significant increases in revertant count in strains TA1535, TA1537, TA98, and TA100 at concentrations up to 7500 μg/plate. A concentration of 2.0×10^{-2} M Maleic Acid did show a positive pattern in a DNA synthesis inhibition test. Maleic Acid at 10%, pH 1.0, applied for 30 s on rabbit eyes, caused permanent opacity. A 1% solution, pH 1.0, applied for 2 min caused cloudiness of the cornea, but no lasting injury, and a 5% solution, also at pH 1.0, had a similar but more intense effect, with recovery delayed 6 to 7 days. Application of 10 μl Maleic Acid (pH not stated) to the volar forearm and labia majora of 21 female Caucasians produced an inflammatory response at 24 and 48 h, which varied from minimal erythema to marked erythema with marked vesiculation. Maleic Acid at 20% (pH not stated) applied to one forearm daily for a period of 6 weeks to 50 human subjects produced acute vesicular dermatitis in 17 subjects, who were dropped from the study. Only five of the remaining subjects accommodated to the treatment, the rest had varying degrees of inflammation or hyperirritable skin. Although Maleic Acid itself may be a dermal and/or ocular irritant, its use as a pH adjustor in cosmetic formulations dictates that most of the acid will be neutralized into various maleate salts. Therefore, the concentration of free Maleic Acid is expected to be low, and dermal or systemic toxicity is not expected to be a concern. The safety of Maleic Acid as a pH adjustor should not be based on the concentration of use, but on the amount of free Maleic Acid that remains after neutralizing the formulation. There is no reason to expect this ingredient to induce any toxicity when used for this purpose. The Cosmetic Ingredient Review (CIR) Expert Panel concluded that Maleic Acid is safe for use in cosmetic formulations as a pH adjustor in the practices of use as described in this safety assessment.

INTRODUCTION

Maleic Acid is a dicarboxylic acid that functions as a pH adjuster and fragrance in cosmetics. This ingredient was selected for review based on the structure-activity software (TopKat®) prediction of developmental toxicity and mutagenesis/carcinogenesis and reports in the Registry of Toxic Effects of Chemical Substances (RTECS) of mutagenic/carcinogenic activity (RTECS 2002). This review presents information relevant to the safety of this cosmetic ingredient as considered by the Cosmetic Ingredient Review (CIR) Expert Panel.

CHEMISTRY

Definition and Structure

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, Maleic Acid (CAS no. 110-16-7 and 6915-18-0) is a *cis* unsaturated organic acid that conforms to the formula shown in Figure 1 (Gottschalck and McEwen 2004).

Synonyms for Maleic Acid include 2-Butenedioic Acid, cis-1,2-Ethylene-dicarboxylic Acid (Gottschalck and McEwen 2004; RTECS 2002), Malenic Acid, Maleinic Acid, and Toxilic Acid (RTECS 2002).

Chemical and Physical Properties

The chemical and physical properties for Maleic Acid are given in Table 1.

Reactivity

Conjugated fatty acids and their esters react readily with Maleic Acid to form Diels-Alder "adducts" (Applewhite 1985).

Method of Manufacture

Maleic Acid is prepared by the catalytic oxidation of benzene over heated vanadium pentoxide (Budavari 1989, Gennaro 1990).

Analytical Methods

Maleic Acid has been identified by infrared (IR) spectroscopy (Brannon et al. 1976) and high-performance liquid chromatography (Mazzo 1984, Lian et al. 1999).

USE

Cosmetic

Maleic Acid is a dicarboxylic acid that functions as a fragrance ingredient and a pH adjuster in cosmetics (Gottschalck

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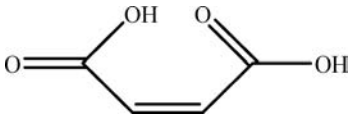

FIGURE 1
Structural formula for Maleic Acid (Gottschalck and McEwen 2004).

and McEwen 2004). This safety assessment considered only its use as a pH adjuster.

The use of cosmetic ingredients as a function of product types are reported voluntarily by the industry to the Food and Drug Administration (FDA). In 2002, Maleic Acid was reported to be an ingredient in three formulations of hair products and shaving creams as shown in Table 2. A survey by the Cosmetic, Toiletry, and Fragrance Association (CTFA), seeking current concentration of use information, did not confirm uses as reported to FDA, but did find a use in the "other" bath products category, at 0.004% (CTFA 2004).

Maleic Acid is not listed as an ingredient that must not be combined in cosmetic products that are marketed in Japan [Ministry of Health, Labor, and Welfare (MHLW) 2001a] or on the list of restricted ingredients for cosmetic products that are marketed in Japan (MHLW 2001b). Maleic Acid is not on the list of substances which must not form part of the composition of cosmetic products in Europe (EEC Cosmetics Directive 1999).

Noncosmetic

Maleic Acid is used in the manufacture of artificial resins, dyeing and finishing wool, cotton, and silk, in salts of antihistamines, and as a preservative for oils and fats (Clayton and Clayton 1981–1982). Maleic Acid may be used as an adhesive on articles intended for use in packaging, transporting, or holding food (21CFR175.105; 21CFR175.300; 21CFR177.1200).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Sacks (1958) injected (site not given) ^{14}C-Maleic Acid into a 9.5-kg dog and a normal (weight not given) human volunteer to

TABLE 1
Physical and chemical properties of Maleic Acid

Property	Value	References
Molecular weight	116.07	Budavari 1989; Gennaro 1990; Lide 1993; Committee of Revision of the United States Pharmacopeial Convention 2000
	116.08	Lewis 1993; Lewis 2000
Odor	Faint	Lewis 1997
	Acidulous	Budavari 1989; Lewis 1993; Lewis 2000
	Odorless	Gennaro 1990; Committee of Revision of the United States Pharmacopeial Convention 2000
Color	Monoclinic prisms	Lide 1993
	Colorless crystals	Lewis 1997; Grant 1972
	White crystals	Budavari 1989; Lewis 1993; Lewis 2000
	White crystalline powder	Gennaro 1990; Committee of Revision of the United States Pharmacopeial Convention 2000
Density	1.590	Budavari 1989; Lide 1993; Lewis 1993; Lewis 2000
Melting point	130–131°C	Lide 1993
	138–139°C	Lewis 1993; Lewis 1997; Grant 1972
	139–140°C	Lewis 2000
Boiling point	N/A—converted to fumaric acid above melting point	Budavari 1989; Lewis 1997
Solubility	Freely soluble in water and alcohol	Budavari 1989
	Soluble in acetone and glacial acetic acid	
	Slightly soluble in ether	
	Practically insoluble in benzene	

TABLE 2
Frequency of use and concentration of use of Maleic Acid

Product Category (Total Formulations in Category) (FDA 2002)	Number of Formulations Containing Maleic Acid (FDA 2002)	Current Maximum Concentration of Use (CTFA 2004)
Other bath products (196)	—	0.004%
Hair straighteners (63)	2	—
Other hair-coloring prep. (55)	1	—
Shaving cream (134)	1	—
Total	4	0.004%

determine the presence of enzyme systems capable of converting maleate salts to CO_2. A total of 5.9 mg of ^{14}C-Maleic Acid was injected in the case of the dog and 11.8 mg in the human volunteer. Blood was taken from the dog's femoral artery, but no site was specified for the human volunteer. In both the dog and the human volunteer, arterial CO_2 labeled with ^{14}C increased as a function of time after injection. The author examined the possibility that conversion of malete salts to fumarate salts in tissue and subsequent oxidation of fumarate salts to produce the arterial levels of $^{14}CO_2$, but rejected that explanation based on different kinetics of fumarate conversion to CO_2. The author concluded that mammalian tissue likely does possess an enzyme capable of metabolizing maleic acid.

Because Maleic Acid has been used instead of hydrochloric acid (HCl) to adjust the pH of plasma, Frazer and Hollifield (1980) studied its effect on plasma renin activity (PRA). When compared to the PRA after pH adjustment with HCl, Maleic Acid produced a significant increase (27% for a 1-h incubation and 34% for a 3-h incubation) in PRA. The method of analysis was a modification of the angiotensin radioimmunoassay method.

ANIMAL TOXICOLOGY

Short-Term Parenteral

Nomiyama et al. (1982) gave two Japanese white rabbits a single subcutaneous injection of Maleic Acid at a dose level of 400 mg/kg. The two rabbits died within 24 h. Pyonephrosis was found at necropsy.

Nephrotoxicity

Harrison and Harrison (1954) reported the experimental production of renal glycosuria, phosphaturia, and aminoaciduria by injection of Maleic Acid. Their study in rats demonstrated that intraperitoneal injection of Maleic Acid can increase the excretion of phosphate, glucose, and amino acids in urine, but that this effect does diminish within several days. When exposure to Maleic Acid was discontinued for a week (excretion of phosphate, glucose, and amino acids in urine returned to normal) and begun again, a similar pattern was seen. The authors noted that the renal glycosuria, phosphaturia, and aminoaciduria induced by Maleic Acid injection was similar to a congenital defect in man known as the Fanconi syndrome.

Everett et al. (1993) fed three male and three female Beagle dogs 0, 9, 14, and 23 mg/kg Maleic Acid. The vehicle for Maleic Acid was purified water. Twenty-four hours after dosing, blood was collected from the jugular vein for determination of serum glucose, urea nitrogen, and creatinine concentrations. The lowest dosage of Maleic Acid resulting in histomorphologic and clinical chemical evidence of nephrotoxicity was 9 mg/kg. Acute tubular necrosis was observed for one of three males and three of three females given Maleic Acid.

Fanconi syndrome

Several studies since the 1950s have confirmed this experimental Fanconi syndrome in rats and dogs associated with Maleic Acid injection, attempted to elucidate its mechanism, and used it to study other phenomena. Since Maleic Acid induction of Fanconi syndrome is a key aspect of these studies, there is no information on the Maleic Acid dose that does not produce the syndrome. One study by Kramer and Gonick (1973) did find a decreased glomerular filtration rate in rats given 9.0 mmol/kg Maleic Acid intraperitoneally, but not with 1.5 mmol/kg. Other parameters such as urinary output increases and NaK-ATPase activity decreases were affected at both doses, however, so even 1.5 mmol/kg via intraperitoneal injection is not a no-effect level.

To summarize this body of work two studies are presented. In the first study, experimental Fanconi syndrome was used to examine the renal response to protein feeding in dogs. The second study examined the mechanisms by which Maleic Acid acts on the kidney.

Woods and Young (1991) reported on the impaired renal hemodynamic response to protein feeding in dogs with experimental Fanconi syndrome induced by Maleic Acid. Introducing the rationale behind the study, these authors described Fanconi syndrome symptoms as including glucosuria, aminoaciduria, phosphaturia, and bicarbonaturia; and they characterized the syndrome itself as a generalized proximal tubular reabsorptive dysfunction. They state that the inhibition of the reabsorption of

amino acids (the focus of their study) may be the result of carrier interference and/or cellular energy utilization effects. They also noted that, although sodium reabsorption in the proximal tubule is impaired by Maleic Acid, reabsorption in the distal tubule is normal and can remove even the extra amounts of sodium.

In this study, eight mixed breed female dogs (23.8 $\pm$ 1.1 kg) were given a 10-g/kg meat meal and the changes in the glomerular filtration rate, the effective renal plasma flow, and the plasma α-amino nitrogen levels were measured over 120 min. All three responses increased. Six dogs were given an intravenous injection of Maleic Acid (25 mg/kg dose) in 20 ml saline, pH 7.3, over 5 min prior to receiving a meat meal. In these animals, no increase in the glomerular filtration rate or effective renal plasma flow was seen, although the plasma α-amino nitrogen levels increased as in the normal dogs. The authors concluded that these findings suggested that normal proximal tubular function is necessary for protein-stimulated renal vasodilation to occur. They postulate that protein feeding may stimulate proximal sodium chloride reabsorption, change the signal to the macula densa, and reduce tubuloglomerular feedback, causing the glomerular filtration rate to increase—by inhibiting sodium chloride reabsorption in the proximal tubule, Maleic Acid interferes with the cascade of effects (Woods and Young 1991).

Eiam-Ong et al. (1995) stated that most work has found that Maleic Acid affects solely the proximal tubule, although one study did postulate some involvement of the distal tubule. They note that solute transport in the proximal tubule is linked to sodium and depends on basolateral NaK-ATPase activity, and that bicarbonate resorption occurs via the brush border Na/H antiporter and an electrogenic sodium-independent H-ATPase pump. An inhibition of the proximal tubule NaK-ATPase, based on studies to date, appears to be the proximate cause for Maleic Acid effects. To examine this hypothesis, these authors gave four groups of six male Sprague-Dawley rats either a control infusion of Ringer-mannitol solution for 105 min, intravenous injection of Maleic Acid (pH 7.4) as a single 50 mg/kg dose, sodium phosphate (2.8 mg/ml) infusion continuously with a single Maleic Acid dose (as above) added at 60 min, followed by 45 more minutes of sodium phosphate infusion alone, or sodium phosphate infusion only for 105 min. The authors concluded that the results demonstrated that Maleic Acid has a selective inhibitory effect on renal ATPases in the proximal tubule. NaK-ATPase and H-ATPase were decreased by 80% and 50%, respectively. They also concluded that phosphate infusion did attenuate bicarbonaturia by improving proximal tubule NaK-ATPase and H-ATPase activities.

Ocular Irritation

Grant (1986) characterized Maleic Acid as toxic (permanent corneal opacity and vascularization at 10%, pH 1.0, applied for 30 s) to the eyes of rabbits in a concentration dependent manner (i.e., at 1%, pH 1.0 for 2 min produced only transient corneal cloudiness).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Stein and Schnieden (1983) compared the ability of Maleic Acid to prevent golden hamster spermatozoa penetration of eggs with that of tricyclic antidepressants. One control group was compared to three drug groups (mianserine, nomifensine, and vilaxazine). Hamster epididymal spermatozoa were incubated for 3 h with each of these compounds at 0.75 mmol/L. While mianserine and vilaxazine had no effect on egg penetration, after preincubation with nomifensine, subsequent egg penetration in vitro was virtually eliminated. Incubation with 0.75 mmol/Lof Maleic Acid had an effect similar to nomifensine; i.e., egg penetration was significantly reduced, virtually to zero.

The spermicidal effect of Maleic Acid was evaluated by Brown-Woodman et al. (1985) by adding the acid to the sperm, and by observing sperm survival and penetration following addition to human cervical mucus. A concentration of 0.1% Maleic Acid reduced the pH from 7.5 to 5.5 and rendered human spermatozoa immotile within 30 min, and 1% (pH 1.5) was almost instantaneously spermicidal. In capillaries filled with cervical mucus, the incorporation of 0.01% Maleic Acid was sufficient to reduce sperm penetration, and at 0.1%, penetration was completely prevented.

GENOTOXICITY

Lake et al. (1988) examined the potential of Maleic Acid to influence his+ revertant rates in Ames *Salmonella* plate incorporation mutagenicity assays. Maleic Acid was examined in plate incorporation assays with the routine tester strains TA1535, TA1537, TA1538, TA98, and TA100. The doses used were 938, 1875, 3750, and 7500 μg/plate. Maleic Acid failed to induce any significant increases in revertant count in any of the strains tested.

Yanagisawa et al. (1987) tested the ability of Maleic Acid to inhibit DNA synthesis using cultures of normal human fibroblasts. The inhibition of DNA synthesis was presented as a percentage of the control incorporation of thymidine into DNA. The relative rate of DNA synthesis was calculated from the $^{3}H/^{14}C$ ratio of the culture exposed to 2.0×10^{-2} M Maleic Acid divided by that of the unexposed culture pulse-labeled at the same time. DNA-damaging and non–DNA-damaging agents could be distinguished by comparing patterns of recovery of the DNA synthesis rate after exposure to the agent. With a DNA-damaging agent, the rate of DNA synthesis would continue to decrease, but with a non–DNA-damaging agent, the rate of DNA synthesis would recover immediately or very soon after treatment of the cells with agents and their removal. In this study, Maleic Acid showed a positive pattern in the DNA synthesis inhibition test: the rate of synthesis at 90 min was greatly suppressed despite considerable recovery at 150 min.

CARCINOGENICITY

No data were available on the carcinogenicity of Maleic Acid.

CLINICAL ASSESSMENT OF SAFETY

Britz and Maibach (1979) tested 20% Maleic Acid in a vehicle of 20% propylene glycol on the volar forearm and labia majora of 21 female Caucasian volunteers. Ten microliters were applied to a circle of skin using a micropipette. All subjects were examined in 24 h; 10 were also seen in 48 h. The clinical inflammatory response varied from minimal erythema to marked erythema with marked vesiculation. The frequency of positive inflammatory response to Maleic Acid was 76% for vulvar skin and 62% for forearm skin.

Rietschel (1995) recruited 50 human subjects to apply 20% Maleic Acid in a vehicle of 20% propylene glycol, 50% ethanol, and 30% water (pH 1.4) to one forearm daily for a period of 6 weeks. These subjects were then observed for clinical accommodation. Between the 4th and 6th weeks of application, 17 subjects developed acute vesicular dermatitis deemed to be the acquisition of allergic contact dermatitis to the irritant. These subjects were dropped from the study. At the end of the 6-week period of treatment, a 4-h closed patch test to 20% Maleic Acid was performed on both the normal and treated forearm to assess the status of the subject. Only five subjects had accommodated; the remainder had varying degrees of inflammation or hyperirritable skin.

SUMMARY

Maleic Acid is a dicarboxylic acid that functions as a fragrance ingredient and as a pH adjuster. In 2002, Maleic Acid was reported to be an ingredient in three hair products and shaving creams. From an industry survey in 2004, Maleic Acid was used in "other bath products" at 0.004%. Noncosmetic uses of Maleic Acid include the manufacture of artificial resins, dyeing and finishing wool, cotton, and silk, in salts of antihistamines, and as a preservative for oils and fats. This safety assessment addresses the use of Maleic Acid as a pH adjuster only.

Maleic Acid is commonly used in research studies to induce Fanconi syndrome in rats and dogs, in an attempt to study the mechanism of this disease. Because Maleic Acid induction of Fanconi syndrome is a key aspect of these studies, there is no information on the Maleic Acid dose that does not produce the syndrome. One study did find a decreased glomerular filtration rate in rats given 9.0 mmol/kg Maleic Acid intraperitoneally, but not with 1.5 mmol/kg. Other parameters such as urinary output increases and NaK-ATPase activity decreases were affected at both doses, however, so even 1.5 mmol/kg via intraperitoneal injection was not a no-effect level.

Representative studies in which Maleic Acid is used to induce Fanconi syndrome were given. In the first study, experimental Fanconi syndrome was used to examine the renal response to protein feeding in dogs. The second study examined the mechanisms by which Maleic Acid acts on the kidney.

Preincubation with 0.75 mmol/L of Maleic Acid reduced sperm penetration of golden hamster eggs to zero.

Maleic Acid failed to induce any significant increases in revertant count in strains TA1535, TA1537, TA98, and TA100. The doses used were 938, 1875, 3750, and 7500 μg/plate. Maleic Acid showed a positive pattern in the DNA synthesis inhibition test.

Maleic Acid (10% at pH 1) applied for 30 s on rabbit eyes, caused permanent opacity. A 1% solution applied for 2 min caused cloudiness of the cornea, but no lasting injury, and a 5% solution had a similar but more intense effect, with recovery delayed 6 to 7 days.

Maleic Acid (10 μl, pH not given) applied to the volar forearm and labia majora of 21 female Caucasians produced clinical inflammatory responses at 24 or 48 h, which varied from minimal erythema to marked erythema with marked vesiculation.

Maleic Acid (20%, pH 1.4) was applied to one forearm daily for a period of 6 weeks to 50 human subjects. Seventeen subjects developed acute vesicular dermatitis between the 4th and 6th weeks of application and had to be dropped from the study. At the end of the 6-week period treatment, a 4-h patch test to 20% Maleic Acid demonstrated only five subjects had accommodated; the remainder had varying degrees of inflammation or hyperirritable skin.

DISCUSSION

Although Maleic Acid may function in cosmetics either as a fragrance ingredient or a pH adjuster, this safety assessment considered only its use as a pH adjuster. The Cosmetic Ingredient Review (CIR) Expert Panel recognized that although Maleic Acid itself may be a dermal and/or ocular irritant, its use as a pH adjustor in cosmetic formulations dictates that most of the acid will be neutralized into various maleate salts. Furthermore, the concentration of Maleic Acid used is dependent on the alkaline content of the formulations. Therefore, the concentration of free Maleic Acid is expected to be low, and systemic toxicity is not expected to be a concern.

The safety of Maleic Acid as a pH adjustor should not be based on the concentration of use, but on the amount of free Maleic Acid that remains after neutralizing the formulation. The Panel decided that the available data support the absence of any risk associated with exposure to low levels of Maleic Acid. There is no reason to expect this ingredient to induce any toxicity when used for this purpose.

CONCLUSION

The CIR Expert Panel concludes that Maleic Acid is safe for use in cosmetic formulations as a pH adjustor in the practices of use as described in this safety assessment.

REFERENCES

Applewhite, T. H., ed. 1985. *Bailey's industrial oil and fat products,* Vol 3, 4th ed. New York: John Wiley & Sons.

Brannon, W. L., G. Schwartzman, and J. Levine. 1976. Infrared identification of maleic acid in pharmaceutical maleate salts. *J. Assoc. Off. Anal. Chem.* 59:680–682.

Britz, M. B., and H. I. Maibach. 1979. Human cutaneous vulvar reactivity to irritants. *Contact Dermatitis* 5:375–377.

Brown-Woodman, P. D., E. J. Post, P. Y. Chow, and I. G. White. 1985. Effects of malonic, maleic, citric and caffeic acids on the motility of human sperm and penetration of cervical mucus. *Int. J. Fertil.* 30:38–44.

Budavari, S., ed. 1989. *The Merck Index. An encyclopedia of chemicals, drugs, and biologicals*, 11th ed. Rahway, NJ: Merck & Co.

Clayton, G. D., and F. E. Clayton, eds. 1981–1982. *Patty's industrial hygiene and toxicology: Volumes 2A, 2B, 2C: Toxicology*, 3rd ed, 4971. New York: John Wiley & Sons.

Committee of Revision of the United States Pharmacopeial Convention. 2000. *The National Formulary*, 19th ed. Rockville, MD: United States Pharmacopeial Convention.

Cosmetic Toiletries and Fragrance Association (CTFA). 2004. Ingredient Use Data—Maleic Acid. March 12, 2004.[2]

Eiam-Ong, S., M. Spohn, N.A. Kurtzman, and S. Sabatini. 1995. Insights into the biochemical mechanism of maleic acid-induced Fanconi sydrome. *Kidney Int.* 48:1542–1548.

European Economic Community. 1999.*EEC Cosmetics Directive 76/768/EEC*, as amended through the 26th Adapting Commission Directive 2002/34/EC, Annexes 1-VII. Brussels: EEC. Document accessible at http://dg3.eudra.org/F3/home.html.

Everett, R. M., G. Descotes, M. Rollin, Y. Greener, J. C. Bradford, D. P. Benziger, and S. J. Ward.1993. Nephrotoxicity of pravadoline maleate (WIN 48098-6) in dogs: Evidence of maleic acid-induced acute tubular necrosis. *Fundam. Appl. Toxicol.* 21:59–65.

Food and Drug Administration (FDA). 2002. Frequency of use of cosmetic ingredients. *FDA database.* Washington, DC: FDA.

Frazer, M. G., and J. W. Hollifield. 1980. Effect of some organic acids in the incubation step on plasma renin activity. *Clin. Biochem*. 13:34–37.

Gennaro, A. R. 1990. *Remington's pharmaceutical sciences*, 18th ed. Easton, PA: Mack Publishing.

Gottschalk, T. E., and G. N. McEwen, Jr., eds. 2004. *CTFA international cosmetic ingredient dictionary and handbook*, 10th ed., vol. 2. Washington, DC: CTFA.

Grant, J., ed. 1972. *Hackh's chemical dictionary*, 4th ed. New York, NY: McGraw-Hill.

Grant, W. M. 1986. *Toxicology of the eye*, 3rd ed., 574. Springfield, IL: Charles C. Thomas.

Harrison, H. E., and H. C. Harrison. 1954. Experimental production of renal glycosuria, phosphaturia, and aminoaciduria by injection of maleic acid. *Science* 120:606–608.

Kramer, H. J., and H. C. Gonick. 1973. Effect of maleic acid on sodium-linked tubular transport in experimental Fanconi syndrome. *Nephron*. 10:306–319.

Lake, R. S., G. L. DeVito, R. J. Szot, and E. Schwartz. 1988. Nonmutagenicity of maleic acid and its sodium salts in *Salmonella* assays. *Mutat. Res.* 207:1–6.

Lewis, R. J., Sr., ed. 1993. *Hazardous chemicals desk reference*, 3rd ed. New York, NY: Van Nostrand Reinhold.

Lewis, R. J., Sr., ed. 1997. *Hawley's condensed chemical dictionary*, 13th ed. New York: John Wiley & Sons.

Lewis, R. J., Sr., ed. 2000. *Sax's dangerous properties of industrial materials*, 10th ed., vol. 1–3, New York: John Wiley & Sons.

Lian, H. Z., L. Mao, X. L. Ye, and J. Miao. 1999. Simultaneous determination of oxalic, fumaric, amleic and succinic acids in tartaric and malic acids for pharmaceutical use by ion suppression reversed-phase high performance liquid chromatography. *J. Pharm. Biomed. Anal.* 19:621–625.

Lide, D. R. ed. 1993.*CRC handbook of chemistry and physics*, 3–311. Ann Arbor, MI: CRC Press.

Mazzo, D. J. 1984. Simultaneous determination of maleic acid and timolol by high-performance liquid chromatography. *J. Chromatogr.* 299:503–507.

Ministry of Health, Labor, and Welfare (MHLW). 2001a. Unofficial translation of MHW Ordinance No. 331, Attached Table 1 [Negative List]. Ministry of Health, Labor, and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

MHLW. 2001b. Unofficial translation of MHW Ordinance No. 331, Attached Table 2 [Restricted List]. Ministry of Health, Labor, and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

Nomiyama, K., H. Nomiyama, and M. Yotoriyama. 1982. Low-molecular-weight proteins in urine from rabbits given nephrotoxic compounds. *Ind. Health* 20:1–10.

Registry of Toxic Effects of Chemical Substances (RTECS). 2002. Chemical Synonyms. *RTECS database*. Bethesda, MD: National Library of Medicine.

Rietschel, R. L. 1995. Physiologic response of chronically inflamed and accommodated human skin. *Curr. Prob. Dermatol*. 23:104–107.

Sacks, W. 1958. Evidence for the metabolism of maleic acid in dogs and human beings. *Science* 127:594.

Stein, D. M., and H. Schnieden. 1983. Effect of antidepressant drugs on the in-vitro egg-penetrating ability of golden hamster epididymal spermatozoa. *J. Reprod. Fertil.* 68:227–233.

Woods, L. L., and E. W. Young. 1991. Impaired renal hemodynamic response to protein feeding in dogs with experimental Fanconi syndrome. *Am. J. Physiol.* 261:F14–F21.

Yanagisawa, K., K. Nishio, and S. Gotoh. 1987. Screening for carcinogens by the DNA synthesis inhibition test using human fibroblasts. *Mutat. Res.* 183:89–94.

[2]Available for review from the Director, CIR, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.