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## **Safety Assessment of Nitrocellulose and Collodion as Used in Cosmetics**

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## **ABSTRACT**

The CIR Expert Panel assessed the safety of nitrocellulose and collodion as used in cosmetics, concluding that these ingredients are safe in the present practices of use and concentration in cosmetic formulations. Both ingredients are used almost exclusively in nail product formulations. The maximum concentration of use of nitrocellulose in nail polish and enamels is 22%; for collodion, the maximum reported concentration of use in nail polish and enamel is 14%. The Panel reviewed available animal and clinical data in making its determination of safety.

## **INTRODUCTION**

This report assesses the safety of nitrocellulose, a cellulose-based ingredient, as used in cosmetics. Nitrocellulose is reported to function in cosmetics as a dispersing agent – non-surfactant and as a film former, and is used almost exclusively in nail products.<sup>1</sup> The safety of collodion, a cosmetic ingredient that appears to be a solution of nitrocellulose dissolved in ethanol and ether and that is reported to function as a binder and a film former, is also addressed in this safety assessment.

Flexible collodion, defined by the *International Cosmetic Ingredient Dictionary and Handbook* as a mixture of collodion, camphor, and castor oil, is not included in this safety assessment.

## **CHEMISTRY**

### **Definition and Structure**

According to the *International Cosmetic Ingredient Dictionary and Handbook*, nitrocellulose (CAS No. 9004-70-0) is defined as a cellulose derivative that conforms generally to the formula  $C_{12}H_{16}N_4O_{18}$ ,<sup>1</sup> which equates to an average of two nitrate groups per mono-sugar repeat unit. (See Figure 1). Collodion (CAS No. 9004-70-0) is defined as a solution of pyroxylin (chiefly nitrocellulose) that contains approximately 6% pyroxylin, 24% ethanol and 70% ether.<sup>1</sup> *The Merck Index* states that pyroxylin is a variable mixture that consists primarily of cellulose tetranitrate, which also equates to an average of two nitrate groups per mono-sugar repeat unit.<sup>2</sup> Based on these definitions, it seems that collodion is simply a pre-formulation solution of nitrocellulose.

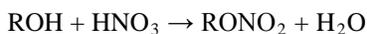
One source states nitrocellulose is a mixture of polymeric nitrate esters, and that three types of nitrocellulose are recognized: (1) collodion (or pyroxylin), with 8-12% nitrogen; (2) pyrocellulose, with 12.6% nitrogen; and (3) guncotton, with a minimum of 13.35% nitrogen.<sup>3</sup> Each name, under each method of nomenclature, relates to a chemical with a cellulose backbone and some degree of nitration (i.e., how many R groups in Figure 1 are  $ONO_2$  versus OH).

### **Chemical and Physical Properties**

Available chemical and physical properties data are provided in Table 1. Nitrocellulose is a white, amorphous solid that is virtually insoluble in water. When dissolved in an organic solvent (collodion is an example of solubilized nitrocellulose) the solution is clear, either colorless or slightly yellow (the yellowness is the result of decomposition that can occur from heat or ultraviolet (UV) irradiation), and precipitates nitrocellulose when mixed with water.

### **Method of Manufacture**

The nitrocellulose used in nail formulations is a nitrate ester obtained by the reaction of a mixture of nitric and sulfuric acids with an alcohol (i.e., one of the hydroxyl groups on the cellulose backbone).<sup>4</sup>



The cellulose used for this reaction is a natural product derived from wood or from cotton, wherein the cellulose polymer is a chain of mono-sugar repeat units, each with three free hydroxyl groups. The degree of nitration affects some physical properties of this polymer, making it more or less useful for different industries. The formula recited in the *International Cosmetic Ingredient Dictionary and Handbook* suggests that only two hydroxyls are typically esterified with nitro groups, per monomer residue, in the cosmetic ingredient.

For military use, cotton linters or wood pulp are treated with mixed nitric acid and sulfuric acid at 30°C.<sup>3</sup> The resulting slurry is centrifuged to remove most of the acid, treated with boiling water, washed with a heavy stream of water, and then screened to remove most of the water. Mechanistically, this is no different than the method above, but likely involves increased equivalents of nitric and sulfuric acids to result in a higher degree of nitration (which comports with the military use as a propellant).

No data were available specifically on the method of manufacture of collodion.

### **Impurities**

Published impurity data were not found for either ingredient.

## USE

### **Cosmetic**

Nitrocellulose is widely used in nail polish formulations, and is reported to function in cosmetics as a dispersing agent – non-surfactant and as a film former.<sup>1</sup> Collodion is reported to function as a binder and a film former. The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA in 2013 reported that nitrocellulose is used in 516 nail product formulations and one “other” makeup formulation.<sup>5</sup> (Table 2). Nitrocellulose is used in 410 of 489 nail polish and enamel formulations and 67 of 79 basecoat and undercoat formulations reported in the VCRP, as shown in Table 3. The results of a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council) report that nitrocellulose is used at concentrations up to 41% in “other” manicuring preparations, namely, in nail “stickers” made from dried nail polish.<sup>6</sup> The reported maximum concentration of use of nitrocellulose in nail polish and enamels is 22%.

Collodion is not reported to be used by the VCRP.<sup>5</sup> However, it should be presumed that there is at least one use of collodion because, according to a concentration of use survey conducted by the Council, collodion is reported to have a maximum concentration of use of 14% in nail polish and enamel.<sup>7</sup>

### **Non-Cosmetic Use**

Nitrocellulose is a prior-sanctioned food ingredient for use in the manufacture of paper and paperboard products used in food packaging (21CFR181.30). Nitrocellulose is also an approved indirect food additive (21CFR175.105; 21CFR175.300; 21CFR176.170; 21CFR177.1200). Nitrocellulose centrifugation tubes are used in biological work for high-speed centrifugation,<sup>8</sup> and nitrocellulose membranes are used in protein blotting.<sup>9</sup> Nitrocellulose is used for coating slides for embedding media; nitrocellulose slides are useful when mounted sections are immersed in alkalis or hot acids.<sup>10</sup> Another use of nitrocellulose is as a binder in printing inks and wood coatings.<sup>11</sup>

Nitrocellulose is a principal ingredient of propellants, smokeless powder, rocket fuel, ball powder, mortar increment, and some explosives.<sup>3</sup> However, these incendiary uses of nitrocellulose are likely related to a polymer with a higher degree of nitration than that of the cosmetic ingredient, and would be better classified as pyrocellulose or guncotton.

Corn and callus remover products containing salicylic acid at 12-17.6 % in a collodion-like vehicle are generally recognized as safe and effective by the FDA for topical application as an over-the counter (OTC) drug (21 CFR 358.503). The collodion-like vehicle is described as a solution containing pyroxylin (nitrocellulose) in an appropriate non-aqueous solvent that leaves a transparent cohesive film when applied to the skin in a thin layer. That non-aqueous vehicle would appear to be alcohol and ether, which would evaporate rapidly, leaving the pyroxylin (nitrocellulose).

## TOXICOKINETICS

### **Absorption, Distribution, Metabolism, and Excretion**

#### Oral

Nitrocellulose (containing 12.9% nitrogen by wt) was not absorbed in rats following oral dosing.<sup>12</sup> One fasted male CD rat was dosed by gavage with 1 ml/100 g (~20,000 dpm/ml) aq. [<sup>14</sup>C]nitrocellulose and another with [<sup>14</sup>C]nitrocellulose suspended in 0.2% methyl cellulose - 0.4% Tween 80; each rat was dosed for 4 days. The labeled compound was prepared by nitrating [<sup>14</sup>C] cotton. For the aq. dose, the fiber was cut and ground and then concentrated by sedimentation. Only fibers small enough to go through an 18-gauge dosing needle were used. The animals were killed 24 h after the last dose. Radioactivity was recovered only in the gastrointestinal tract and in the feces. No detectable radioactivity was found in any other tissues or body fluids.

A mass-balance metabolism study was performed in which one Beagle dog was fed 90 g wet nitrocellulose (27.9 g on a dry basis).<sup>13</sup> The nitrocellulose contained 13.08% nitrogen. Feces were collected every 24 h for 4 days. Over a 4-day period, 9.5 g of nitrocellulose (34% of the dose) were recovered; 8.8 g were recovered after 24 h and 0.7 g after 48 h.

## TOXICOLOGICAL STUDIES

### **Single Dose (Acute) Toxicity**

#### Oral

The oral LD<sub>50</sub> of a 5% nitrocellulose suspension was >5000 mg/kg in mice and rats.<sup>14</sup> The tested material was a military-produced nitrocellulose with a nitrogen content of 13.1%. (This test article is used in multiple studies, and will be described simply as 13.1% nitrogen, 65.6% >88 µm). Fasted male and female albino Swiss mice and male and female CD rats were dosed by gavage with 5000 mg/kg of 5% ground nitrocellulose in water; the dose was administered in two portions 30 min apart due to the large volume. (The number of female mice and male and female rats dosed was not specified). Two of 10 male mice died; no gross lesions were observed.

The LD<sub>50</sub> of a nitrocellulose-based propellant was >5000 mg/kg in mice and rats upon oral administration. The test substance (ball powder®) is composed of 83.23% nitrocellulose, 10.235% nitroglycerin, 0.685% dinitrotoluene, 1.105% diphenylamine, 5.255% dibutyl phthalate, 1.045% total volatiles, 0.895% moisture and volatiles, 0.49% residual solvent, 0.09% calcium carbonate, and 0.12% sodium sulfate. Ten male and 10 female ICR mice<sup>15</sup> and seven male and seven female Sprague-Dawley rats<sup>16</sup> were dosed by gavage with 5000 mg/kg test article in 1% carboxymethylcellulose. Five male and five female mice and five male and five female rats served as controls and were dosed with 10 ml/kg of vehicle only. None of the mice or the rats died during the study.

### Repeated Dose Toxicity

#### Oral

In 13-wk repeated-dose dietary studies in mice, rats, and dogs, administration of 1 and 3% nitrocellulose (nitrogen content, 13.1%) in feed (calculated on a dry basis) had no adverse effects; effects seen at 10% were attributed to the fiber content and not the chemical nature of the test article.<sup>12</sup> For each species, a “cotton control” group was fed a diet containing 10% cotton linters and a negative control group was given untreated feed. Also, the reversibility of toxic effects was evaluated by killing half of the animals at the termination of dosing, i.e., 13 wks, and the remainder after a 4-wk recovery period, i.e., 17 wks.

In mice, groups of 8 male and 8 female albino Swiss mice were used. By the end of week 2, four cotton control males, four cotton control females, one low dose male, and six high dose male mice died; the deaths of the high dose and cotton control animals were attributed to intestinal impaction of the fibers. Body weights of mice in the low and mid-dose groups were similar to the negative controls; severe weight loss was reported for the high dose animals during wk 1 of the study. Feed consumption was increased slightly in the low and mid-dose group and considerably in the high-dose group; however, mice of the high-dose group scattered much of the feed. The absolute and/or relative spleen weights of mice in the 10% group and in the cotton control group killed at 13 wks were statistically significantly decreased compared to controls; at 17 wks, the spleen weights were normal. No adverse effects due to the chemical nature of nitrocellulose were observed and no test article-related gross or microscopic lesions, changes in hematological parameters, or alterations in serum IgE concentrations were found.

Groups of 8 male and 8 female CD rats were fed the test or control diets. Four animals/sex/group were killed at 13 wks, and the remainder at 17 wks. Blood samples were taken at 0, 4, 8, 13, and 17 wks. No adverse effects were observed. Because no adverse effects were observed and test article-related lesions were not found during the 13-wk necropsy, a 17-wk necropsy and blood analysis was not performed. Body weight gains of rats in the 1 and 3% groups were similar to untreated controls. Body weight gains of rats in the 10% group and the cotton control group were decreased compared to the untreated controls; body weights of the recovery animals of the 10% group, but not the cotton control group, approached those of the negative control animals. Rats in the test groups had increased feed consumption with increased dose. In the low and mid-dose groups, increased feed consumption was attributed to compensation for the non-nutritive fiber; the high-dose animals scattered their feed. Decreases in liver, kidney, and/or spleen weights in male rats of the high-dose group were attributed to decreased body weight gain. No adverse effects due to the chemical nature of nitrocellulose were observed, and no test article-related gross or microscopic lesions or changes in hematological or clinical chemistry parameters were observed.

Two male and two female Beagle dogs per group received treated feed for 13 wks. One male and one female from each group were killed at 13 wks, and the remaining two animals were killed at 17 wks. Blood samples were taken prior to dosing and at 4, 8, 13, and 17 wks. No adverse effects were observed. As with the rats, because no adverse effects were observed and no test article-related lesions were found during the 13-wk necropsy, the 17-wk necropsy and blood analysis was not performed. No test article-related changes in weight were observed. Feed consumption was greater in all test animals than in controls; again, this was attributed to non-nutritive bulk. Dietary administration of nitrocellulose did not cause gross or microscopic lesions or changes in organ weights, hematological parameters, or serum IgE concentration in dogs.

Nitrocellulose was also not toxic in 2-yr dietary studies in mice, rats, and dogs; effects due to fiber content were similar to the 13-wk studies described previously. Each species was fed a diet containing 1, 3, and 10% nitrocellulose (calculated on a dry basis); as in the 13-wk studies, a cotton control group was fed a diet containing 10% cotton linters and a negative control group was given untreated feed.<sup>13</sup> Also in each species, there were four subgroups: one subgroup was killed after 12 mos of dosing; one was started on an untreated recovery diet at 12 mos and killed at 13 mos; one subgroup was killed after 24 mos of dosing; and one was started on a recovery diet at 24 mos and killed at 25 mos. Details for each species follow.

In the mouse study, 58 male and 58 female CD-1 mice per group were used at study initiation. Four mice/sex/group were killed for the interim 12-mos necropsy and for the 13-mos recovery group; with the exception of four mice/sex/group that were used as the 25-mos recovery group, all remaining animals were killed at 24 mos. Blood samples were taken at necropsy from the animals killed at 12 mos and from eight mice/sex/group killed at 24 mos. During the first 3 wks of the study, nine males and five females of the 10% nitrocellulose group and five males and one female of the cotton control group died due to intestinal blockage by the fibers. Additional mice were added to these groups. Also, around month 9 of the study, a number of high-dose and cotton-control animals died; no explanation for this cluster of deaths was found. The researchers did state,

however, that because there were three times more deaths among the high dose animals than the cotton control mice, the presence of a compound-related effect could not be dismissed. Hyperemia was observed in a number of the cotton controls and some of the 10% nitrocellulose animals; the researchers did not have an explanation for this observation, but did hypothesize that it may have been an irritation reaction to the fibers the mice pulled from the feed. Body weight gains for animals of the 10% nitrocellulose and cotton control groups were initially decreased compared to controls. As the study progressed, a dose-relationship for increased feed consumption was observed in the control, low, and mid-dose groups. Feed scattering in the high dose group and the cotton controls made it difficult to quantitate actual feed consumption. Other than a treatment-related statistically significant lack of bronchoalveolar carcinomas in high dose male mice, no test article-related gross or microscopic lesions or changes in organ weights were reported. No effects on clinical chemistry or hematology parameters were found.

For rats, groups of 32 male and 32 female CD rats were used at study initiation. An additional eight/sex/group were added after 6 mos; four of the eight/sex/group were killed for the interim 12-mos necropsy and the other four as the 13-mos recovery group. With the exception of four rats/sex/group that were used as the 25-mos recovery group, all remaining animals were killed at 24 mos. Blood samples were taken from four rats/sex/group at 0, 6, 12, 18, and 24 mos. Blood samples were also taken at necropsy from the animals killed at 12 mos and from eight rats/sex/group killed at 24 mos. Test article-related toxic effects were not observed. Body weight gains of high dose and cotton control animals initially were decreased compared to controls; weight gains in these groups were increased, becoming closer to control values, later in the study. Tumors not related to dosing were observed in all groups. A dose-related increase in feed consumption was attributed to the non-nutritive bulk of the fibers; scattering was also observed. No test-article related gross or microscopic lesions or changes in organ weights were found, there was no effect on clinical chemistry or hematology parameters.

Groups of six male and six female Beagle dogs were used in the 2-yr study. One animal/sex/group was killed for the 12 mos and as the 13 mos (recovery group), and two/sex/group were killed at 24 mos and as the 25-mos recovery group. Blood samples were taken from all dogs at 0, 3, 9, 12, 18, and 24 mos. No signs of toxicity were observed. Dose-related differences in body weights were not found. Animals of the 10% nitrocellulose group and the cotton control group had increased feed consumption; this difference was not considered to be toxicologically significant. Test article-related changes in clinical chemistry and hematology parameters or organ weights were not found, nor were any test article-related gross or microscopic lesions. Because no changes were found in the animals after 12 or 24 mos, the respective recovery groups were not necropsied.

### **Ocular Irritation**

A 33% aq. solution of nitrocellulose (nitrogen content, 13.1%) was not a primary irritant in rabbit eyes.<sup>14</sup> A modified Draize test was performed in six New Zealand White (NZW) rabbits, and the eyes were evaluated for irritation at 24 and 72 h.

Ball powder (defined previously) was not a primary ocular irritant in rabbits in a modified Draize test.<sup>17</sup> The test material, 0.113 g, was instilled into the lower conjunctival sac of one eye of each of six male NZW rabbits, and the eye was not rinsed. The test material, a 0.5-1.5 mm spheroidal pellet, was administered neat. The contralateral eye served as the untreated control. The eyes were graded 1, 4, 24, 48, and 72 h after dosing; fluorescein staining was used at the 24, 48, and 72 h observations. Significant amounts of the test article were present in the conjunctival sac of each eye 1 and 4 h after instillation. Small pinpoint erosions of the cornea were present in two animals at 24, 48, and 72 h. A small corneal erosion in one animal on day 7 of dosing was considered incidental. Slight conjunctival vasodilation (all animals at 4 h; score of 1) and chemosis (3 animals at 4 h; score of 1), indicative of mild inflammation, was observed. Ball powder produced minimal irritation.

## **REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

### **Oral**

Nitrocellulose did not cause reproductive or developmental toxicity. In a three-generation reproduction study, the F<sub>0</sub> generation, consisting of groups of 10 male rats (from the 2-yr study described previously) and 20 female rats, was fed a diet containing 1, 3, or 10% nitrocellulose (calculated on a dry basis; nitrogen content, 13.1%).<sup>13</sup> A cotton control group was fed a diet containing 10% cotton linters and a negative control group was given untreated feed. The rats were mated after 6 mos of dosing. The initial offspring (i.e. the F<sub>1a</sub> generation) were killed at weaning. The animals of the F<sub>0</sub> generation were mated a second time; 20-24 pups/sex (i.e., the F<sub>1b</sub> generation) were retained at weaning. Ten to 12 pairs of F<sub>1b</sub> animals were mated within their dose group at 3 mos of age. As before, the F<sub>2a</sub> generation was discarded and the F<sub>2b</sub> rats were retained. The mating procedure was repeated with the F<sub>2b</sub> rats, and the study was terminated upon weaning of the F<sub>3b</sub> rats.

At the time of the first matings for males of all parental generations, the mean body weights of the 10% nitrocellulose group and the cotton control group were statistically significantly decreased compared to the controls. In females, the mean body weights were only decreased in the cotton control group. As in other repeated-dose studies, feed consumption in the 10% nitrocellulose and cotton control groups was increased. Statistically significant decreases in the lactation index and pup weight at weaning were observed in the 10% nitrocellulose and the cotton control group; these decreases were primarily observed in the F<sub>1b</sub> through F<sub>2b</sub> litters and attributed to a lack of parental nutrition caused by the inert increased bulk in this feed. Fertility was not affected by dosing, and no test article-related effects were seen on reproductive indices.

## **GENOTOXICITY**

### **In Vitro**

Nitrocellulose (13.1% nitrogen; 65.6% >88 µm) was not mutagenic in the Ames test.<sup>18</sup> Nitrocellulose, prepared as a suspension in 1-5 mg/ml distilled water, was evaluated at concentrations of 100, 1000, and 5000 µg/plate in *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, and TA100 with and without metabolic activation.

### **In Vivo**

Nitrocellulose was not genotoxic in cytogenicity assays. The cytogenetic effect of nitrocellulose was evaluated in lymphocytes and kidney cells from CD rats fed a diet containing 10% nitrocellulose in the previously-described 13 wk-study<sup>12</sup> and in lymphocytes and bone marrow cells from rats fed a diet containing 1, 3, or 10% nitrocellulose in the previously-described 1 and 2 year studies, respectively.<sup>13</sup> Kidney cells from rats in the long-term study were also analyzed. Nitrocellulose did not produce chromosomal aberrations in any of these cells.

## **CARCINOGENICITY**

No statistically significant increase in tumors due to the administration of nitrocellulose were reported in the previously-described 2-yr dietary studies in mice, rats, or dogs when compared to the respective controls.<sup>13</sup>

### **Epidemiology**

A matched case-control study nested in a retrospective cohort study examined mortality among workers in a plastics producing plant located in Springfield, MA.<sup>19</sup> The retrospective cohort study identified 2490 male workers who were employed a minimum of 1 year between January 1949 and December 1966, and mortality was examined from January 1950 to December 1976. In the case-control study, each case was matched with four controls by race and age (Series 1 controls) or by race, age, and date of hire (Series 2 controls), and in each case of digestive cancer, Series 2 controls were also matched by place of birth. Using Series 1 controls, the odds ratio of digestive system cancers (combined) was slightly but not statistically significantly increased for cellulose nitrate production workers (i.e., using cellulose nitrate, ethyl alcohol, and camphor) and for cellulose nitrate processing workers (i.e., exposed to finished cellulose nitrate). Although statistical significance was not reached, the odds ratio for cellulose nitrate processing increased with increasing exposure times; odds ratios of 1.07, 1.91, and 2.85 were reported for exposures of 1 month, 5 yrs, and 10 yrs, respectively. For individual digestive cancers, the only statistically significant increase in odds ratio was that of an odds ratio of 8.90 (p<0.05) for rectal cancer in cellulose nitrate production workers exposed for >5 yrs; however, the researchers stated that because very little was known about their other chemical exposures, a reliable interpretation of these data could not be made. Findings using Series 2 controls were consistent with those found using Series 1 controls. In examining the incidence of genitourinary system cancers, the odds ratios for cellulose nitrate production and for cellulose nitrate processing were not increased.

A population-based case-control study was performed using 497 male workers (various occupations) from Montreal that had histologically-confirmed cases of colon cancer that were diagnosed between 1979 and 1985; 1514 cancer-controls (with cancers at other sites) and 533 population-based controls were used.<sup>20</sup> Face-to-face in-depth interviews using a structured questionnaire for numerous possible confounders and a semi-structured questionnaire regarding job details were performed. Concentration of exposure was assessed on a relative scale of low, medium, or high exposure. When the odds ratio was adjusted for age and other non-occupational risk factors, there were nine cases of colon cancer in workers with substantial exposure to nitrocellulose, and the non-occupationally-adjusted odds ratio was 2.6 with a 95% confidence interval of 1.0-6.4. With non-substantial exposure to cellulose nitrate, there were five cases of colon cancer and the non-occupationally-adjusted odds ratio was 0.5 with a 95% confidence interval of 0.2-1.3. When the odds ratio was adjusted for non-occupational risk factors and occupational exposure, the fully-adjusted odds ratio in the nine cases of colon cancer with substantial exposure to cellulose nitrate was 2.8 and the 95% confidence interval was 1.1-7.5. With non-substantial exposure to cellulose nitrate, the fully-adjusted odds ratio was 0.4 with a 95% confidence interval of 0.1-1.2 for the five cases of colon cancer. The researchers stated that although the relative risk was significantly high with substantial exposure to cellulose nitrate, a number of associations with occupational substances had less than 10 colon cancer cases with substantial exposure, so there was considerable statistical variability associated with the estimate of relative risk.

## **IRRITATION AND SENSITIZATION**

### **Non-Human**

A 33% aq. solution of nitrocellulose (13.1% nitrogen; 65.6% >88 µm) was not a primary skin irritant in rabbits.<sup>14</sup> A modified Draize test was performed in six NZW rabbits, and the test solution was applied to intact and abraded skin. The primary irritation score was <0.2.

Ball powder (defined previously) was not irritating in rabbits in a modified Draize irritation test.<sup>21</sup> Two occlusive patches, one-inch each, containing a thick paste of 0.5 g of the test article in approximately 0.5 ml isotonic saline were applied for 4 h to clipped skin on the back of four male and four female NZW rabbits. Sham and vehicle controls were used. The test sites

were wiped with saline upon removal and scored for erythema and edema at 30 and 60 min and 24, 48, and 72 h after patch removal. Very slight erythema (score of 1) was observed at the test and the control sites in some of the rabbits; therefore, the test product had a peak net mean score of 0 and was classified as a non-irritant.

### **Human**

A nail enamel containing 10.5% nitrocellulose was not a primary irritant in a 48-h patch test completed in 51 subjects.<sup>22</sup> Semi-occlusive patches, 1" x 1" in size, containing approximately 0.2 ml of the test material were applied to the back of each subject for 48 h. The test site was evaluated upon patch removal and 24 h later. No signs of irritation were observed in any of the subjects.

A nail lacquer containing 8.85% nitrocellulose was not an irritant or a sensitizer in a human repeated insult patch test (HRIPT) completed in 108 subjects.<sup>23</sup> The nail lacquer was applied to semi-occlusive patches as received and was allowed to dry prior to application. Patches were applied to the upper back for 24 h three times/wk for 3 wks, for a total of nine induction applications. The tests sites were scored 24 or 48 h after patch removal. Following a 2-wk non-treatment period, a 24-h challenge patch was applied to a previously untreated site on the back, and the site was evaluated upon patch removal and at 48 and 72 h. No visible skin reactions were observed at any site during induction or challenge.

## **Provocative Testing**

### **Human**

Patch tests with nitrocellulose solution in butyl acetate as well as other nail polish ingredients were performed in 25 patients with various dermatoses and 19 patients with nail-polish dermatitis; details of the test procedure (for this study performed in the early 1940s) were not provided.<sup>24</sup> In the patients with various dermatoses, erythema was seen in 17/25 subjects; erythema and edema was observed in one subject; and vesiculation was observed in one subject. In the patients with nail polish-dermatitis, there was a marked increase in the irritation reactions; all of the subjects reacted, and vesiculation or vesiculation with marked erythema was observed in many of the subjects. It was determined that benzol was present in the solution.

Thirty patients with reactions to nail polish were patch tested with 29 nail lacquers and some of the component ingredients.<sup>25</sup> (Details of the patch testing were not provided; this study was also performed in the early 1940s). Nitrocellulose elicited a reaction in nine of the patients and was a primary irritant. Ten control subjects had negative reactions to the nail polishes and the individual ingredients.

A study was performed from September 1977 – August 1983 to examine contact dermatitis in dermatology patients.<sup>26</sup> During that period, 281,100 patients were seen by twelve dermatologists; 13,216 were determined to have contact dermatitis, and in 713 cases, it was determined to be cosmetic dermatitis. In those 713 cases, patch testing found only one reaction to nitrocellulose.

## **Case Reports**

### **Nitrocellulose**

A female patient presented with eczema of the neck that had been recurrent for 15 yrs and permanent for 3 mos.<sup>27</sup> Patch testing found contact sensitivity to two of her nail varnishes, and further testing reported that she was allergic to toluene-sulfonamide-formaldehyde resin, which was an ingredient in those nail varnishes. Subsequent use of a nail varnish that did not contain this ingredient resulted in eczema of the forearm, face, and neck. Additional patch testing reported the patient had contact sensitivity to nitrocellulose; positive reactions were observed with testing of nitrocellulose at the same concentration used in the product (i.e. 13.3%), when diluted as 10 or 50% of that found in the product, and when either a mixture of 88.7% ethyl/butyl acetate and 11.3% isopropyl alcohol or a mixture of 49.45% ethyl/butyl acetate, 41.35% toluene, 8.1% isopropyl alcohol, and 1.1% diacetone alcohol was used as the solvent. Subsequent testing of the same concentrations in the same solvents in 100 subjects did not elicit any reactions.

### **Collodion**

Two female subjects presented with contact sensitivity to a wart paint vehicle (i.e., colophony).<sup>28</sup> Patch tests and repeated open application tests with collodion BP (a solution of ~10% pyroxylin in a mixture of 90% alcohol [1 volume] and solvent ether [3 volumes])) were negative.

## **SUMMARY**

Nitrocellulose is a cellulose derivative produced by nitrating cellulose. Collodion seems to be a pre-formulation solution of nitrocellulose, and is defined in the *International Cosmetic Ingredient Dictionary and Handbook* as a solution of pyroxylin (chiefly nitrocellulose) that contains approximately 6% pyroxylin, 24% ethanol and 70% ether. Nitrocellulose is reported to function in cosmetics as a dispersing agent – non-surfactant and as a film former and collodion is reported to function as a binder and a film former. VCRP data report that nitrocellulose is used in 516 nail product formulations and one other make-up formulation. According to an industry survey, nitrocellulose is used at concentrations up to 41% in “other” manicuring preparations, i.e., in nail “stickers” made from dried nail polish; the reported maximum concentration of use in nail polish

and enamels is 22%. Collodion is not reported to be used according to VCRP data; however, there must be at least one use of collodion because the results of an industry survey report the maximum concentration of use of collodion is 14% in nail polish and enamels.

Nitrocellulose was not absorbed in rats following dosing by gavage with 1 ml/100 g (~20,000 dpm/ml) aq. [<sup>14</sup>C]nitrocellulose or [<sup>14</sup>C]nitrocellulose suspended in 0.2% methyl cellulose - 0.4% Tween 80. In a mass-balance metabolism study performed in a Beagle dog, 9.5 g of nitrocellulose (34% of the dose) was recovered in the feces over a 4-day period.

The oral LD<sub>50</sub> of a 5% nitrocellulose suspension and of a nitrocellulose-based propellant (i.e., ball powder) was >5000 mg/kg in mice and rats. In 13-wk and 2-yr repeated-dose dietary studies in mice, rats, and dogs, 1 and 3% nitrocellulose in feed (calculated on a dry basis) had no toxic or carcinogenic effects; effects seen at 10% were attributed to the fiber content and not the chemical nature of the test article. No tumors due to the administration of nitrocellulose were reported in the 2-yr study. Nitrocellulose was not a reproductive or developmental toxicant and did not affect fertility in a three-generation dietary study in rats; in testing with 1, 3, and 10% nitrocellulose, the only adverse effects observed, a statistically significant decrease in the lactation index and in pup weight at weaning in the 10% F<sub>1b</sub> through F<sub>2b</sub> litters, was attributed a lack of parental nutrition.

A 33% aq. solution of nitrocellulose was not a primary skin or ocular irritant in rabbits in Draize tests. Ball powder also was not a skin or ocular irritant. A nail enamel formulation containing 10.5% nitrocellulose was not a primary irritant in a 48-h semi-occlusive patch test completed in 51 subjects, and a nail lacquer containing 8.85% nitrocellulose was not an irritant of a sensitizer in a HRIPT completed in 108 subjects and tested using semi-occlusive patches. Provocative testing in the early 1940s with a nitrocellulose solution in butyl acetate that contained benzol resulted in reactions in 17/25 patients with various dermatoses and 19/19 patients with nail polish-dermatitis; reactions were much greater in the nail polish-dermatitis patients. In another 1940s study with patients with allergic eczema to nail polish, patch testing with nitrocellulose elicited a reaction in nine of the 30 patients tested. In a 64-mos study (1977-1983), a reaction to nitrocellulose was observed in only one of 713 cases with cosmetic dermatitis.

Nitrocellulose (100-5000 µg/plate) was not mutagenic in the Ames test with or without metabolic activation. Nitrocellulose did not produce chromosomal aberrations in lymphocytes or kidney cells of rats fed a diet containing 10% nitrocellulose for 13-mos or in lymphocytes (1 yr), bone marrow cells, or kidney cells from rats fed a diet containing 1, 3, or 10% nitrocellulose for 1 or 2 yrs.

In epidemiology studies, although some increases in odds ratios for digestive system cancers were observed with occupational exposure to cellulose nitrate, no definitive link was identified.

## **DISCUSSION**

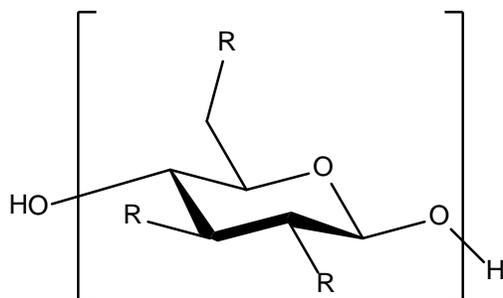
As a cosmetic ingredient, nitrocellulose is used almost exclusively in nail product formulations. The molecular weight and chemical properties of nitrocellulose support an absence of significant dermal absorption, and there is little possibility of bio-transformation. Nitrocellulose did not produce toxic effects in single or repeated-dose studies, was not a reproductive or developmental toxicant, and was not carcinogenic in animal studies. Nitrocellulose was not mutagenic in an Ames test or genotoxic in chromosomal aberration assays. A human repeated insult patch test in which patches of a nail formulation containing 8.85% nitrocellulose were applied to the skin of subjects did not produce any irritation or sensitization reactions, and no visible irritation was observed in another human study when patches of a nail formulation containing 10.5% nitrocellulose were applied for 48 h. Nitrocellulose is used in formulations at higher concentrations than those tested in the human irritation and sensitization studies, but because nitrocellulose is typically used in nail products and significant exposure to the skin would be minimized, it is the opinion of the Expert Panel that neither irritation nor sensitization will be a concern.

Collodion, although listed in the *International Cosmetic Ingredient Dictionary and Handbook* as a separate cosmetic ingredient, simply seems to be a solution of nitrocellulose in alcohol and ether. As used in formulations, the volatile components would be expected to evaporate, leaving nitrocellulose. Therefore, from a toxicological standpoint, there are no concerns relative to the potential use of collodion in cosmetics, and it is considered safe for use in cosmetics in the same practices of use and concentration as given for nitrocellulose.

## **CONCLUSION**

The CIR Expert Panel concluded that nitrocellulose and collodion are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

## FIGURES



wherein R is OH or ONO<sub>2</sub>

**Figure 1.** Nitrocellulose

## TABLES

**Table 1. Chemical and physical properties**

Property	Description	Reference
<b>Nitrocellulose</b>		
appearance	white, amorphous solid non-fibrous, cotton-like white solid in a military-produced nitrocellulose with a nitrogen content of 13.1%: particles that were >44 μm were normal fibers, while the particles <44 μm appeared in several forms, including amorphous and spherical	29 3 12
molecular weight	297.14 (formula wt of the trinitrated monomer unit)	3
nitrogen content	11.5-12% (as used nail products)	4
decomposition range	160-170°C	3
specific gravity	1.66 g/ml	29
solubility	practically insoluble in water; generally, soluble in esters, aldehydes, and ketones; the more completely nitrated, the smaller the range of solvents in which there is solubility nitrocellulose that is commonly used in nail polishes is soluble in esters (ethyl and butyl acetate)	3 4
wt distribution by particle size	65.6%, >88 μm; 23.2%, 44-88 μm; 11.2%, <44 μm (military-produced nitrocellulose with a nitrogen content of 13.1%)	12
flashpoint	12.8°C	3
stability	non-volatile; decomposes in the presence of UV light and at temperatures >100°C	3
<b>Collodion</b>		
appearance	colorless or slightly yellow, clear or slightly opalescent, syrupy liquid	30
odor	ether-like	30
solubility	very soluble in methanol, benzene, toluene, and mixtures of ether and alcohol	3
physical stability	the pyroxylin precipitates on the addition of water	30
d <sub>25</sub> <sup>25</sup>	0.765-0.775	30

**Table 2. Frequency and concentration of use according to duration and type of exposure**

	<b>Nitrocellulose</b>		<b>Collodion</b>	
	<i># of Use</i> <sup>5</sup>	<i>Max. Conc. of Use (%)</i> <sup>6</sup>	<i># of Use</i> <sup>5</sup>	<i>Max. Conc. of Use (%)</i> <sup>7</sup>
<b>Totals*</b>	<b>517</b>	<b>0.04-41</b>	<b>NR</b>	<b>14</b>
<b><i>Duration of Use</i></b>				
<i>Leave-On</i>	517	13-41	NR	14
<i>Rinse Off</i>	NR	0.04- 11	NR	NR
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR
<b><i>Exposure Type</i></b>				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation - Spray	NR	NR	NR	NR
Incidental Inhalation - Powder	NR	NR	NR	NR
Dermal Contact	1 (“other” makeup formulation)	0.04 (skin cleanser)	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	516	11-41 <sup>a</sup>	NR	14
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

NR – none reported

<sup>a</sup> the 41% use is in nail “stickers” made from dried nail polish**Table 3. Use of nitrocellulose in nail products by individual category**

<b>Product Category</b>	<b>Total No. of Formulations</b> <sup>5</sup>	<b>Formulations Containing Nitrocellulose</b> <sup>5</sup>	<b>Reported Maximum Concentrations</b> <sup>6</sup>
Basecoats and Undercoats	79	67	13-15%
Nails Creams and Lotions	14	none reported	13-16%
Nail Extenders	62	1	none reported
Nail Polish and Enamel	489	410	13-22%
Nail Polish and Enamel Removers	63	none reported	11%
Other Manicuring Preparations	173	38	17-41% (41% in nail “stickers” made from dried nail polish)

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