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# Final Report on the Safety Assessment of Chloroacetamide

Chloroacetamide is a chlorinated aliphatic amide used as a preservative in U.S. cosmetic formulations at concentrations of less than or equal to 1.0%. The antimicrobial spectrum for certain test microorganisms required concentrations up to 0.3% for minimal inhibition and 0.5% for a minimal germicidal effect.

The acute oral LD<sub>50</sub> for this compound was 155 mg/kg for mice, 70 to 138 mg/kg for rats, 31 mg/kg for dogs, and 122 mg/kg for rabbits. Chloroacetamide was neither an ocular nor a skin irritant when tested at 5.0% in the rabbit. No sensitization was reported in three separate studies using guinea pigs at test concentrations of 0.07%, 0.21%, and 1.0%.

In a 13-week subacute oral study in rats, Chloroacetamide at concentrations of 12.5 and 50 mg/kg produced testicular atrophy but no other observable external effects. In a 90-day oral toxicity study in rats, Chloroacetamide at concentrations of 500 mg/kg produced an increase in leukocytes. In a teratogenic study, Chloroacetamide was toxic at a dose of 50 mg/kg but did not produce teratomas in the surviving young rats.

Chloroacetamide was nonmutagenic in the Ames assay, both with and without activation, in a micronucleus study, and in dominant lethal assays.

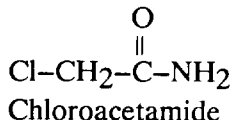
In predictive RIPT sensitization studies, Chloroacetamide was a human sensitizer at concentrations of 0.5% and 1.25%. A third RIPT study on 150 subjects confirmed the sensitization results at 0.5%.

Based on the data included in this report and the reconfirmation that Chloroacetamide is a potential human sensitizer at use concentrations, it is concluded that Chloroacetamide is unsafe for use as a cosmetic ingredient.

## CHEMISTRY

### Definition and Structure

Chloroacetamide (CAS No. 79-07-2) is the aliphatic amide with a formula of C<sub>2</sub>H<sub>4</sub>ClNO and molecular weight of 93.52. It conforms to the structure<sup>(1)</sup>:



Synonyms for Chloroacetamide include chloracetamide; acetamide, 2-chloro, 2-chloroacetamide; alpha-chloroacetamide; 2-chloroethanamide; mergal AF; chloracetamid and microcide.<sup>(2)</sup>

## Chemical and Physical Properties

Chloroacetamide is a white to pale yellow powder with a faint characteristic odor. It is soluble in water and alcohol and very slightly soluble in ether<sup>(3)</sup> (Table 1).

**TABLE 1.** CHEMICAL AND PHYSICAL PROPERTIES OF CHLOROACETAMIDE

<i>Property</i>	<i>Chloroacetamide</i>	<i>Reference</i>
Description	White to pale yellow powder	3
Melting range	114–121°C	3
Boiling point	224.5°C	4
Acetamide	0.2 max.	3
Chloroacetic acid	2.0 max.	3
Moisture	0.5 max.	3

## Method of Manufacture

Chloroacetamide is prepared from reactions of ethyl chloroacetate with ammonia or from reactions of chloroacetyl chloride and ammonium acetate.<sup>(5)</sup>

## Impurities

One European manufacturer of Chloroacetamide listed the following specifications<sup>(6)</sup>:

2-Chloroacetamide	99.5–99.8%
Ammonium chloride	0.1–0.2%
Monochloroacetic acid	0.03%
Water	0.1–0.3%

## Analytical Methods

Analytical methods for the separation and/or determination of Chloroacetamide include thin layer chromatography,<sup>(7)</sup> fluorometry, infrared spectrometry, and gas chromatography.<sup>(8)</sup>

## Chemical Reactions

Chloroacetamide is suitable for use with anionic, cationic, and nonionic surfactants. However, it is incompatible when used with strong acids or bases.<sup>(9)</sup>

## USE

### Cosmetic Use

Chloroacetamide is used as a preservative and antiseptic in cosmetics. Its function is to retard the deterioration of cosmetic products by slowing the growth of bacteria or fungi.<sup>(10)</sup> The antimicrobial spectrum of Chloroacetamide is presented in Table 2.

**TABLE 2.** ANTIMICROBIAL SPECTRUM OF CHLOROACETAMIDE<sup>(9)</sup>

Test organisms ( $\sim 10^6$ CFU/ml)	Minimal germicidal concentration ( $\mu\text{g/ml}$ ) (suspension test; contact times of 24 and 72 h)	Minimal inhibitory concentration ( $\mu\text{g/ml}$ ) (serial dilution test; incubation times of 24 and 72 h)
<i>Staphylococcus aureus</i>	5000	2000
<i>Escherichia coli</i>	3000	3000
<i>Klebsiella pneumoniae</i>	3000	3000
<i>Pseudomonas aeruginosa</i>	5000	2500
<i>Candida albicans</i>	2500	500
<i>Aspergillus niger</i>	5000	500
<i>Penicillium notatum</i>	2500	500

**TABLE 3.** PRODUCT FORMULATION DATA FOR CHLOROACETAMIDE<sup>(11)</sup>

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%) $\leq 1.0$
Mascara	285	1	1
Foundations	430	4	4
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	707	12	12
Moisturizing and related skin care preparations	2020	15	15
Other skin care preparations	941	13	13
1987 Totals		44	44

Data submitted to the Food and Drug Administration (FDA) in 1987 by cosmetic firms participating in the voluntary cosmetic registration program indicated that Chloroacetamide was used in a total of 44 formulations. This preservative is used in a variety of products, including bath, eye, and facial products, at concentrations less than 1.0%<sup>(11)</sup> (Table 3).

The FDA cosmetic product formulation computer printout<sup>(12)</sup> is compiled through voluntary filing of such data in accordance with Title 21 Part 720.4 of the Code of Federal Regulations.<sup>(13)</sup> Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product. The actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Chloroacetamide is listed in Annex VI, Part 1, of the European Economic Community (EEC) Cosmetics Directive as a preservative allowed for use in cosmetics. The maximum authorized concentration for Chloroacetamide is 0.3%, and the warning "contains chloroacetamide" must be printed on the label.<sup>(14)</sup>

Cosmetic products containing Chloroacetamide are typically applied to the eye area, skin, face, and hair. Cosmetics formulated with Chloroacetamide may be applied from once a day to several times a day and may stay in contact with the skin for several hours. The formulations also have the potential for repeated application over the course of many years.

### **Noncosmetic Use**

Chloroacetamide is cited as an indirect food additive in the Code of Federal Regulations. It may be used as a component of adhesives used in articles intended for packaging, transporting, or holding food provided the adhesive is either separated from the food by a functional barrier or does not exceed the limits of good manufacturing practice.<sup>(13)</sup>

Chloroacetamide also is used as a preservative for emulsions, cutting oils, hides, and paintings.<sup>(9)</sup>

## **GENERAL BIOLOGY**

### **Biochemical Effects**

Chloroacetamide was added to isolated hepatocytes to study the relation of hepatic glutathione (GSH) depletion to lipid peroxidation and cell lysis. In cells incubated with a concentration of 0.2 mM Chloroacetamide, malondial-dehyde increased during the third hour of incubation. GSH depletion was observed after 30 min, followed by an increase in plasma membrane permeability. The authors stated that Chloroacetamide, as a GSH-depleting compound, "promoted lipid peroxidation and subsequent cellular lysis."<sup>(15)</sup>

Chloroacetamide acted as a reversible inhibitor of carbonic anhydrase B prepared from human erythrocytes. However, it did not inactivate the enzyme, which catalyzes the hydration of CO<sub>2</sub>, the dehydration of carbonic acid, and the hydrolysis of some esters.<sup>(16)</sup>

## **ANIMAL TOXICOLOGY**

### **Acute Toxicity**

#### **Oral**

Although the number of animals used to determine acute oral toxicity was not stated, there is general agreement in the acute oral toxicity tests of Chloroacetamide in laboratory animals as reported in two different summary reports.

Acute LD<sub>50</sub> values in mice have been reported as 150 mg/kg<sup>(9)</sup> and 155 mg/kg.<sup>(2)</sup> Values of 70 mg/kg<sup>(2)</sup> and 138 mg/kg<sup>(9)</sup> have been listed for the acute LD<sub>50</sub> of Chloroacetamide in rats. Chloroacetamide in dogs and rabbits had LD<sub>50</sub> values of 31 mg/kg and 122 mg/kg, respectively<sup>(2)</sup> (Table 4). Chloroacetamide is highly toxic, according to the classification of Hodge and Stener.<sup>(17)</sup>

### Intraperitoneal

Chloroacetamide has a reported i.p. LD<sub>50</sub> of 100 mg/kg in mice.<sup>(2)</sup> The maximum tolerated dose of Chloroacetamide in mice (number not stated) was 100 mg/kg; 150 mg/kg was reported as the minimum lethal dose<sup>(18)</sup> (Table 4).

**TABLE 4.** ACUTE TOXICITY OF CHLOROACETAMIDE

<i>Route of administration</i>	<i>Animal</i>	<i>LD<sub>50</sub> value</i>	<i>Reference</i>
Oral	Mouse	150 mg/kg	9
Oral	Mouse	155 mg/kg	2
Oral	Rat	138 mg/kg	9
Oral	Rat	70 mg/kg	2
Oral	Dog	31 mg/kg	2
Oral	Rabbit	122 mg/kg	2
Intraperitoneal	Mouse	100 mg/kg	2
Intraperitoneal	Mouse	100 mg/kg (maximum tolerated dose)	18
Intraperitoneal	Mouse	150 mg/kg (minimum lethal dose)	18

### Hepatotoxicity

Male Sprague-Dawley rats, weighing 180 to 200 g, were used in a study of the effects of Chloroacetamide on the liver. A single intraperitoneal dose of 37.5 mg/kg Chloroacetamide, dissolved in a 0.9% NaCl solution, had no apparent effect on the lipid peroxidation or hepatic morphology. Doses of 112.5 mg/kg resulted in a high mortality within 5 to 6 h. The dose selected for the study was 75 mg/kg because it was nonlethal but induced morphological and biochemical changes. There was a rapid drop in hepatic glutathione concentration during the first hour after the administration of the Chloroacetamide. Lipid peroxidation, measured by the thiobarbituric acid method, increased after 3 h and reached a peak by 24 h after the dose. Swelling, hydropic degeneration, and single, necrotic hepatocytes were seen by light microscopy in the livers from rats treated with the 75 mg/kg dose. These alterations were diffused after 3 h but were accentuated in the peripheral and midzonal areas after 6 and 8 h. After 8 h, Kupffer cell proliferation was noted, although no infiltration of leukocytes could be seen. There were faint signs of hydropic degeneration in the peripheral two thirds of the lobule 1 week after the single dose of 75 mg/kg was administered. A microscopic examination of the livers from rats that had received the dose of 112.5 mg/kg revealed fatty degeneration and extensive necrosis of the centrilobular areas accompanied by leukocytic infiltration. Pronounced capillary congestion with hemorrhages and disruption of the normal lobular structure was seen in the peripheral lobular areas. Massive Kupffer cell proliferation as well as necrosis and hyalinization of hepatocytes could be seen in some areas in the periphery. After 2 weeks of repeated injections every second day with 37.5 mg/kg Chloroacetamide, changes similar to those described for a single

dose of 75 mg/kg were induced. Fasting the rats overnight prior to treatment augmented the response to a single dose of 75 mg/kg of Chloroacetamide.<sup>(19)</sup>

### Ocular Irritation

Six albino rabbits were used in a Draize eye irritation test of a solution containing 70% Chloroacetamide and 30% sodium benzoate. No irritation was observed after 0.1 ml of a 5% solution of Chloroacetamide was instilled into the conjunctival sac of the rabbit eye.<sup>(6)</sup>

### Skin Irritation and Sensitization

No sensitization or irritation was observed when Chloroacetamide in white petroleum jelly was tested at 9.0% and challenged with a 3.0% aqueous solution.<sup>(20)</sup> A modified Magnusson and Kligman procedure was used on 20 Pirbright guinea pigs; groups of 10 animals were used for the positive and negative controls.

A Buehler test for sensitization was performed in which a 0.3% solution of 70% Chloroacetamide and 30% sodium benzoate (0.21% effective ingredient test concentration) on 20 Pirbright guinea pigs. The test material was applied one time per week for 3 weeks on abraded skin and covered by an occlusive patch. After a 2-week nontreatment period, the test animals were challenged with the preservative solution used for induction. No sensitization effect was observed.<sup>(6)</sup>

No sensitization was observed when a 1% Chloroacetamide solution was used in a skin painting study on the intact skin of 10 Pirbright guinea pigs. The aqueous test material was applied 9 times at 48-h intervals. After a 2-week nontreatment period, the animals were challenged with the 1% solution. The same procedure, but applied to the abraded skin of guinea pigs, did not induce observable signs of sensitization.<sup>(6)</sup>

No sensitization was induced by a skin-cleaning formulation containing 0.07% equivalent concentration of Chloroacetamide. The material was applied to the skin of 8 guinea pigs, one time per week for 3 weeks; following a 2-week nontreatment period, the test animals were challenged with the same formulation. A similar test procedure on the abraded skin of 8 guinea pigs failed to induce sensitization.<sup>(6)</sup>

### Subchronic Oral

Four groups of 20 Wistar rats (10 male, 10 female) were used in a 90-day oral toxicity study. The animal groups were given food one time per day containing 0, 20, 100, or 500 mg Chloroacetamide (100 mg/kg food was considered to be equivalent to approximately 10 mg/kg body weight). All animals survived. An increase in leukocytes occurred in all the animals fed the highest concentration of Chloroacetamide. There was a decrease in liver weight in the females and a decrease in testicular weight in the males at the highest dose. Spermatogenesis was blocked in the male at the high dose.<sup>(6)</sup>

### Teratogenicity

A study was conducted to investigate the teratogenic potential of Chloroacetamide. The Chloroacetamide was tested on CD and BD IX rats. A dose of 50 mg/kg was the highest dose tested, representing 71% of the reported LD<sub>50</sub> of 70 mg/kg. A single 50 mg application was given by gavage to 3 pregnant females of each strain on the 13th and

14th day of gestation. The dose of 50 mg/kg resulted in the postnatal death of approximately half of the young animals. The surviving offspring developed entirely normally. Chloroacetamide had no effect on prenatal development even at high dosages.<sup>(21)</sup>

Long Evans strain of rats (number not stated) received 20 mg/kg oral doses of Chloroacetamide at the 7th, 11th, and 12th day of gestation. There was no toxicity produced to either the dam or fetus, and no teratological effect was found in fetuses.<sup>(22)</sup>

## MUTAGENICITY

Chloroacetamide was tested for mutagenicity using the Ames test with *Salmonella typhimurium* strains TA98, TA100, TA1538, TA1537, and TA1535. The ingredient, tested as a 70% Chloroacetamide and 30% sodium benzoate mixture, was nonmutagenic, both with and without metabolic activation. The Chloroacetamide mixture was tested at concentrations of 0.5 µg to 1000 µg per plate. Four positive controls were included in the testing program.<sup>(6)</sup>

There was no increase of structural and numerical chromosome aberrations when Chloroacetamide, as a 70% solution with 30% sodium benzoate, was tested at 12.5, 25, and 50 mg/kg in the micronucleus test assay. The number of Chinese hamsters used in the study was not reported.<sup>(6)</sup>

A mixture containing 70% Chloroacetamide and 30% sodium benzoate was nonmutagenic in a dominant lethal assay carried out with intraperitoneal injections of 114 and/or 123 mg/kg of the mixture in 30 male and 720 female NMRJ mice.<sup>(6)</sup>

Chloroacetamide did not produce morphological transformations in a Syrian hamster embryo cell transformation assay. The highest concentration tested, 50 µg/ml, did not reduce the cell survival rate below 40% of the solvent control. The testing program included both positive and negative controls.<sup>(23)</sup>

## CLINICAL ASSESSMENT OF SAFETY

### Dermal Irritation and Sensitization

A modification of the Draize patch test was completed with Chloroacetamide and 147 volunteers, 114 males and 33 females. An aqueous solution of 0.5% Chloroacetamide was applied to the same site on the upper back on Monday, Wednesday, and Friday for 3 consecutive weeks. The patches were left in contact with the skin until the next replacement patch was applied. After a 2-week nontreatment period, two consecutive challenge patches were applied for 48 h to the same previously untreated site. Positive reactions at challenge were seen in 47 of the 147 subjects tested, an approximate sensitization rate of 32%. The sensitization rate for females, 19/33 positive or 58%, was significantly different from that of the males, 28/114 positive or 25%<sup>(24)</sup> (Table 5).

Chloroacetamide was tested in a modified Draize procedure at a concentration of 1.25% in a cream base on 205 volunteers. The test material, 0.5 g, was applied to the upper arm under an occlusive patch for 48 or 72 h in 10 successive applications. After a nontreatment period of 2 weeks, a challenge patch was applied to the skin. The reactions were scored after the challenge application was in contact with the skin for 72

**TABLE 5.** SUMMARY OF HUMAN SENSITIZATION STUDIES OF CHLOROACETAMIDE

Concentration (%)	No. of subjects	Type	Procedure	Results	Reference
1.25	205	Volunteer	RIPT	35/205	25
0.5	147	Volunteer	RIPT	47/147	24
0.7	14	Patients	1 application	0/14	34
0.7	18	Normal patients	1 application	0/18	34
	84	Eczema patients	1 application	0/84	
0.35	209	Eczema patients	1 application	0/209	33
0.2	296	Eczema patients	1 application	7/296	27
0.14	100	Selected dermatological patients with skin disease and drug treatment	Single patch	12/100	30
0.14	125	Patients not treated with drug ointment	Single patch	1/125	30
0.2	501	Dutch contact dermatitis selected patients	Single patch	3/501	32
0.18	18	Patients	1 application	2/18	31
	200	Patients	1 application	1/200	31
0.1	465	Eczema patients	1 application	7/465	27
0.1	180	House painters	1 48 h patch	5/180	28
2.0	6	Total of 6 subjects	1 application,	4/6	26
0.5		who were previously	6 months after	1/6	
0.1		positive in Draize	positive Draize	0/6	
0.05		procedure at 10%	procedure at 10%	0/6	

h. A positive reaction had both erythema and edema. Of the 205 subjects tested, 35 had positive reactions, a sensitization rate of 17%<sup>(25)</sup> (Table 5).

Six subjects were used in a study of the effect of elicitation concentration in contact dermatitis testing. All of the subjects had positive reactions to a 1% solution of Chloroacetamide in a Draize test conducted 6 months before the study reported here. Chloroacetamide at four concentrations in petrolatum (6.05, 0.1, 0.05, and 2%) was applied to the upper back of the subjects, and the reactions were scored. Four of the 6 subjects had positive reactions to the 2% concentration, and 1 subject had a positive reaction to the 0.5% concentration. None of the subjects had reactions to the 0.1 and 0.05% concentrations<sup>(26)</sup> (Table 5).

Chloroacetamide was patch tested on 465 dermatological patients ranging in age from 2 to 80 years, with an average age of 37 years. Chloroacetamide, 0.1% in petrolatum, was applied using the ICDRG procedure and scored at 24, 48, and 72 h. Seven of the 465 subjects had a positive reaction to Chloroacetamide. Of the 7 subjects who had positive reactions, 5 were younger women who had mainly facial lesions. The investigators stated, "it is certain that the majority of patients were sensitized by cosmetics"<sup>(27)</sup> (Table 5).

Chloroacetamide was tested at a concentration of 0.1% in petrolatum on 180 house painters who had a skin disease at the time of testing. Patches were left in contact with



the skin for 48 h, and reactions were scored 24 h after the removal of the patch. Of the 180 painters tested, 5 (2.8%) had a positive reaction to the Chloroacetamide.<sup>(28)</sup> Four of the 5 painters who had positive reactions had been in contact with glue A, which contained 0.12% Chloroacetamide, and had positive reactions to the glue and to dilutions of 20 and 50%. Glue B, which contained 0.15% Chloroacetamide, produced positive reactions in both of the 2 painters who had been tested with it. The fifth painter had been in contact with glue C, which contained 0.18% Chloroacetamide, and reacted to the glue and dilutions of 50 and 20%. The authors stated that "chloroacetamide is an essential etiological factor in painters with occupation hand eczema"<sup>(29)</sup> (Table 5).

In a 1.5 year period, 15 patients were seen with an allergic reaction to an ointment used in the treatment of chronic venous insufficiency of the legs. Subsequently, 100 patients with this disturbance were tested for their sensitivity to the ointment. The ointment contained preservative CA 24, a mixture of 70% Chloroacetamide and 30% sodium benzoate. The preservative concentration was 0.2%, corresponding to a Chloroacetamide concentration of 0.14%. In the study, 12 of the 100 patients tested had an allergic reaction to the ointment. As a control, patch tests were performed on 125 patients who were not known to be under treatment with the ointment. One of the 125 had a positive reaction, and this patient had been treated previously with the ointment for an ulcer of the leg. The 27 patients with known ointment allergy were tested with several of the components of the ointment. In the 22 patients tested with preservative CA 24 in a 0.2% aqueous solution, 17 had a positive reaction. Chloroacetamide, 0.2% in aqueous solution, was tested in 19 patients, and 17 had positive reactions. The authors speculated that sensitization to Chloroacetamide might occur more easily when it is applied to broken skin and concluded that Chloroacetamide should be omitted from products destined for the treatment of skin diseases<sup>(30)</sup> (Table 5).

A group of 18 subjects was used to investigate the irritating effects of a cosmetic cream. Positive reactions were seen in 2 women, and patch testing of components of the cream determined that the allergen was the preservative that had Chloroacetamide (70%) and sodium benzoate (30%) as active ingredients. The amount of preservative used in the cream was not stated. Both positive subjects were tested subsequently with Chloroacetamide at a concentration of 0.18%. Positive reactions in both subjects were reported. Sodium benzoate was tested in one patient, and no sensitization was produced. Subsequent to this testing, Chloroacetamide, at a concentration of 18%, was included in the standard patient patch test procedure. One positive reaction to Chloroacetamide was observed in 1 of 200 patients tested<sup>(31)</sup> (Table 5).

The Dutch Contact Dermatitis Group included Chloroacetamide in its contact allergy patient testing program. The test procedures were carried out in accordance with the International Contact Dermatitis Group (ICDRG) on patients who were suspected of having contact dermatitis. Three of 501 patients gave a positive allergenic response to 0.2% Chloroacetamide in petrolatum.<sup>(32)</sup>

A 0.5% mixture of Chloroacetamide (70%) and sodium benzoate (30%) was patch tested using 209 subjects. Some of these subjects had undescribed allergies before this test. No irritation, sensitization, nor photosensitization resulted from the test<sup>(33)</sup> (Table 5).

Additional single patch test data on humans at concentrations of 0.7% (14 subjects), 0.35% (10 subjects), 0.7% (18 subjects plus 84 patients), 0.07% (8 subjects), and 0.14% (17 subjects) have been reported.<sup>(34)</sup> The test material was nonirritating and well tolerated.

## Ocular Irritation

A mixture of 70% Chloroacetamide and 30% sodium benzoate was tested for ocular irritation in humans. A 5% solution of this mixture was instilled without rinse into the human eye and caused slight discomfort, lachrimation, and blurred vision lasting 15 to 30 min.<sup>(33)</sup>

## SUMMARY

Chloroacetamide is a chlorinated aliphatic amide used as a preservative in U.S. cosmetic formulations at concentrations of less than or equal to 1.0%. The antimicrobial spectrum for certain test microorganisms required concentrations up to 0.5% for the minimal germicidal effect and 0.3% for minimal inhibition. The European Economic Community (EEC) permits a maximum use concentration of 0.3%. A warning label also is required.

The acute oral LD<sub>50</sub> was 155 mg/kg for mice, 70 to 138 mg/kg for rats, 31 mg/kg for dogs, and 122 mg/kg for rabbits.

Chloroacetamide was neither an ocular nor a skin irritant when tested at 5.0% in the rabbit. No lesions were observed in rabbits treated with 50 mg/kg of the ingredient for 30 days. No sensitization was reported in three separate studies using guinea pigs at test concentrations of 0.07%, 0.21%, and 1.0%.

In a 13-week subacute oral study in rats, Chloroacetamide at concentrations of 12.5 and 50 mg/kg produced testicular atrophy but no other observable external effects. In a 90-day oral toxicity study in rats, Chloroacetamide at doses of 0, 20, 100, and 500 mg/kg produced an increase in leukocytes at the highest dose. Liver weight was decreased in females, and there was a decrease in the testicular weight of the males at the 500 mg/kg dose group. Spermatogenesis was arrested also in the males of the high dose group. In a teratogenic study, Chloroacetamide was toxic at a dose of 50 mg/kg but did not produce effects in the surviving young rats. In another teratogenic study using rats, results also were negative at a nontoxic dose of 20 mg/kg.

Chloroacetamide was nonmutagenic in the Ames assay, both with and without activation, in a micronucleus study, and in dominant lethal assays.

Two predictive human RIPT sensitization studies on volunteers have been reported. At Chloroacetamide concentrations of 0.5 and 1.25%, 47/147 and 53/205 subjects were sensitized. Numerous provocative, single application patch tests reports are available over a concentration range of 0.07 to 0.7%. Some positive results were reported for studies in which concentrations between 0.1 and 0.2% were used. No indications of sensitization was reported for concentrations below 0.1% or above 0.35%.

Blurred vision and lachrimation occurred in humans when a 5% solution containing 70% Chloroacetamide and 30% sodium benzoate mixture was instilled into the lacrimal sac without a rinse. The discomfort and blurred vision lasted for 15 to 30 min.

On August 31, 1988, the CIR Expert Panel released a Tentative Final Report on Chloroacetamide with the following discussion.

In predictive RIPT sensitization studies Chloroacetamide was a human sensitizer at concentrations of 0.5% and 1.25%. The available positive provocative patient patch test data, which may or may not be statistically significant, occurs

in the mid-concentration test range, but not at the higher test levels. In the absence of adequate predictive RIPT data at use concentrations, adequate reproductive toxicity data, and genotoxicity data, the Panel cannot, at this time, reasonably conclude that Chloroacetamide can be safely used in cosmetic products.

During the Expert Panel's public meeting in which the Tentative Final Report on Chloroacetamide was discussed, the Panel stated that it would delay the release of the Final Report if new data were obtained.

During the 90-day public comment period on the Tentative Final Report, a manufacturer agreed to conduct a RIPT sensitization study at a concentration of 0.5% Chloroacetamide on 150 subjects.<sup>(35)</sup> The issuance of the Final Report was subsequently delayed.

CIR has now been informed that the results of the RIPT sensitization study on 150 subjects at a concentration of 0.5% Chloroacetamide confirmed the original study.<sup>(36)</sup> Due to the sensitization potential of 0.5% Chloroacetamide, the manufacturer recommends its use in cosmetic products be limited to rinse-off products. Data available from FDA and cited in this report indicate that the use of Chloroacetamide in cosmetic products in the U.S. has been reported only for products designed to remain on the skin for prolonged periods of time. Confirmation of the Panel's original concern for the potential of Chloroacetamide to act as a human sensitizer at use concentrations and the absence of adequate reproduction toxicity data and genotoxicity data are sufficient to conclude that Chloroacetamide is unsafe for use in all cosmetic products.

## CONCLUSION

Based on the data included in this report and the reconfirmation that Chloroacetamide is a potential human sensitizer at use concentrations, the Expert Panel concludes that Chloroacetamide is unsafe for use as a cosmetic ingredient.

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