Final Report on the Safety Assessment of Corylus Avellana (Hazel) Seed Oil, Corylus Americana (Hazel) Seed Oil, Corylus Avellana (Hazel) Seed Extract, Corylus Americana (Hazel) Seed Extract, Corylus Rostrata (Hazel) Seed Extract, Corylus Avellana (Hazel) Leaf Extract, Corylus Americana (Hazel) Leaf Extract, and Corylus Rostrata (Hazel) Leaf Extract[1]

These ingredients are all derived from hazelnut trees. The two seed oils are expressed from the nuts of the hazelnut tree of the particular species identified. Most current reported cosmetic uses are of the seed oils. The seed extracts are the extract of the nuts of the identified species tree. There is one current report of use of seed extract in cosmetics. The leaf extracts are the extract from the leaves of the particular species tree. There are no current reports of use of these extracts in cosmetics. Analysis of seed oil from one species identified Oleic Acid, Palmitoleic Acid, Linoleic Acid, Eicosaenoic Acid, Docosenoic Acid, Eicosanoic Acid, Palmitic Acid, Linolenic Acid, Stearic Acid, and Tetraeicosanoic Acid. Little information is available to characterize the extracts, however. The functions of most of these ingredients in cosmetics are not reported. In studies of hazelnuts from Spain and Egypt, aflatoxin was reported as a possible contaminant. Aflatoxins are considered carcinogenic in humans. Virtually no safety test data are available on these ingredients. Negative results in one comedogenicity study using a seed oil are reported. Cross-sensitivity to proteins in peanuts and those in hazelnuts are reported, but the presence or absence of protein in nut extract and plant extract from hazelnut trees is not known. Additional data were provided regarding concentration of use, method of extraction and contaminants, comedogenicity, and ultraviolet (UV) radiation absorption, but these data related to nut oil from only one species, and were not overall sufficient to resolve questions about irritation, sensitization, and photosensitization. Because of the absence of data, it is concluded that the available data are insufficient to support the safety of these ingredients in cosmetic products. Because of the limited information that characterizes any of these oils or extracts, data are needed on each (except that items 1, 2, and 3 below are not needed for Hazel [Corylus Avellana] Nut Oil). The additonal data needs include: (1) current concentration of use; (2) method of extraction/manufacture and quality control (i.e., chemical analyses); (3) contaminants and methods of extraction (especially pesticides and heavy metals); (4) dermal irritation and sensitization; (5) UV absorption; if there is significant absorption, then a photosensitization study will be needed; (6) 28-day dermal toxicity; (7) reproductive and developmental toxicity; and (8) two genotoxicity assays, one in a mammalian system; if positive, then a 2-year dermal carcinogenesis study using National Toxicology Program (NTP) methods may be needed.

INTRODUCTION

The terminology with which the ingredients addressed in this safety assessment has changed recently. Table 1 shows the terminology used in the 7th edition of the *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger and McEwen 1997) and the 8th edition (Wenninger, Canterbery, and McEwen 2000). This report will use the new terminology. Accordingly, what follows is a compilation of information concerning: Corylus Avellana (Hazel) Seed Oil, Corylus Americana (Hazel) Seed Oil, Corylus Avellana (Hazel) Seed Extract (CAS No. 84012-21-5), Corylus Americana (Hazel) Seed Extract, Corylus Rostrata (Hazel) Seed Extract, Corylus Avellana (Hazel) Leaf Extract (CAS No. 84012-21-5), Corylus Americana (Hazel) Leaf Extract, and Corylus Rostrata (Hazel) Leaf Extract.

Minimum information was found in the published literature about ingredients obtained from the *Corylus americana* or *Corylus rostrata* hazel trees. Therefore, the terms Hazel Extract, Hazelnut Extract or Hazelnut Oil refers to the respective ingredients obtained from the hazel *Corylus avellana* tree unless otherwise noted.

CHEMISTRY

Definition and Structure

The two nut oils, Corylus Avellana (Hazel) Seed Oil and Corylus Americana (Hazel) Seed Oil are the oils expressed from the nuts of the hazelnut trees, *Corylus avellana* and *C. americana*,

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TABLE 1
New and old terminology for corylus-derived ingredients

1997 Terminology[a]	2000 Terminology[b]
Hazel (Corylus Americana) Extract	Corylus Americana (Hazel) Leaf Extract
Hazel (Corylus Avellana) Extract	Corylus Avellana (Hazel) Leaf Extract
Hazel (Corylus Rostrata) Extract	Corylus Rostrata (Hazel) Leaf Extract
Hazel (Corylus Avellana) Nut Extract	Corylus Avellana (Hazel) Seed Extract
Hazel (Corylus Americana) Nut Extract	Corylus Americana (Hazel) Seed Extract
Hazel (Corylus Rostrata) Nut Extract	Corylus Rostrata (Hazel) Seed Extract
Hazel (Corylus Americana) Nut Oil	Corylus Americana (Hazel) Seed Oil
Hazel (Corylus Avellana) Nut Oil	Corylus Avellana (Hazel) Seed Oil

[a]Wenninger and McEwen 1997.
[b]Wenninger, Canterbery, and McEwen 2000.

respectively (Wenninger, Canterbery, and McEwen 2000). Cosmetic Hazel (Corylus Avellana) Nut Oil is described as a natural oil that contains no contaminants, additives, or solvents. The Oil is extracted by high pressure systems followed by a slow process of decantation and natural filtration on paper (Bertin 1997).

Similarly, the three hazelnut extracts, Corylus Avellana (Hazel) Seed Extract, Corylus Americana (Hazel) Seed Extract, and Corylus Rostrata (Hazel) Seed Extract are the extract of the nuts of the hazelnuts *C. avellana*, *C. americana*, and *C. rostrata*, respectively (Wenninger, Canterbery, and McEwen 2000).

The three hazel leaf extracts, Corylus Avellana (Hazel) Leaf Extract, Corylus Americana (Hazel) Leaf Extract and Corylus Rostrata (Hazel) Leaf Extract are the extract of the leaves of the hazel trees, *C. avellana*, *C. americana*, and *C. rostrata*, respectively (Wenninger, Canterbery, and McEwen 2000).

Chemical and Physical Properties

Researchers in Venezuela analyzed Hazelnut (Corylus Avellana) Oil by gas liquid chromatography and reported the average acid composition cited in Table 2 (Villarroel et al. 1989). Some of the acids have been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel and their status is also noted in the table.

TABLE 2
Fatty acid composition of Corylus Avellana (Hazel) Seed Oil

Acid composition (Villarroel et al. 1989)	CIR safety assessment (reference)
39.5% Oleic Acid	Safe as used* (Elder 1987)
37.0% Palmitoleic Acid	
6.9% Linoleic Acid	
4.6% Eicosaenoic Acid	
3.4% Docosenoic Acid	
2.3% Eicosanoic Acid	
2.3% Palmitic Acid	Safe as used* (Elder 1987)
1.1% Linolenic Acid	
0.5% Stearic Acid	Safe as used* (Elder 1987)
0.3% Tetraeicosanoic Acid	

*Reported use concentration to FDA was 0.1% to 25%.

Aflatoxin Impurities

In 50 samples of hazelnuts from Spain, all samples showed fungal contamination, but no aflatoxin contamination. Of the 59 fungal strains identified, 25 were aflatoxigenic strains (Sanchis et al. 1988). In 20 hazelnut samples collected in Egypt, however, aflatoxin (25–175 μg/kg) was reported as a contaminant in 90% of samples (Abdel-Hafez and Saber 1993). Aflatoxins are metabolic products of the molds *Aspergillus flavus* and *A. parasiticus*. They are most often produced in stored agricultural crops when growth conditions and genetic requirements are favorable (Budavari 1989).

The International Agency for Research on Cancer (IARC) categorized aflatoxins as group 1 agents, "carcinogenic to humans" (IARC 1976; 1987). Epidemiological studies noted, "positive correlation between estimated aflatoxin intake or level of aflatoxin contamination of market food samples and cooked food and incidence of hepatocellular cancer." The observations were supported by positive results in laboratory carcinogenicity and mutagenicity studies.

The United States Department of Agriculture has required imported filberts (hazelnuts) to be "free from foreign material, mold, rancidity, decay or insect injury;" these requirements are codified in 7 CFR 999.400. Mold is defined as "a visible growth of mold either on the outside or inside of the kernel." A 2% tolerance for mold is allowed. These requirements are stated to be the same standards as for filberts (hazelnuts) grown in Oregon and Washington.

USE

Cosmetic

The two Hazelnut Oils can be used as occlusive skin-conditioning agents (Wenninger, Canterbery, and McEven 2000). As

TABLE 3
Frequency of use (FDA 1998)

Product category	Total no. of formulations in category	No. containing ingredient
Hazelnut Bark Extract*		
Paste masks (mud packs)	255	1
1998 total for Bark Extract		1
Hazelnut Extract		
Other manicuring preparations	61	1
1998 total for Hazelnut Extract		1
Hazelnut Oil		
Bath oils, tablets, and salts	124	2
Other eye makeup preparations	120	2
Shampoos (noncoloring)	860	1
Foundations	287	2
Other manicuring preparations	61	1
Other personal cleanliness products	291	1
Cleansing	653	4
Face and neck skin care (excluding shaving)	263	15
Body and hand skin care (excluding shaving)	796	26
Moisturizing skin care	769	7
Night skin care	188	5
Paste masks (mud packs)	255	3
Other skin care preparations	692	14
Suntan gels, creams, and liquids	136	2
1998 total for Hazelnut Oil		85

*Ingredient not listed in *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger, Canterbery, and McEwen 2000).

of January 1998 Hazelnut Oil (Table 3) was reported to be used in 85 cosmetic formulations (FDA 1998). The Food and Drug Administration (FDA) data do not distinguish which Hazelnut Oil was used. Concentration of use data are no longer reported to the FDA (FDA 1992). Historical data (FDA 1984) indicated that although Hazelnut Oil was used in one formulation at 25% to 50%, all other 10 uses of the ingredient were at ≤5%. Current data from an industry source indicated use of Hazel (Corylus Avellana) Nut Oil at concentrations up to 100% (Bertin 1997).

The functions in cosmetics of Corylus Avellana (Hazel) Seed Extract, Corylus Americana (Hazel) Seed Extract, Corylus Rostrata (Hazel) Seed Extract, Corylus Americana (Hazel) Leaf Extract, and Corylus Rostrata (Hazel) Leaf Extract are not reported (Wenninger, Canterbery, and McEwen 2000).

Corylus Avellana (Hazel) Leaf Extract is reported to function in cosmetics as a skin-conditioning agent—miscellaneous; Corylus Americana (Hazel) Seed Oil as a skin conditioning agent—occlusive; and Corylus Avellana (Hazel) Seed Oil as a fragrance ingredient (Wenninger, Canterbery, and McEwen 2000).

As of January 1998 there were no reported uses of Hazel Extracts. Hazelnut Extract was used in one formulation (FDA 1998) (see Table 2). The FDA data do not distinguish which Hazelnut Extract was used.

In addition, the FDA data (Table 3) note that Hazelnut Bark Extract was used in one formulation (FDA 1998). This ingredient is not listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger, Canterbery, and McEwen 2000).

International Cosmetic

Hazelnut Oil is listed in the *Comprehensive Licensing Standards of Cosmetics by Category* (CLS). That which conforms to the specifications of the *Japanese Cosmetic Ingredients Codes* has precedent for use without restriction in all CLS categories (Rempe and Santucci 1997).

GENERAL BIOLOGY

Anti-inflammatory Activity

Corylus avellana L. was among several plants selected by Tunón, Olavsdotter, and Bohlin (1995) for evaluation of anti-inflammatory activity. Leaf and bark collected in Sweden were dried, extracted twice with water, and lyophilized. The extracts were tested in two in vitro assays.

In the prostaglandin biosynthesis assay, 0.2 mg/ml of the extract and [^{14}C]arachidonic acid were incubated with bovine seminal vesicle microsomes that had been pre-incubated with

a cofactor solution (reduced glutathione and 1-adrenaline). Reactions were stopped 10 minutes later with the addition of hydrochloric acid and a carrier solution of prostaglandin. Unmetabolized arachidonic acid was separated from the prostaglandin products by chromatography. Prostaglandins were eluted with ethyl acetate/methanol and the activity was counted using a scintillation spectrometer. Indomethacin was used as a reference compound. The extract of *C. avellana L.* leaves enhanced prostaglandin release by 14% (mean value of triplicate trials). The bark extract inhibited release by 54% which was considered a moderate effect.

The platelet activating factor (PAF)-induced exocytosis assay is based on PAF's capacity to induce exocytosis in neutrophils thereby releasing the enzyme elastase which reacts with the substrate SAAVNA (added to the test mixture) to form a colored product. Extract (0.25 mg/ml) was incubated with SAAVNA and neutrophils isolated from the peripheral blood of healthy volunteers. PAF (0.1 μM) was added to start the reaction and the reaction was stopped after 10 minutes with the addition of citric acid. Tubes were centrifuged and the absorbance by the supernatant of 405 nm light was measured. A relative decrease in absorbance of test samples compared to distilled water indicated an inhibition of PAF-induced release of elastase. The compound BN 52021 was used as a reference compound. The leaf and bark extracts of *C. avellana L.* inhibited PAF-induced exocytosis by 69% and 88%, respectively (mean value of duplicate trials). The activity of the leaf and bark extracts was considered moderate and high, respectively.

The investigators considered that tannins and other polyphenols present in the bark extract may explain why it was active in both assays whereas the leaf extract was only active in the PAF-induced assay (Tunón, Olavsdotter, and Bohlin 1995).

ANIMAL TOXICOLOGY

Dermal

Comedogenicity

A comedogenicity study was conducted in which 0.1 ml of "huile de noisettes vierge" (a yellow oil with a pH of 6; submitted as study on Hazel [Corylus Avellana] Nut Oil) was applied to the internal fold and the pinna of the right ear of six male albino rabbits, 5 days per week for 2 weeks. Animals were killed at the end of the study and epidermal samples were obtained from both ears of each rabbit. The samples were examined both by a magnifying glass and microscopically. No local irritation was noted at the application site. A "slight difference in the number and size of the pilosebaceous follicles" was noted via magnifying glass. A "slight excess of sebum and a dilatation of the follicles" was noted upon microscopic examination of the treated areas (Biogir 1988).

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

A patch testing reference book by DeGroot (1994) noted that the published literature does not contain recommended test concentrations concerning Hazelnut Oil. To serve as a guide to the reader, DeGroot reported that an unpublished (and at the time, ongoing) study found no irritant reaction in 1 to 20 patients suffering from or suspected to suffer from cosmetic product contact allergy who had been patch tested with 30% Hazelnut Oil in petrolatum.

Hypersensitivity

People with IgE-dependent allergic hypersensitivity to food proteins such as hazelnuts can have cross-sensitivity to hazel pollen and peanuts (as well as to other nuts and pollen of the Fagales family) (Eriksson et al. 1987; Hirschwehr et al. 1992; Higgins et al. 1995). The hazelnut protein inducing such reactions was considered to have the same binding proteins as that of the major pollen allergens of hazel, Cor a *I* and birch, Bet v *I* (Hirschwehr et al. 1992; Breiteneder et al. 1993).

PREVIOUS SAFETY ASSESSMENTS

Because the seed oils (see Table 2) contain fatty acids that previously have been assessed (Elder 1987), it was considered germaine to summarize those findings.

Oleic, Palmitic, and Stearic Acids are fatty acids with hydrocarbon chains ranging in length from 12 to 18 carbons and a terminal carboxyl group. Monounsaturated Oleic Acid (18C) is a liquid at standard temperature and pressure; the saturated acids, Palmitic (16C), and Stearic (18C) are solids. The fatty acids are obtained by the hydrolysis of animal fats and vegetable oils.

Fatty acids are absorbed, digested, and transported in animals and humans. They have been detected in tissue, blood, and lymph following administration via various routes. Placental transfer of fatty acids has been documented in several species, but no teratogenicity studies have been found.

Oral-dose studies using rats noted little toxicity after acute exposure to 2.2% to 13% Oleic, Stearic, or Palmitic Acid at doses of 15 to 19 g/kg; thrombosis, aortic atherosclerosis, anorexia, and mortality following subchronic exposure to 5% to 50% Oleic, Stearic, or Palmitic Acid; and impaired reproductive capacity in female rats following chronic exposure to 15% Oleic Acid.

Results of dermal-exposure studies in which Oleic Acid (50% to as commercially supplied) was applied to the skin of mice, rabbits, and guinea pigs ranged from no toxicity to erythema, hyperkeratosis, and hyperplasia. Intradermal administration of Oleic Acid to guinea pigs resulted in local inflammation and necrosis. A formulation containing 2.2% Palmitic Acid, and a topical dose of 5 g/kg commercial grade Stearic Acid (separate studies) were nontoxic to rabbits. Intradermal administration of 10 to 100 mM Stearic Acid to guinea pigs produced mild erythema and slight induration. Fatty acids applied at 18 mmol% to the skin of the external ear canals of albino rabbits for 6 weeks produced no irritation (Stearic Acid), slight irritation (Palmitic Acid), and defined erythema, desquamation, and persistent follicular keratosis (Oleic Acid).

Slight local edema was noted in New Zealand white rabbits after 4 weeks of dermal exposure to a formulation containing

2.0% Stearic Acid. Two formulations containing, at most, 5% Stearic Acid, produced moderate skin irritation in rats following 13 weeks of dermal application. Mild reactions were noted in single-insult occlusive patch tests of rabbits with 35% to 65% commercial-grade Stearic Acid (in vehicle), or 1% to 13% commercial-grade Oleic or Palmitic Acid (in formulation).

Studies using formulations containing Oleic and Stearic Acids indicated that neither is a sensitizer nor a photosensitizing agent. Oleic and Stearic Acids were noncarcinogenic in separate animal studies.

In clinical primary and cumulative dermal irritation studies, Oleic, Myristic, and Stearic Acids, at concentrations of 100% or 40% to 50% in mineral oil, were nonirritating. Repeat-insult patch tests (open, occlusive, and semiocclusive), maximization tests, and prophetic patch tests of formulations containing <1% to 13% Oleic, Stearic, and Palmitic Acids reported no primary or cumulative irritation or sensitization. Reactions to induction patches were noted in <5% (of almost 4000 panelists), and in <2% of panelists when challenge patches were applied at the induction site, but were not considered related to the fatty acid concentration of the formulations. Formulations containing <1% to 13% Oleic, Stearic, and Palmitic Acids were not photosensitizing; some reactions were noted during induction.

No treatment-related ocular irritation was noted in female panelists, some of whom were contact lens wearers, involved in two 3-week exaggerated-use studies of mascara formulations containing 2% and 3% Oleic Acid.

In the discussion section of the report, the Expert Panel remarked on the lack of data concerning Myristic Acid, but concluded that its structural similarity to the other fatty acids allowed its inclusion in the safety assessment. The Panel also acknowledged that application of Oleic (and Lauric) Acid to rabbit skin produced follicular keratosis and/or formation of comedones. On the basis of available data from studies using animals and humans, the Expert Panel concluded that Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are safe in the present practices of use and concentrations in cosmetics (Elder 1987).

DISCUSSION

Although information on the fatty acids present in the seed oil from one species was available, and these fatty acids are considered safe, little information is available to characterize the extracts. Also, there was uncertainty as to the extent to which the limited data characterizing the one seed oil can be generalized. Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety."

In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on Hazel (Corylus Avellana) Nut Oil, Hazel (Corylus Americana) Nut Oil, Hazel (Corylus Avellana) Nut Extract, Hazel (Corylus Americana) Nut Extract, Hazel (Corylus Rostrata) Nut Extract, Hazel (Corylus Avellana) Extract, Hazel (Corylus Americana) Extract, and Hazel (Corylus Rostrata) Extract were not sufficient for determination whether the ingredient, under relevant conditions of use, was either safe or unsafe. The Panel released a Notice of Insufficient Data on April 4, 1997, outlining the data needed to assess the safety of these ingredients. Comments regarding concentration of use, method of extraction and contaminants, a comedogenicity study, and a ultraviolet (UV) absorption curve were received during the 90-day public comment period. The Panel reviewed the submission and decided that these studies were inadequate because (a) they were done on Hazel (Corylus Avellana) Nut Oil only, (b) a comedogenicity study was not sufficient to assess dermal irritation and sensitization, and (c) the UV absorption curve was unclear. Therefore data needed[2] to make a safety assessment are:

1. Current concentration of use
2. Method of extraction/manufacture and quality control (i.e., chemical analyses)
3. Contaminants and methods of extraction (especially pesticides and heavy metals)
4. Dermal irritation and sensitization
5. UV absorption; if there is significant absorption, then a photosensitization study will be needed
6. 28-Day dermal toxicity[3]
7. Reproductive and developmental toxicity[3]
8. Two genotoxicity assays, one in a mammalian system; if positive, then a 2-year dermal carcinogenicity study using National Toxicology Program (NTP) methods may be needed

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of Hazel (Corylus Avellana) Nut Oil, Hazel (Corylus Americana) Nut Oil, Hazel (Corylus Avellana) Nut Extract, Hazel (Corylus Americana) Nut Extract, Hazel (Corylus Rostrata) Nut Extract, Hazel (Corylus Avellana) Extract, Hazel (Corylus Americana) Extract, and Hazel (Corylus Rostrata) Extract for use in cosmetic products.

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[2]Data are needed on each species and form; however, data needs 1, 2, and 3 are not needed for Hazel (Corylus Avellana) Nut Oil.

[3]Although the CIR Expert Panel has specified a "28-day dermal toxicity study," there is concern that specifying a type of study may inhibit those who want to gather data using other study designs. The types of data the Panel is seeking include the gross pathology and histopathology in skin and other major organ systems, along with certain other toxicity parameters, associated with repeated exposures. A 28-day dermal toxicity study would generate the needed data; but there are other approaches. For example, the Expert Panel would consider a dermal reproductive and developmental study in which gross pathology and histopathology data are gathered on the F_0 generation to be sufficient to meet both the "28-day dermal toxicity" and "reproductive and developmental toxicity" data requested, if done at or above current concentrations of use of the ingredient.

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