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Final Report on the Safety Assessment of Melamine/Formaldehyde Resin[1]

Abstract: Melamine/Formaldehyde Resin is intended for use as a film former in cosmetic formulations, but there are no current uses reported. Respiratory distress, bleeding in the lungs, significant weight loss, and macrophage influx into the alveoli were observed during inhalation studies in rats. A 2-year chronic feeding study in rats at concentrations ≤10% produced little toxicity. Similar results were found in dogs at concentrations of 2.5, 3, and 5%. Reproductive toxicity was evaluated in rats through two generations with no evidence of reproductive effects. Case reports in the clinical literature have reported sensitization to Melamine/Formaldehyde Resin, not all of which were attributed to the presence of formaldehyde. Available data on melamine were reviewed. No irritation or sensitization was produced by 1% (aqueous) melamine in guinea pigs. In an oral carcinogenesis assay in male rats, melamine caused transitional-cell carcinomas of the urinary bladder, but produced no tumors in female rats. Adverse effects of formaldehyde were summarized from an earlier review of that ingredient by the Cosmetic Ingredient Review. The adverse effects included respiratory damage, skin irritation and sensitization, and carcinogenesis. The available data were insufficient to support the safety of Melamine/Formaldehyde Resin. Additional data were considered necessary in order to evaluate the safety of this ingredient, including chemical and physical data (such as pH), amount of free formaldehyde as a function of pH, and the aqueous or alcohol vehicle used; impurities (or purity); physical form of the ingredient as it would be used; UV absorption data (if the ingredient absorbs in the UVB or UVA regions of the electromagnetic spectrum, photosensitization studies would be needed); 28-day dermal toxicity tests; and human irritation and sensitization. It cannot be concluded that this ingredient is safe for use in cosmetic products until the listed safety data have been obtained and evaluated. **Key Words:** Melamine/Formaldehyde Resin—Cosmetic use—Respiratory damage—Skin irritation—Carcinogenesis—Rat—Human.

Melamine/Formaldehyde Resin is the resin formed by the reaction between melamine and formaldehyde. It functions as a film former in cosmetics. The Cosmetic Ingredient Review (CIR) Expert Panel reviewed formaldehyde in 1984, and the final report on the safety assessment of this ingredient can be found in the

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

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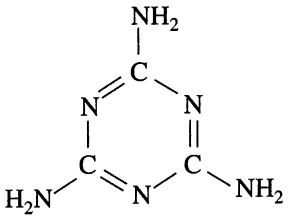
Journal of the American College of Toxicology (Elder, 1984). The present report reviews the safety data on Melamine/Formaldehyde Resin.

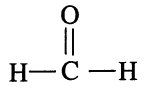
CHEMISTRY

Definition and Structure

Melamine/Formaldehyde Resin (MFR) (CAS No. 9003-08-1) is the reaction product of melamine (q.v.) with formaldehyde (Nikitakis et al., 1991). The components of MFR conform to the following formulas (Estrin et al., 1982; Elder, 1984):



Melamine



Formaldehyde

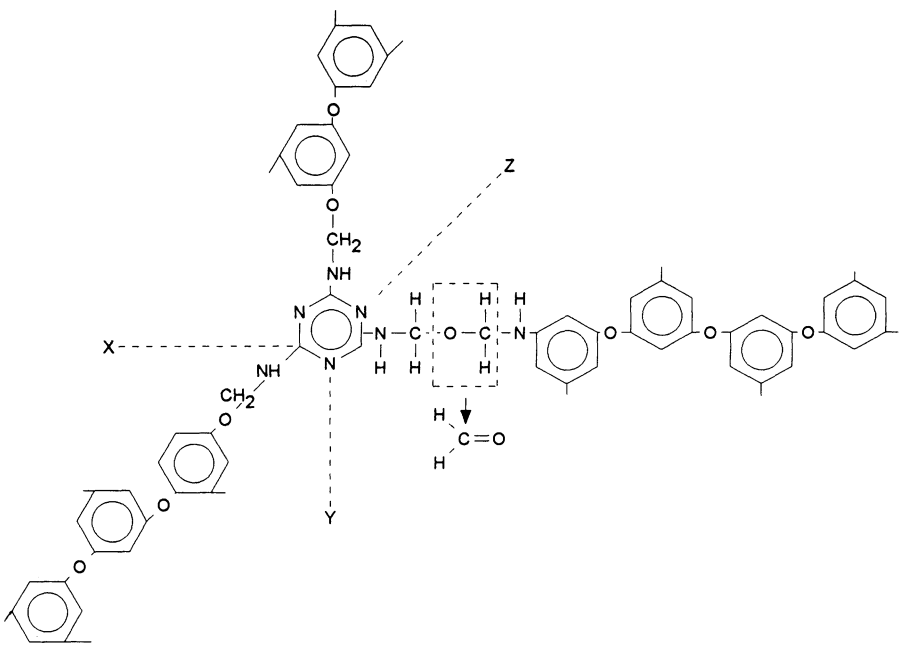
MFR is also called 1,3,5-Triazine-2,4,6-Triamine, Polymer with Formaldehyde (Nikitakis et al., 1991). One of the trade names for MFR is Parez 607 (Chemline, 1992).

Chemical and Physical Properties

The chemical and physical properties of MFR were not available in the published literature.

Method of Manufacture

MFR may be formed for use as a water-embedding medium for electron microscopy by reacting melamine with formaldehyde at low or high pH to form (mono- to hexa-) methylol-melamine. Hexa-methylol-melamine is etherified with methanol and washed with chloroform to produce hexamethylol-melamine-(mono- to hexa-) methyl-ether. These intermediates are condensed and cross-linked to form the resins. The reactivity of the intermediates is dependent on the degree of etherification; -mono-methyl-ether is highly reactive, while -hexa-methyl-ether is inert. In general, the monomers (hexamethylol-melamine-1-6 methyl ethers) are connected via ether bridges (at acidic pH, when water is cleaved off two methylol groups) or via methylene bridges (at alkaline pH, when formaldehyde is cleaved off an ether bridge). The basic framework of a polymerized melamine resin is presented in Fig. 1 (Frosch and Westphal, 1989).



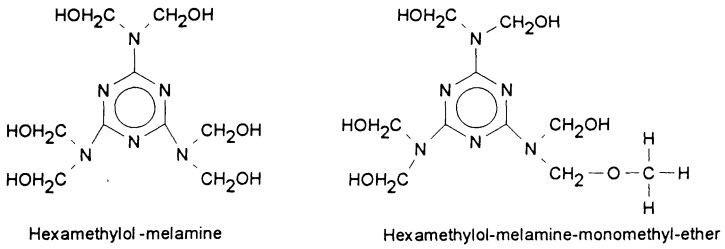


FIG. 1. Structure of the basic framework of a polymerized melamine resin. The monomers (hexamethylol-melamine-1-6 methyl-ethers) are connected via ether bridges (forming preferentially at low pH, when water is cleaved off two methylol groups) or via methylene bridges (forming preferentially at high pH, when formaldehyde is cleaved off an ether bridge, as indicated by the dotted window) (Frosch and Westphal, 1989).

Component Release from MFR

Ishiwata et al. (1986) and Sugita et al. (1990) reported that the potential exists for melamine and formaldehyde to migrate from tableware made with melamine resin. Such migration is strongly affected by heating and acidity.

Impurities

After a commercial batch of MFR was dried into a powder, it was tested for lead, arsenic, and mercury. Lead and arsenic were present below 1 ppm, and mercury content was present below 2 ppm. These values were the limits of sen-

sitivity for the colorimetric testing method used. The total concentration of heavy metals was <10 ppm (American Cyanamid Company, 1960, 1961*a*, 1961*b*).

USE

Cosmetic Use

MFR is a synthetic polymer that functions as a film former in cosmetic formulations (Nikitakis, 1988). No product formulation data on MFR were submitted to the Food and Drug Administration (FDA) in 1993 (FDA, 1993).

Noncosmetic Use

MFR is approved as an indirect food additive. It is used as a stabilizer for polyoxymethylene copolymer intended for use in contact with foods (Federal Register, 1987) and may be used as the food-contact surface of molded articles (Rothschild, 1989). Melamine resins are also used as water-embedding media for electron microscopy (Frosch and Westphal, 1989) and to impart wrinkle-resistance to fabrics (Hatch and Maibach, 1986).

ANIMAL TOXICOLOGY

Subchronic Inhalation Toxicity

A 28-day inhalation study of a formulation containing 68–71% MFR and cellulose was conducted using a liquid aerosolized form of the material. Ten male Fischer 344 rats were exposed to gravimetric concentrations of 50.7 mg/m^3 of the formulation 6 h per day for 5 days during the first 3 weeks and then for 4 days a week during the last week of the study. The mean mass median aerodynamic diameter of the formulation was 4.6 μm. A control group of rats was exposed to ambient air only. The rats were monitored throughout the study for toxicity, hematological analyses and urinalyses were conducted at the end of the study, and necropsy was performed on all of the animals.

One of the rats died on day 19 of the study, and hemorrhagic foci were found in the lungs at necropsy. All of the rats had respiratory distress (gasping), an unkempt appearance, and nasal discharge. A significant reduction in body weight gain was also observed. Alterations were found in blood and urine analyses, but the researchers attributed these changes to the debilitated condition of the rats rather than to direct target organ toxicity. At necropsy, two rats had hemorrhagic foci in the lungs. Significant changes in absolute and relative organ weight values were found for some of the rats, but the authors also attributed these changes to the debilitated state of the rats. At histopathological evaluation, an influx of macrophages into the alveoli was found in half of the rats (National Technical Information Service, 1987).

Chronic Oral Studies

Groups of 40 male and 40 female Carworth Farms Wistar Colony albino rats were fed diets containing 2.5, 5.0, and 10.0% MFR for 2 years. A control group of

rats was fed untreated feed. The animals were observed daily, and body weight and feed intake were monitored weekly. Hematology analyses were conducted on 10 rats from each group at 25, 51, 79, and 105 weeks. Following hematology testing, rats from the control and 10.0% treatment groups were killed, and necropsy and microscopic examination were performed.

No treatment-related deaths occurred, and the behavior and appearance of the MFR-treated animals were normal throughout the study. The only significant change during the study was light, whitish-colored feces from rats fed 5.0 and 10.0% MFR diets. Attention to the rate of growth was focused on the first year of the study. In general, when feed intake was adjusted on the basis of caloric intake, the male rats fed the 5.0% MFR diet and the females fed the 5.0 and 10.0% MFR diets gained significantly less weight than the controls. Caloric intake was similar between the experimental groups and the control group.

Low hemoglobin and hematocrit values were observed in male rats fed the experimental diets throughout the study, but there was no consistent relationship between dietary intake and hematology values (mean control values obtained were relatively high or relatively low at different times during the study as compared with historical values; the mean test values were similar to those normally encountered). No significant differences in mean hemoglobin or hematocrit values were observed with the female rats. Male rats from the 10.0% MFR treatment group had increased neutrophil and lowered lymphocyte counts at 25 weeks. However, these parameters were normal when evaluated at later intervals. A few test animals had increased leukocyte counts at 105 weeks, but the number of affected animals was small.

Male rats from all of the treatment groups had changes in hepatic and renal weights during the study, but these changes were not considered treatment related because the mean test weights were within historical ranges and the mean control weights were relatively low or high. Additionally, there did not appear to be a dose relationship, and the changes occurred sporadically during the study. However, at the end of the study there was a significant reduction in the testis weights of the male rats fed the 10.0% MFR diet. In the female rats, changes in organ weights were observed only at the end of the study. Females from the 5.0 and 10.0% treatment groups had increased mean hepatic and renal weights. The renal weights were greater in the females fed the 5.0% diet than in those fed the 10.0% diet. No other significant organ weight changes were observed.

At necropsy, no gross lesions related to treatment were found. Microscopic examination of the testes from the male rats on the 10.0% MFR diet indicated a significant incidence of aspermiogenesis. However, the authors suggested that this lesion may have been attributable to senile changes of vascular origin. A number of other microscopic lesions were observed, the most common being chromophobe adenoma of the pituitary, but these lesions were typical manifestations of aging, and the distribution and incidence of these lesions were similar to those of the control group (American Cyanamid Company, 1961*a*).

The chronic toxicity of MFR was also studied using dogs. Groups of two male and two female beagles were fed diets containing 2.5 and 5.0% MFR for 2 years. A control group of dogs was fed untreated feed. The dogs were observed for

clinical signs of toxicity and hematology, and clinical chemistry analyses were performed. At the end of the study, the dogs were killed with nembutal for necropsy, and microscopic examinations were performed on the major organs and tissues.

One dog from the control group was accidentally killed during the 9th month of the study. The other dogs survived the testing period and appeared normal throughout. Several cases of warts or semitransparent blebs on the tip of the tongue, lips, or other oral surfaces were observed. The MFR-treated feed appeared to be less palatable than the regular feed, but >90% of the treated feed was eaten in both groups. MFR did not appear to have any direct effect on weight gain in either of the treatment groups. During the first year of the study, hematological and clinical chemistry parameters were similar to those of the control group. In the second year, one male dog in the 5.0% MFR treatment group had reduced hemoglobin and hematocrit values. However, the researchers did not attribute this to MFR treatment, since the other dogs receiving the same treatment had normal blood values. Female dogs fed 2.5% MFR also had reduced hemoglobin and hematocrit values, but this effect was not observed in females from the 5.0% MFR treatment group. Leukocyte counts were similar for all of the animals. The authors also noted that blood urea nitrogen values sometimes exceeded 18 mg/100 ml; however, this rise was also observed during the pretreatment period and in control animals. There were no changes in either bromsulfalein excretion or blood glucose values.

At necropsy, the only significant change in organ weight was found in the testis weights of the treated dogs. One dog in the group treated with 2.5% MFR had a reduced testis weight, and both males fed the 5.0% MFR diet had markedly reduced testis weights. At microscopic examination of the testes, one dog fed 5.0% MFR was aspermatogenic, and the other dog had quantitative depression of spermatogenesis. The only other microscopic change that was attributed to MFR treatment was mild inflammation of the alimentary tract in three dogs. Other lesions were also seen in the control animals and were attributed to colony stresses of infectious and/or parasitic origin (American Cyanamid Company, 1960).

In another study, three dogs were fed 3.0% MFR in their diet for 53 weeks, and clinical, hematological, and microscopic examinations were performed. A control group of dogs was fed an untreated diet. One dog fed the experimental diet died during week 24 of the study, and its death was attributed to pneumonia. The remaining two dogs survived until the end of the study. During the first week of the study, these dogs vomited after ingesting the treated feed, but vomiting ceased during the following weeks. Behavior was normal throughout the study. Both dogs gained weight normally until weeks 42 and 48, when both had reduced feed intake and weight loss. Tapeworms were present in several fecal samples during the study, and at necropsy the intestines of both dogs contained worms.

Hematological values, urine analyses, and the results of the liver and kidney function tests were similar to those of the control dogs. No gross lesions were found at necropsy, and no treatment-related lesions were found when microscopic examinations were performed on the major organs and tissues (Hazelton Laboratories, 1953).

Reproduction Study

The effects of MFR on reproduction and lactation were investigated using Carworth Farms Nelson Colony rats. Groups of 15 male and 20 female rats (F_0 generation) were fed diets containing 2.5 or 10.0% MFR, and matings were conducted at 110 days of age (~13 weeks on test diet) (Table 1). Three successive matings were performed with the F_0 animals. In each case, matings were performed 11 days after the youngest F_1 generation was weaned. The three litters were designated as F_{1a}, F_{1b}, and F_{1c}. Fertility, gestation, viability (the percentage of newborn that survived 4 days), and lactation were monitored. After the third litter was sired, the males from the F_0 generation (≈9 months old) were killed and necropsied. The female rats from this generation (≈10.5 months old) were killed and necropsied after the third litter was weaned. The first and third litters (F_{1a} and F_{1c}) were killed after weaning. Most rats of the second litter (F_{1b}) were killed, except for the offspring from control rats (Group 1) and from 10.0% MFR–treated rats (Group 7), in order to represent as many different litters as possible. These offspring were fed the same diet as the adults. All of the F_0 rats and the remaining F_{1b} rats were examined for gross lesions. The testes of the control male rats and those fed the 10% MFR diet were examined microscopically.

None of the rats had changes in appearance or behavior at any time during the study, and no treatment-related deaths occurred. Fertility, gestation, viability, and lactation were all within the parameters observed in the control group, and no treatment-related gross lesions were found in any of the animals. Testis weights were unaffected by the ingestion of MFR. However, at microscopic examination, zonal aspermiogenesis was observed in two of 18 in the F_0 generation controls, four of 13 in the F_0 generation fed 10.0% MFR, one of eight in the F_{1b} generation controls, and none of the 12 in the F_{1b} generation fed 10.0% MFR. The authors suggested that there was a possibility that the testicular specimens were autolyzed before fixation was complete, and they noted that reduced spermiogenesis, the predecessor to aspermiogenesis, was not present. Therefore, they concluded that there was no qualitative difference in the occurrence of either testicular lesions or aspermiogenesis in the F_0 generation. Additionally, no evidence of adverse effects on spermiogenesis was found in any of the F_{1b} generation fed the 10.0% MFR diet (American Cyanamid Company, 1961*a*).

Dermal Irritation and Sensitization to Melamine

In a study with guinea pigs, 1% aqueous melamine caused little or no irritation and was not a sensitizer, but details of this study were not provided (Sutton, 1963).

TABLE 1. *Matings at 110 days of age*

Group	Male	Female
1	Control	Control
2	Control	2.5% MFR
3	Control	10.0% MFR
4	2.5% MFR	Control
5	2.5% MFR	2.5% MFR
6	10.0% MFR	Control
7	10.0% MFR	10.0% MFR

CARCINOGENICITY

Chronic oral toxicity studies with rats and dogs were presented earlier in this report. As described in these studies, no treatment-related gross lesions were found in the animals from any of the studies. However, reduced testis weights were found in both rats and dogs. Microscopic examination of the testes indicated aspermiogenesis and/or depression of spermatogenesis (see Chronic Oral Toxicity for details).

Carcinogenicity data are available on the components of MFR, formaldehyde, and melamine. According to the International Agency for Research on Cancer (IARC), "there is sufficient evidence that formaldehyde gas is carcinogenic to rats." They noted that concentrations of formaldehyde that cause nasal neoplasms also cause acute degeneration, necrosis, inflammatory changes, and increased cell replication (hyperplasia) of the nasal mucosa of rats and mice following inhalation exposure (IARC, 1982).

In an oral carcinogenic bioassay, melamine caused transitional-cell carcinomas of the urinary bladder of male F344/N rats. Urinary bladder stones were found in all but one of the rats. Melamine was not carcinogenic for female F344/N rats and for male and female B6C3F1 mice (National Technical Information Service, 1983).

CLINICAL STUDIES

Observed clinical effects of MFR exposure appear to be primarily related to the presence of formaldehyde gas. CIR published a safety assessment on formaldehyde, reporting that airborne formaldehyde is an ocular and respiratory irritant and may induce hypersensitivity and other effects [see Table 2 (National Research Council, 1981)]. In its report, the CIR Expert Panel stated that it could not be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized (Elder, 1984). Based on an assessment of all of the available data, however, the Expert Panel concluded that formaldehyde in other cosmetic formulations is safe to the great majority of consumers. The Expert Panel concluded, based on skin sensitivity of some individuals to this agent (Marzulli and Maibach,

TABLE 2. *Reported human health effects of formaldehyde at various airborne concentrations*

Reported effect	Approximate formaldehyde concentration (ppm)
None	0–0.05
Neurophysiologic effects	0.05–1.5
Odor threshold	0.05–1.0
Eye irritation	0.01–2.0[a]
Upper-airway irritation	0.10–25
Upper-airway and pulmonary effects	5–30
Pulmonary edema, inflammation, pneumonia	50–100
Death	100+

[a] The low concentration (0.01 ppm) was observed in the presence of other pollutants that may have been acting synergistically.

1974; Jordan et al., 1979; North American Contact Dermatitis Group, 1980; Fielder, 1981; National Research Council, 1981; Elder, 1984), that cosmetic products containing formaldehyde should be formulated to ensure use at the minimal effective concentration, not to exceed 0.2% measured as free formaldehyde (Elder, 1984).

Dermal Irritation and Sensitization

Several case reports of contact dermatitis in patients wearing orthopedic casts containing 10% MFR have been detailed in the literature. Sensitization was attributed to the release of formaldehyde from the cast material (Logan and Perry, 1972; Logan and Perry, 1973). In another study, an orthopedic plaster technician developed vesicular eczema after working with MFR-reinforced plaster bandages for 14 months. When he was patch-tested with 10% MFR and with 1% formaldehyde, he reacted only to MFR (Ross et al., 1992). In a case report, a man involved in the manufacture of casting molds showed signs of contact dermatitis. This condition was attributed to free formaldehyde found in the molds, which were made from a gypsum-MFR mixture (Fregert, 1981).

Case reports of contact dermatitis from textiles treated with formaldehyde resins have also been reported. Most cases of sensitization have been attributed to free formaldehyde (Schwartz, 1941; Marcussen, 1962; O'Quinn and Kennedy, 1965; Shellow and Altman, 1966). A few studies have reported sensitivity to formaldehyde resins (Malten, 1964; Hatch and Maibach, 1986). Most recently, Fowler et al. (1992) reported on 17 patients with contact dermatitis due to formaldehyde textile resins, who were patch-tested with both the resins and formaldehyde alone. Five of the patients (30%) had positive responses to the resins alone, while the others responded positively to both the resins and formaldehyde.

Environmental and Occupational Exposure

Clinical evaluations were made of six male workers employed in the production of MFR. A detailed medical history, clinical examination, chest radiograph, and complete blood count were counted for each worker. Formic acid excretion in the urine was also measured. The greatest number of subjective adverse symptoms was reported by the subject who excreted the most formic acid. All of the subjects had adverse clinical effects, the majority of which were attributable to free formaldehyde exposure. However, three individuals had total lymphocyte counts >3,500, and four subjects low hemoglobin values. These blood effects were not characteristic of formaldehyde exposure (Srivastava et al., 1992).

Contact Dermatitis

Markuson et al. (1943) investigated a severe dermatitis outbreak among industrial workers due to exposure to formaldehyde resins. Of 2,370 workers from four different plants, 355 had dermatitis. Many of the cases required hospitalization. In a field study of occupational dermatoses in a prefabrication construction factory, none of the 272 workers patch-tested for a variety of potential allergens responded

to 10% MFR (Goh et al., 1986). Fowler et al. (1992) did a retrospective evaluation of patients referred for patch-testing for eczematous dermatitis thought to be allergic in nature. The patients were seen at two institutions between January 1988 and April 1990. Each patient was patch-tested with commercially prepared textile allergens, the standard screening tray of the North American Contact Dermatitis Group, and a series of other allergens selected individually by the investigators. Of the 1,022 patients evaluated, 17 were allergic to formaldehyde resins. Five of the cases were occupationally related, and the others were related to exposure to garments treated with formaldehyde resins.

Carcinogenicity

Blair et al. (1990) studied a historical cohort of 26,561 workers employed in formaldehyde industries to evaluate the cancer risks associated with exposure to formaldehyde. Formaldehyde alone could not be directly linked with elevated risks for lung cancer. However, elevated mortality from lung cancer was associated with workers involved in the production of formaldehyde resins and molding compounds who had contact with melamine. The standardized mortality ratios (SMR) for workers exposed to melamine and formaldehyde ranged from 0.8 to 2.0. A control group of workers not exposed to formaldehyde had an SMR of 0.9. The SMR for workers exposed to formaldehyde alone was 1.0.

SUMMARY

MFR is the resin produced by the reaction between melamine and formaldehyde, which functions as a film former in cosmetic products. Although it is not presently used in cosmetic formulations, the cosmetic industry has expressed an interest in using MFR in future formulations. Aerosolized MFR (50.7 mg/m^3) was toxic to rats in a subchronic study. Alterations were observed in body weight gain, blood and urine analyses, and absolute and relative organ weight values. Hemorrhagic foci were found in the lungs of two animals, and alveolar histiocytosis was observed in half of the animals. However, no direct evidence of specific target organ toxicity was observed.

In chronic oral toxicity studies, MFR caused a reduction in the weight of the testes in both rats and dogs. Microscopic examination of the testes indicated aspermiogenesis and/or depression of spermatogenesis. Mild inflammation of the alimentary tract was also observed in dogs. No other treatment-related lesions were found in these studies. In a reproduction study, rats were administered MFR at $\leq$10% in their feed. There was no evidence of adverse effects on fertility, gestation, viability of the fetuses, and lactation through three successive matings. Clinical contact dermatitis following exposure to MFR is primarily related to exposure to free formaldehyde. However, in some studies the resin itself was a sensitizer.

In its evaluation of formaldehyde, the CIR Expert Panel concluded that it was not safe for use in cosmetic products intended to be aerosolized. Other cosmetic products containing formaldehyde should be formulated to ensure use at the minimal effective concentration, not to exceed 0.2% measured as free formaldehyde.

DISCUSSION

Although oral toxicity data are included in the report, the CIR Expert Panel concluded that a 28-day dermal toxicity study specifically examining the effects on the skin was needed. They were also concerned about the potential release of formaldehyde from MFR and noted a lack of information about the physical form and properties of MFR used in cosmetics, as well as data on irritation and sensitization.

Section 1, paragraph (p), of the CIR Procedures states that "A lack of information about an ingredient shall not be enough to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on MFR are insufficient to determine whether MFR, under each relevant condition of use, is either safe or unsafe. The Expert Panel released a "Notice of Insufficient Data Announcement" on June 1, 1993, outlining the data needed to assess the safety of MFR. The types of data required included: (1) chemical and physical data (pH, percentage free formaldehyde at pH of use in aqueous or alcohol vehicles), (2) impurities, (3) physical form of MFR used in cosmetics and the concentration of use, (4) UV absorption data (if MFR absorbs in the UVA or UVB region, photosensitization studies will be required), (5) 28-day dermal toxicity, and (6) human irritation and sensitization. No offer to supply the data was received. In accordance with section 45 of the CIR procedures, the Expert Panel will issue a Final Report–Insufficient Data. When the requested new data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

CONCLUSION

The safety of this ingredient has not been documented and substantiated. The CIR Expert Panel cannot conclude whether Melamine/Formaldehyde Resin is safe for use in cosmetic products until such time as the appropriate safety data have been obtained and evaluated.

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