

---

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

---

Status: Scientific Literature Review for Public Comment  
Release Date: November 21, 2012  
Panel Meeting Date: March 18-19, 2013

*All interested persons are provided 60 days from the above release date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. F. Alan Andersen.*

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer.

**© Cosmetic Ingredient Review**

1101 17<sup>th</sup> Street, NW, Suite 412 ♦ Washington, DC 20036-4702 ♦ ph 202.331.0651 ♦ fax 202.331.0088 ♦  
cirinfo@cir-safety.org

## TABLE OF CONTENTS

Introduction .....	1
Chemistry .....	1
Definition .....	1
Physical and Chemical Properties .....	1
Method of Manufacture .....	1
Impurities .....	1
Use .....	1
Cosmetic .....	1
Non-Cosmetic Use .....	2
Toxicokinetics .....	2
Absorption, Distribution, Metabolism, and Excretion .....	2
Oral .....	2
Toxicological studies .....	2
Single Dose (Acute) Toxicity .....	2
Oral .....	2
Repeated Dose Toxicity .....	2
Oral .....	2
Ocular Irritation .....	4
Reproductive and Developmental Toxicity .....	4
Oral .....	4
Genotoxicity .....	4
In Vitro .....	4
In Vivo .....	4
Carcinogenicity .....	5
Epidemiology .....	5
Irritation and Sensitization .....	5
Non-Human .....	5
Provocative Testing .....	5
Human .....	5
Case Reports .....	6
Information Sought .....	6
Summary .....	6
Tables .....	8
Table 1. Chemical and physical properties .....	8
Table 2. Nitrocellulose - Frequency and concentration of use according to duration and type of exposure .....	8
References .....	9

## **INTRODUCTION**

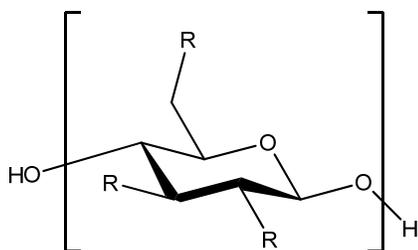
This Scientific Literature Review is the first step in reviewing the safety of nitrocellulose and collodion as used in cosmetics. Nitrocellulose is reported to function in cosmetics as a dispersing agent – non-surfactant and as a film former and collodion is reported to function as a binder and a film former.<sup>1</sup>

## **CHEMISTRY**

### **Definition**

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  $C_{12}H_{16}N_4O_{18}$ . Collodion (CAS No. 9004-70-0) is a solution of pyroxylin (chiefly nitrocellulose) that contains approximately 6% pyroxylin, 24% ethanol and 70% ether.<sup>1</sup> Pyroxylin is a variable mixture that consists primarily of cellulose tetranitrate.<sup>2</sup> It should be noted that flexible collodion, defined by the *International Cosmetic Ingredient Dictionary and Handbook* as a mixture of collodion, camphor, and castor oil,<sup>1</sup> is not included in this safety assessment.

Nitrocellulose and cellulose, nitrate are listed as technical names for collodion, and cellulose, nitrate is also listed as a technical name for nitrocellulose.<sup>1</sup>



wherein R is OH or NO<sub>3</sub>

Figure 1. Nitrocellulose

One source states nitrocellulose is a mixture of polymeric nitrate esters, and that three types of nitrocellulose are recognized: collodion (or pyroxylin), with 8-12% nitrogen; pyrocellulose, with 12.6% nitrogen; and guncotton, with a minimum of 13.35% nitrogen.<sup>3</sup>

### **Physical and Chemical Properties**

The available physical and chemical properties data are provided in Table 1.

### **Method of Manufacture**

Nitrocellulose is produced by nitrating cellulose; as many as three hydroxyl groups in the cellulose monomer (anhydroglucose unit) are replaced by NO<sub>3</sub> groups, and the resulting polysaccharide chains of β' 1-4 linked units constitute nitrocellulose.<sup>3</sup> However, the formula recited in the *International Cosmetic Ingredient Dictionary and Handbook* suggests that only two hydroxyls are typically replaced with nitro groups, per monomer residue.

For military use, cotton linters or wood pulp are treated with mixed nitric acid and sulfuric acids 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.

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 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.<sup>1</sup> 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 2012 report that nitrocellulose is used in 463 cosmetic formulations, primarily nail products, and that collodion is not reported to be used.<sup>4</sup> Data received in response to 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 nail products.<sup>5</sup> Results of a concentration of the use survey conducted on collodion have not yet been received.

#### **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) Additionally, nitrocellulose is a principal ingredient of propellants, smokeless powder, rocket fuel, ball powder, mortar increment, and some explosives.<sup>3</sup>

Corn and callus remover drug products containing salicylic acid 12 to 17.6 percent in a collodion-like vehicle are generally recognized as safe and effective by 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. As described earlier, 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>6</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>7</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 was 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>8</sup> The nitrogen content of the nitrocellulose was 13.1%. The weight distribution according to particle size was 65.6%, >88 µm; 23.2%, 44-88 µm; and 11.2%, <44 µm; the particles that were >44 µm were normal fibers, while the particles <44 µm appeared in several forms, including amorphous and spherical. 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>9</sup> and seven male and seven female Sprague-Dawley rats<sup>10</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, 1 and 3% nitrocellulose 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>6</sup> (The nitrogen content and particle size distribution of nitrocellulose was described in the single-dose toxicity section). 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, for 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 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 were fed 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 at 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.

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 (13% nitrogen; dose was 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>7</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 as 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 animals died; no explanation for this cluster of deaths was found. 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 decrease in 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.

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. Tumors were observed in all groups and occurrences were not considered test article-related. 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. 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 was not a primary irritant in rabbit eyes.<sup>8</sup> A modified Draize test was performed in six New Zealand White (NZW) rabbits; eyes were evaluated for irritation at 24 and 72 h. (The nitrogen content and particle size distribution of nitrocellulose were described previously in the single-dose toxicity section).

Ball powder (defined previously) was not a primary ocular irritant in rabbits in a modified Draize test.<sup>11</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 (13% nitrogen; dose was calculated on a dry basis).<sup>7</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 weight loss and attributed to a lack of parental nutrition. Fertility was not affected by dosing, and no test article-related effects were seen on reproductive indices.

## **GENOTOXICITY**

### **In Vitro**

Nitrocellulose was not mutagenic in the Ames test.<sup>12</sup> (The nitrogen content and particle size distribution of nitrocellulose were described in the single-dose toxicity section). Nitrocellulose, 1-5 mg/ml in 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 for 13 wks<sup>6</sup> and in lymphocytes and bone marrow cells from rats fed a diet containing 1, 3, or 10% nitrocellulose for 1 and 2 years, respectively.<sup>7</sup> (These studies were de-

scribed previously). 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 tumors due to the administration of nitrocellulose were reported in 2-yr dietary studies in mice, rats, or dogs.<sup>7</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>13</sup> The retrospective cohort study identified 2490 male workers who were employed a minimum of 1 year between Jan 1949 and Dec 1966, and mortality was examined from Jan 1950 to Dec 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 (i.e., using cellulose nitrate, ethyl alcohol, and camphor) and for cellulose nitrate processing (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>14</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 was not a primary skin irritant in rabbits.<sup>8</sup> A modified Draize test was performed in six NZW rabbits, and the test solution was applied to intact and abraded skin. (The nitrogen content and particle size distribution of nitrocellulose was described in the single-dose toxicity section). The primary irritation score was  $< 0.2$ .

Ball powder (defined previously) was not irritating in rabbits in a modified Draize irritation test.<sup>15</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.

### **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 were not provided.<sup>16</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>17</sup> (Details of the patch testing were not provided). 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>18</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>19</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>20</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.

### **INFORMATION SOUGHT**

1. Chemical characterization data for nitrocellulose and collodion; specifically information on the similarity and differences of the two ingredients.
2. If the differences between nitrocellulose and collodion are significant, then all types of data used in CIR safety assessments – included by not limited to toxicokinetics, animal toxicity, genotoxicity, and dermal irritation and sensitization data – are requested.

### **SUMMARY**

Nitrocellulose is a cellulose-derivative that is produced by nitrating cellulose. Collodion is 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 463 cosmetic formulations, primarily in nail products; according to an industry survey, nitrocellulose is used at concentrations up to 41% in nail products. Collodion is not reported to be used according to VCRP data; results of a concentration of the use survey have not yet been received.

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 adverse 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. In provocative testing with a nitrocellulose solution in butyl acetate, 17/25 patients with various dermatoses and 19/19 patients with nail polish-dermatitis reacted to the solution; reactions were much greater in the nail polish-dermatitis patients. Benzol was found in the solution. In patients with allergic eczema to nail polish, patch testing

with nitrocellulose elicited a reaction in nine of the 30 patients tested. In a 64-mo study, 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.

## TABLES

**Table 1. Chemical and physical properties**

Property	Description	Reference
<b>Nitrocellulose</b>		
appearance	white, amorphous solid	21
	non-fibrous, cotton-like white solid	3
molecular weight	504.3	21
	297.14 (formula wt of the trinitrated monomer unit)	3
decomposition range	160-170°C	3
specific gravity	1.66 g/ml	21
solubility	practically insoluble in water; generally, soluble in esters, aldehydes, and ketones; the more completely nitrated, the smaller the range of material in which there is solubility	3
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	22
odor	ether-like	22
solubility	very soluble in methanol, benzene, toluene, and mixtures of ether and alcohol	3
stability	the pyroxylin precipitates on the addition of water	22
d <sub>25</sub> <sup>25</sup>	0.765-0.775	22

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

	# of Use <sup>4</sup>	Max. Conc. of Use (%) <sup>5</sup>
<b>Totals*</b>	<b>463</b>	<b>0.04-41</b>
<b>Duration of Use</b>		
Leave-On	463	11-41
Rinse Off	NR	0.04
Diluted for (Bath) Use	NR	NR
<b>Exposure Type</b>		
Eye Area	NR	NR
Incidental Ingestion	NR	NR
Incidental Inhalation - Spray	NR	NR
Incidental Inhalation - Powder	NR	NR
Dermal Contact	1	0.04
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	462	11-41
Mucous Membrane	NR	NR
Baby Products	NR	NR

NR – none reported

## REFERENCES

1. Gottschalek TE and Breslawec H. International Cosmetic Ingredient Dictionary and Handbook. Washington, DC: Personal Care Products Council, 2012.
2. Merck & Co., Inc. The Merck Index.  
<http://themerckindex.cambridgesoft.com/themerckindex/Forms/Search/ContentArea/ChemBioVizSearch.aspx?FormGroupId=200000&AppName=THEMERCKINDEX&AllowFullSearch=true&KeepRecordCountSynchronized=false&SearchCriteriaId=23&SearchCriteriaValue=collodion&CurrentIndex=1>. 2012. Date Accessed 11-19-2012.
3. US Army Medical Bioengineering Research and Development Laboratory. Data summary for nitrocellulose. Technical report 8609. 1986. NTIS ADA186413\*DL.
4. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. 2012. Washington, DC: FDA. Received in May 2012.
5. Personal Care Products Council. 9-24-2012. Concentration of Use by FDA Product Category: Nitrocellulose. Unpublished data submitted by Personal Care Products Council. 2 pages.
6. Midwest Research Institute. Mammalian toxicity of munitions compounds. Phase II: Effects of multiple doses; Part IV: nitrocellulose. Progress report No. 5. 1976. <http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA062016>. Date Accessed 9-5-2012.
7. Midwest Research Institute. Mammalian toxicity of munitions compounds. Phase III: Effects of life-time exposure. Part III: Nitrocellulose. Progress report No. 9. 1980. NTIS ADA079353.
8. Midwest Research Institute. Mammalian toxicity of munitions compound Phase I: Acute oral toxicity, primary skin and eye irritation, dermal sensitization, disposition and metabolism, and Ames test of additional compounds. Report No. 1. 7-22-1975. NTIS ADB011150.
9. Letterman Army Institute of Research. Acute oral toxicity of ball powder<sup>®</sup> in ICR mice. Institute Report No. 351. 1989. <http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA212011>. Date Accessed 9-5-2012. Report No. 351.
10. Letterman Army Institute of Research. Acute oral toxicity of ball powder<sup>®</sup> in Sprague-Dawley rats. Institute Report No. 350. 1989. <http://www.dtic.mil/dtic/tr/fulltext/u2/a211317.pdf>. Date Accessed 9-5-2012. Report No. 350.
11. Letterman Army Institute of Research. Primary ocular irritation potential of ball powder<sup>®</sup> in male rabbits. Institute Report No. 352. 1989. <http://www.dtic.mil/cgi-bin/GetTRDoc?Location=U2&doc=GetTRDoc.pdf&AD=ADA212080>. Date Accessed 9-5-2012.
12. Midwest Research Institute. Mammalian toxicity of munitions compound Phase I: Acute oral toxicity, primary skin and eye irritation, dermal sensitization, disposition and metabolism, and Ames test of additional compounds. Progress report No. 6. 12-8-1978. <http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA069333>. Date Accessed 11-6-2012.
13. Marsh GM. Mortality among workers from a plastics producing plant: A matched case-control study nested in a retrospective cohort study. *J Occup Med*. 1983;25(3):219-230.
14. Goldberg MS, Parent M-É, Siemiatycki J, Déry M, Nadon L, Richardson L, Lakhani R, Latreille B, and Valois M-F. A case-control study of the relationship between the risk of colon cancer in men and exposures to occupational agents. *Am J Indus Med*. 2001;39:531-546.
15. Letterman Army Institute of Research. Primary dermal irritation potential of ball powder<sup>®</sup> in rabbits. Institute Report No. 349. 1989. <http://www.dtic.mil/dtic/tr/fulltext/u2/a211285.pdf>. Date Accessed 9-6-2012.
16. Burgess JF. Nail-polish dermatitis. *Canadian Medical Association Journal*. 1941;45:336-339.
17. Dobes WL and Nippert PH. Contact eczema due to nail polish. *Archives of Dermatology and Syphilology*. 1944;49:183-187.
18. Adams RM and Maibach HI. A five-year study of cosmetic reactions. *J Am Acad Dermatol*. 1985;13:1062-1069.

19. Castelain M, Veyrai S, Laine G, and Montastier C. Contact dermatitis from nitrocellulose in nail varnish. *Contact Dermatitis*. 1997;36:266-267.
20. Lachapelle J-M and Leroy B. Allergic contact dermatitis to colophony included in the formulation of flexible collodion BP, the vehicle of a salicylic and lactic acid wart paint. *Dermatologic Clinics*. 1990;8(1):143-146.
21. Sax's Dangerous Properties of Industrial Materials. 10 ed. New York: John Wiley & Sons, 2000.
22. Merck & Co., Inc. The Merck Index.  
<http://themerckindex.cambridgesoft.com/themerckindex/Forms/Search/ContentArea/ChemBioVizSearch.aspx?FormGroupId=200000&AppName=THEMERCKINDEX&AllowFullSearch=true&KeepRecordCountSynchronized=false&SearchCriteriaId=23&SearchCriteriaValue=collodion&CurrentIndex=0>. 2012. Date Accessed 11-19-2012.