October 24, 2007

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Dear Dr. von Eschenbach:

The National Toxic Encephalopathy Foundation (NTEF), hereinafter referred to as the petitioner, respectfully submits this petition under the following Code of Federal Regulations (CFR), United States Code (USC) and Food, Drug Cosmetic Act (FD&C):

Chapter I Subchapter G (Title 21 CFR- Food and Drug -Subpart B 740.10(a)
Chapter I Subchapter G (Title 21 CFR- Food and Drug -Subpart A 740.1(a)
Chapter IX Subchapter VIII (21`U.S.C. Subchapter VIII Section 381 (a)(3))
Chapter IX Subchapter III (21`U.S.C. Subchapter III Section 334(a)(1)(B))
Chapter IX Subchapter II (21`U.S.C. Subchapter II Section 321(g)(1)(B)(C))
Chapter IX Subchapter III (21`U.S.C. Subchapter III Section 331(a)(b)(c))
Chapter IX Subchapter VIII (21`U.S.C. Subchapter VIII Section 381(a)(3)(b))
Chapter IX Subchapter VI (21`U.S.C. Subchapter VI Section 362(a)(c))
Chapter IX Subchapter VI (21`U.S.C. Subchapter VI Section 362(a))
Chapter IX Subchapter II (21`U.S.C. Subchapter II Section 321(n))
Chapter IX Subchapter VI (21`U.S.C. Subchapter VI Section 361(a))
Chapter IX Subchapter V Part A (21`U.S.C. Subchapter V Section 351(d)(1))
Chapter I Subchapter G (Title 21 CFR- Food and Drug -Subpart A 740.1(b)
Chapter I Subchapter G (Title 21 CFR- Food and Drug -Subpart A 740.2(a)

Chapter I Subchapter A (Title 21 CFR –Food and Drug –Subpart A Section 2.5 (a)(1)(2))
21CFR 5.10 subpart (A)(1):
21CFR Sections 701.3 and 701.11-701.13

These regulations are under the auspices of the Commissioner of the Federal Food, Drug Cosmetic Administration under:

21CFR 5.10 subpart (A)(1):

Sec. 510

"(A) "The Secretary of Health and Human Services (the Secretary) has redelegated to the Commissioner of Food and Drugs (Commissioner), with authority to redelegate (except when specifically prohibited), all authority as follows:
(1) Functions vested in the Secretary under the Federal Food, Drug and Cosmetics Act (21 U.S.C. 301 et seq.)."

Petitioner hereby requests that the Commissioner initiate administrative action against Clarins USA for violations of the aforementioned USC, CRF and FD&C rules and regulations.

I. ACTION REQUESTED:

The NTEF after careful review of all the ingredients disclosed on the label and attached exhibits hereby submits their request that "Angel" eau de Parfum and "Angel" eau de toilette by Theirry Mugler (Angel), must be designated as being misbranded. The Commissioner of the Food & Drug Administration, herein after referenced as FDA, as cited above has the power and authority in order to make this declaration and request the immediate and full compliance by Clarins USA. The commerce and importation of Angel is in violation of numerous codes and must be declared misbranded for failure to provide necessary labeling on this consumer product.

Manufacturer:

Thierry Mugler Parfums
13 rue Madeleine Michelis
92200 Neuilly-France

Imported into the United States by:

Clarins
4, rue Berteaux-Dumas
92200 Neuilly-sur-Seine-France

Distributed by:

Clarins USA
110 East 59th Street
NY, NY 10022.

II. STATEMENT OF GROUNDS:

Chapter IX Subchapter II (21`U.S.C. Subchapter II Section 321(n))
Sec. 321

"(n) If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual."

Any consumer commodity which is a food, drug, device, or cosmetic, as each such term is defined by **section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321**), and which is introduced or delivered for introduction into commerce in violation of any of the provisions of this chapter, or the regulations issued pursuant to this chapter, shall be deemed to be misbranded within the meaning of chapter III of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 331 et seq.], but the provisions of section 303 of that Act (21 U.S.C. 333) shall have no application to any violation of section 1452 of this title.

The following violations are associated with this product:

Misbranding and Adulteration:

Chapter I Subchapter G (Title 21 CFR- Food and Drug -Subpart A 740.2(a)
Sec. 740.2

"(a) A warning statement shall appear on the label prominently and conspicuously as compared to other words, statements, designs, or devices and in bold type on contrasting background to

render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use, but in no case may the letters and/or numbers be less than1/16inch in height, unless an exemption pursuant to paragraph (b) of this section is established."

There is no warning label or statement regarding the allergenistic properties, known skin, eye and respiratory irritants, ingredients whose toxicity has not been evaluated, reproductive effectors and carcinogenetics associated with this product. The consumer is not given relevant information to make an informed decision when purchasing Angel.

VIOLATION CHARGE CODES, Exhibit 1:

Reason: LABELING

Section: Section 4 (a); MISBRANDING
Charge: The article appears in violation of FPLA because of its placement, form and/or contents statement.

FPLA: Fair Packaging and Labeling Act

SUPPORTING STATEMENT
Cosmetic Labeling Regulations
0910-0599

21CFR Sections 701.3 and 701.11-701.13

2. Information User:
The information required to be disclosed in FDA's cosmetic labeling regulations is used by consumers of cosmetic products when evaluating, purchasing and using the products. FDA uses the information to evaluate cosmetic products currently on the market and to verify compliance with the requirements for labeling cosmetic purchases. **Exhibit 2.**

Reason: REDUCED

Section: 501 (d)(1), ADULTERATION
Charge: It appears to be a drug that a substance has been mixed or packed with so as to reduce its strength

Chapter IX Subchapter V Part A (21`U.S.C. Subchapter V Section 351(d)(1))
Sec. 351

"(d) Mixture with or substitution of another substance. If it is a drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength "

Reason: POISONOUS

Section: 601 (a), ADULTERATION

Charge: The cosmetic appears to bear or contain a poisonous or deleterious substance which may render it injurious to users under the conditions prescribed in the labeling thereof, or, under such conditions of use as are customary

Chapter IX Subchapter VI (21`U.S.C. Subchapter VI Section 361(a))
Sec. 361

"(a) If it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under such conditions of use as are customary or usual"

Reason: COSM MISB

Section: 602 (a) MISBRANDING

Charge: The cosmetic's labeling appears to be false or misleading within the meaning of Section 201 (n).

Chapter 9 Subchapter II (21`U.S.C. Subchapter II Section 321(n))
Sec. 321

"(n) If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual."

Reason: COSM MISB2

Section: 602 (a) MISBRANDING

Charge: The article is subject to refusal of admission pursuant to Section 801 (a)(3) in that it appears that its labeling is false or misleading in any particular [Misbranding, Section 602 (a)].

Chapter IX Subchapter VI (21`U.S.C. Subchapter VI Section 362(a))
Sec. 362

"(a) If its labeling is false or misleading in any particular."

Reason: CSTIC LBLG

Section: 602 (a) and/or (b), and/or (c), MISBRANDING
Charge: The labeling appears to fail to comply with cosmetic labeling requirements of Section 602 (a) and/or (b), and/or (c), and as identified by 21 C.F.R. Part 701.

Chapter IX Subchapter VI (21`U.S.C. Subchapter VI Section 362(a)(c))
Sec. 362.

"(a) If its labeling is false or misleading in any particular.
(c) If any word, statement, or other information required by or under authority of this chapter to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use."

IMPORT VIOLATIONS:

Reason: COSM MISB

Section: 801 (a)(3); MISBRANDING
Charge: The cosmetic's labeling appears to be false or misleading within the meaning of Section 201 (n).

Reason: COSM MISB2

Section: 801 (a)(3); MISBRANDING
Charge: The article is subject to refusal of admission pursuant to Section 801 (a)(3) in that it appears that its labeling is false or misleading in any particular [Misbranding, Section 602 (a)].

Reason: CSTIC LBLG

Section: 801 (a)(3); MISBRANDING

Charge: The labeling appears to fail to comply with cosmetic labeling requirements of Section 602 (a) and/or (b), and/or (c), and as identified by 21 C.F.R. Part 701.

Reason: POISONOUS

Section: 801 (a)(3), ADULTERATION

Charge: The cosmetic appears to bear or contain a poisonous or deleterious substance which may render it injurious to users under the conditions prescribed in the labeling thereof, or, under such conditions of use as are customary

Reason: REDUCED

Section: 801 (a)(3); ADULTERATION

Charge: It appears to be a drug that a substance has been mixed or packed with so as to reduce it's strength

Reason: LABELING

Section: 801 (a)(3) MISBRANDING

Charge: The article appears in violation of FPLA because of its placement, form and/or contents statement, **Exhibit 2.**

Chapter IX Subchapter VIII (21`U.S.C. Subchapter VIII Section 381(a)(3)(b))

Sec. 381

(a) Imports; list of registered foreign establishments; samples from unregistered foreign establishments; examination and refusal of admission(3) such article is adulterated, misbranded, or in violation of section 355 of this title, then such article shall be refused admission, except as provided in subsection (b) of this section. The Secretary of the Treasury shall cause the destruction of any such article refused admission unless such article is exported, under regulations prescribed by the Secretary of the Treasury, within ninety days of the date of notice of such refusal or within such additional time as may be permitted pursuant to such regulations. Clause (2) of the third sentence of this paragraph \1\ shall not be construed to prohibit the admission of narcotic drugs the importation of which is permitted under the Controlled Substances Import and Export Act [21 U.S.C. 951 et seq.]."

Sec. 951. Definitions

"(a) For purposes of this subchapter -

“(1) The term "import" means, with respect to any article, any bringing in or introduction of such article into any area (whether or not such bringing in or introduction constitutes an importation within the meaning of the tariff laws of the United States).”

SEIZURE

Chapter IX Subchapter III (21`U.S.C. Subchapter III Section 331(a)(b)(c))
Sec.331.

“(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.
(b) The adulteration or misbranding of any food, drug, device or cosmetic in interstate commerce.
(c) The receipt in interstate commerce of any food, drug, device or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.”

Chapter IX Subchapter III (21`U.S.C. Subchapter III Section 334(a)(1)(B))
Sec. 334.

“(a) (1) Any article of food, drug, or cosmetic that is adulterated or misbranded when introduced into or while in interstate commerce or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which may not, under the provisions of section 344 or 355, be introduced into interstate commerce, shall be liable to be proceeded against while in interstate commerce, or at any time thereafter, on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which the article is found. No libel for condemnation shall be instituted under this Act, for any alleged misbranding if there is pending in any court a libel for condemnation proceeding under this Act based upon the same alleged misbranding, and not more than one such proceeding shall be instituted if no such proceeding is so pending, except that such limitations shall not apply
(B) when the Secretary has probable cause to believe from facts found, without hearing, by him or any officer or employee of the Department that the misbranded article is dangerous to health, or that the labeling of the misbranded article is fraudulent, or would be in a material respect misleading to the injury or damage of the

> *purchaser or consumer. In any case where the number of libel for condemnation proceedings is limited as above provided the proceeding pending or instituted shall, on application of the claimant, seasonably made, be removed for trial to any district agreed upon by stipulation between the parties, or, in case of failure to so stipulate within a reasonable time, the claimant may apply to the court of the district in which the seizure has been made, and such court (after giving the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business, to which the case shall be removed for trial."*

The voluntary disclosure by Clarins of their chemical ingredients, **Exhibit 3.**

The label on the box references only the following ingredients: Alcohol denatured, Fragrance (parfum), Purified water (aqua), Benzophenone-2, Butylphenyl Methylpropional, Coumarin, Limonene, Linalool, Amyl Cinnamal, Geraniol, Citronellol, Benzyl Salicylate, Hexyl Cinnamal, Citral, Eugenol, Isoeugenol, D&C Violet No. 2 (CI 60725) and FD&C Blue No. 1 (CI 42090).

The chemical deformulation for the generic reference to Fragrance (Parfum) is suspect. The undisclosed chemical ingredients in the fragrance reference may contain additional amounts of known irritants that potentially could cause the industry recommended "acceptable levels" to be exceeded, resulting in further allergic reactivity or incorporation of other known irritants.

TESTING ON "ANGEL"

Clarins own laboratories declared that their product "is the proof of the cellular necrosis as soon as the first hour of contact", **Exhibit 4.**

The designation of the terms eau de parfum and eau de toilette need to be defined when discussing the fragranced product "commonly" referred to as Angel. Eau de parfum "Lighter than perfume, with an 8-15% concentration…" " Eau de toilette "This is a lighter more delicate fragrance, with a 4-8% concentration of the essence..."

Since there are clearly defined concentration levels of fragrance, when discussing either eau de parfum or eau de toilette, this delineation must be taken into consideration regarding the heighten effects from the eau de toilette when equating it to the eau de parfum, and possibly a shorter time period for the cellular necrosis.

The only known testing on Angel was done in 1999 with ingredients that are not consistent with the disclosure on their current product. **Exhibit 3.** In 2004, a chemical analysis was done, **Exhibit 5**, MSDS sheets for the finished product as provided by Clarins, whereby, the first MSDS, **Exhibit 6,** identified the alcohol content as being classified as hazardous, with no reference to the hazardous nature on their label, **Exhibit 3**, the second MSDS, **Exhibit 7**, was created to downplay the health risks associated with the product. The 2004 deformulation identifies ingredients that are not referenced on the current packaging. An independent laboratory determined that there were respiratory problems associated with this product, **Exhibit** .

Applied Consumer Laboratories located in Hialeah, Florida provided the independent chemical analysis, **Exhibit 5**, which has the following certifications; ACSI certification, GLP certification (per 40 CFR, Part 10, USEPA) and USP, ASTM, ANSI, APHA, and AOAC testing services**.** They provide services to deformulate, and testing of most consumer products cosmetics. They conduct a deformulation by separations and chemical analysis to determine the ingredients and their levels.

Anderson Laboratories located in West Hartford, Vermont provided the independent inhalant challenge, **Exhibit 8,** which used the ASTM E 981 method to determine the respiratory effects of Angel.

Chapter I Subchapter G (Title 21 CFR- Food and Drug -Subpart A 740.1(a)
Sec. 740.1

> *"(a)"The label of a cosmetic product shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product."*

A preponderance of chemicals in Angel carry known health warnings; documented allergens, harmful ingredients, skin penetrators, irritants (skin, respiratory, eyes), skin sensitizers and reproductive effects, as referenced by the attached Material Safety Data Sheets (MSDS), **Exhibits 9 (a-p).**

The following warnings are associated with Angel's chemicals:

IRRITANTS:

Eyes:

Denatured alcohol, Benzophenone-2, Coumarin (Hazardous), d-Limonene, Linalool, Amyl Cinnamal, Geraniol, Citronellol, Benzyl Salicylate, Citral (Hazardous), Eugenol, Isoeugenol, Violet 2, Blue 1.

Respiratory:

Denatured Alcohol, Benzophenone-2, d-Limonene, Linalool, Amyl Cinnamal, Geraniol, Citronellol, Benzyl Salicylate, Citral (Lung irritant), Eugenol (Toxic to lungs), Isoeugenol, Violet 2 (Lung irritant), Blue 1

Skin:

Denatured Alcohol, Benzophenone-2, Buytlphenyl Methylpropional (Sensitizer with skin contact), Coumarin (Sensitizer with skin contact, and absorbed thru skin), d-Limonene (Sensitizer with skin contact, an allergic reaction which becomes evident upon reexposure. Prolonged repeated contact may cause defatting of the skin and dermis), Linalool (Sensitizer with skin contact), Amyl Cinnamal (Sensitizer with skin contact), Geraniol (Sensitizer with skin contact, hazardous with skin contact "permeator"), Citronellol (Sensitizer with skin contact, severe irritant), Benzyl Salicylate (Sensitizer with skin contact), Hexyl Cinnamal (Sensitizer with skin contact), Citral (Sensitizer with skin contact), Eugenol (Sensitizer with skin contact, slightly hazardous with skin contact "Permeator"), Isoeugenol, Violet 2, Blue 1

Mutagen:

Benzophenone-2, Coumarin, Linalool, Citral, Isoeugenol

Reproductive Effectors:

Butylphenyl Methylpropional, Coumarin, Citral,

Tumorigen:

Coumarin, Isoeugenol, Citral

Possible Carcinogenic:

d-Limonene, Eugenol,

NFPA Hazard Identification System Health Warning (Blue Diamond) Numbers, Exhibit 10:

Number 2: "Material that on intense or continued but not chronic exposure could cause temporary incapacitation or possible residual injury";

d-Limonene, Linalool, Amyl Cinnamal, Geraniol, Citronellol, Benzyl Salicylate, Hexyl Cinnamal, Citral, Isoeugenol, Violet 2, Blue 1

Number 3: "Material that on short exposure could cause serious temporary or residual injury;"

Butylphenyl methylpropional, Coumarin, Eugenol

Chapter I Subchapter G (Title 21 CFR- Food and Drug -Subpart B 740.10(a)

Sec. 740.10

"(a)Each ingredient used in a cosmetic product and each finished cosmetic product shall be adequately substantiated for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing is misbranded unless it contains the following conspicuous statement on the principal display panel:

"Warning--The safety of this product has not been determined.""

There are numerous ingredients in which the chemical, physical and toxicological properties and data have not been thoroughly investigated, determined or evaluated:

Denatured Alcohol, Benzophenone-2, Butylphenyl methylpropional, Coumarin, d-Limonene, Linalool, Amyl Cinnamal, Geraniol, Citronellol, Benzyl Salicylate, Hexyl Cinnamal, Citral, Eugenol, Isoeugenol, Blue 1

DISCLOSURE OF INGREDIENTS, DISCUSSION OF ANGEL'S ADVERSE REACTIONS AND WARNING ASSOCIATED WITH INGREDIENTS

Most consumers are under the misguided impression that cosmetics and fragrances are fully tested and therefore safe to use. Without the full disclosure of ingredients on the label, consumers are unable to determine if they could react to an ingredient that they know they are sensitive to. Failure to incorporate known warnings on the labels that a product has, for example, known skin sensitizers, skin penetrators, common fragrance allergens, that could exacerbate the consumers dermatological and medical problems. The generic reference of fragrance makes this non-disclosure problematic to those who have allergic predispositions.

Allergenisitc Nature:

The allergenistic properties of fragrance chemicals have been well documented and highly researched for years. A preponderance of the chemicals in Angel are known to be skin irritants and appropriate warnings have been excluded on their packaging. The exclusion of the chemical makeup of the generic reference to "fragrance (Parfum)" probably includes additional quantities of the known chemical irritants in addition to other known allergens. There is an increase in the reporting of contact dermatitis primarily from fragrance related products.

The most frequent allergens in allergic contact dermatitis; "In a study of 9948 patients to determine the frequency of sensitization to the top 10 most common contact allergens, fragrance mix came in second. They concluded:…after the healing of the skin…allergic contact dermatitis, it must be considered that the sensitization persists indefinitely. Therefore, patients have to be informed exactly about their relevant contact allergens to ensure complete avoidance"[1]

Patch testing with a new fragrance mix detects additional patients sensitive to perfumes and missed by the current fragrance mix. "There are numerous contact allergens that have been identified and utilized in patch testing for sensitization through fragrance mixes (FM). Initially in the 8% FM I, it did not identify all patients with a positive history of adverse reactions. The FM II incorporated 6 chemicals in a study of 1701 patients at 6 different dermatological centers in Europe. FM II used three different strengths of ….citral, coumarin, citronellol. Concluding the new FM II detects additional patients sensitive to

fragrances missed by FM I; the number of false-positive reactions is lower than FM II than with FM I." [2]

The frequency of fragrance allery in a patch-test population over a 17-year period. " We have reviewed our patch test data from 1980 to 1996 to establish whether the pattern of fragrance allergy has changed with time. …25,545 were patch tested. The frequency of allergic reactions to eugenol and gerinoil remained relatively constant. Isoeugenol..sensitivity increased." [3]

Sensitization to 26 Fragrances to be labeled according to current European regulations. Resultf of the IVDK and review of the literature. Out of the 26 ingredients studied, 9 of these are part of the chemical makeup of Angel; Benzyl Salicylate, Citral, Citronellol, Coumarin, Lilial, Eugenol, Geraniol, Isoeugenol, Limonene and Linalool." [4]

In March of 2005, the seventh amendment of the European Union (EU) Cosmetics Directive required that the 26 named fragrances must be identified when present in concentrations of > 10 parts per million in leave-on products.

Fragrance ingredient labeling in products on sale in the U.K. "The top six identified products were "linalool, limonene, citronellol, geraniol, butylphenyl methypropional and hexyl cinnamal" They concluded that "There is ongoing consumer exposure to the most frequent sensitizers in FM I…isoeugenol and the cinnamon fragrances cinnamal….Linalool and limonene, fragrance turpenes which are significant allergens in their oxidized state". [5]

Natural ingredients based cosmetics. Content of selected fragrance sensitizers; "Geraniol, eugenol, isoeugenol, citral and coumarin are considered natural ingredients. "compounds not yet regarded as natural substances, may be present in products claimed to be based on natural ingredients." [6]

Selected important fragrance sensitizers in perfumes-current exposures. "Isoeugenol is considered to be an important fragrance allergen in a hydroalcoholic product. Determining that there is still a wide-spread exposure to potent fragrance allergens in perfumes." [7]

Novel approach for classifying chemicals according to skin sensitizing potency by non-radioisotopic modification of the local lymph node assay. "The murine local lymph node assay (LLNA) is currently recognized as a stand-alone sensitization test for determining the sensitizing potential of chemicals, and

it has the advantage of yielding a quantitative endpoint that can be used to predict the sensitization potency of chemicals. …. Nine chemicals (i.e. …. cinnamicaldehyde, citral, eugenol,…) categorized as human contact allergen classes 1-5 were tested by the non-RI LLNA with the following reference allergens… isoeugenol as a class 2 human contact allergen. Sensitization potency data are useful for evaluating the sensitization risk to humans of exposure to new chemical products. …."[8]

Clinical forms of skin manifestations in allergy to perfume. "Perfumes are increasingly used in an ever wider variety of fields, including perfumes proper, cosmetic products, hygienic products, drugs, detergents and other household products, plastics, industrial greases, oils and solvents, foods, etc. Their composition is usually complex; it involves numerous natural and synthetic sweet-smelling constituents, more than 5,000 of which are known (13). Perfumes may produce toxic and, more often, allergic respiratory disorders (asthma), as well as neurological (10) and cutaneous disorders. They are the most common cause of skin allergy to cosmetic products (1, 11) and one of the most important causes of skin allergy to topical drugs or even to syrups which may reactivate contact dermatitis (24). People engaged in the manufacturing of these products may become sensitized to perfumes." [9]

Strong allergic patch test reactions may indicate a general disposition for contact allergy. "RESULTS: With an increasing strength of a positive reaction to nickel or to fragrance mix the likelihood of further positive reactions to unrelated contact allergens increased significantly, and the mean strength of such additional reactions raised steadily with an increasing strength of a nickel or fragrance reaction." [10]

Principles and methodology for identification of fragrance allergens in consumer products.
"Ingredients supplied by the manufacturer …Benzophenone-2.. were found to be responsible for the patients contact allergy to the commercial product. These substances contain chemical structural alerts giving them antigenic ability. The common use of new chemicals to manufacture fragrances, and the increased number of patients sensitive to them but with negative fragrance mix reactions, makes it necessary to identify new potential fragrance sensitizers in commercial products." [11]

<u>Coumarin:</u>

The following terms as defined by the United States Code are enforceable and applicable to the incorporation of Coumarin in this product. Incorporation of Coumarin which has an effect on the developing fetus renders this product to be reclassified as a drug and misbranded, as it is classified as a poisonous or deleterious substance.

Chapter IX Subchapter VIII (21`U.S.C. Subchapter VIII Section 381 (a)(3))
COUMARIN Violation Code:
Sec. 381

"(a)(3)The article appears to bear or contain Coumarin, a poisonous or deleterious substance, which may render it injurious to health."

In Vitro Dermal Absorption of Coumarin in Rat and Human Skin: **"**Coumarin is widely used as a fragrance in cosmetics, perfumes and soaps. Safety concerns have been raised by NTP toxicity testing. Therefore, we measured coumarin absorption and metabolism in skin. … These studies indicate that coumarin absorption is significant in skin. Systemic coumarin absorption must be expected after dermal contact with coumarin-containing products." [12]

Percutaneous absorption and metabolism of Coumarin in human and rat skin. "These studies indicate that coumarin absorption is significant in skin. Systemic coumarin absorption must be expected after dermal contact with coumarin-containing products." [13]

BfR Federal Institute for Risk Assessment: "it is common knowledge that relatively low doses can already cause liver damage in a small group of particularly sensitive individuals if the medicinal products are administered over a few weeks." **Exhibit 11.**

Target Organs and Levels of Evidence NTP Technical Report Number 422 " FM: CLEAR EVIDENCE Lung Alveolar/Bronchiolar Adenoma, Alveolar/Bronchiolar Carcinoma" **Exhibit 12.**

Behavioural outcome of school-age children after prenatal exposure to coumarins." Based on the results of both questionnaires, we conclude that behavioural development may be negatively influenced in school-age children after in utero exposure to coumarins, leading to less favourable task-oriented and social-emotional behaviour." [14]

Neurological outcome in school-age children after in utero exposure to coumarins. 'The results suggest that coumarins have an influence on the development of the brain which can lead to mild neurological dysfunctions in children of school age." [15]

Geraniol

Fragrance Compound Geraniol Forms Contact Allergens on Air Exposure. Identification and Quantification of Oxidation Products and Effect on Skin Sensitization. "Analogous to other monoterpenes studied, such as limonene and linalool, geraniol has the potential to autoxidize on air exposure and form highly allergenic compounds… The autoxidation of geraniol greatly influenced the sensitizing effect of geraniol. The oxidized samples had moderate sensitizing capacity, quite different from that of pure geraniol" [16]

Citral:

Citral is a fragrance allergen and irritant. "Citral is a well known contact allergen and a contact irritant." [17]

Linalool:

Contact allergens formed on air exposure of linalool, Identification and quantification of primary and secondary oxidation products and the effect on skin sensitization. "The air-exposed samples of linalool produced clearly positive responses, and the hydroperoxides were the strongest allergens of the tested oxidation products. The study demonstrated the importance of autoxidation on the sensitizing potential of linalool. We also conclude that the sensitizing potential differs with the composition of the oxidation mixture and thus with the air exposure time." [18]

Studies on the autoxidation and sensitizing capacity of the fragrance chemical linalool, identifying a linalool hydroperoxide. "The two monoterpenes linalool and d-limone are the most frequently incorporated fragrance chemicals in scented products. Previous studies on d-limonene show that this monoterpine oxidizes on air exposure (autoxidation) and that allergenic oxidation products are formed. Due to structural similarities, linalool might also form allergenic oxidation products on air exposure. The aim of the present study was to study the autoxidation of linalool and to investigate the sensitizing potential of linalool before and after air exposure…Linalool was oxidized for 10

weeks…It is concluded that autoxidation of linalool is essential for its sensitizing potential." [19]

Denatured Alcohol

Transdermal permeability of N-acetyl-D-glucosamine. "Negligible permeability was observed for NAG in neat solutions of known membrane permeation enhancers ethanol" [20]

Potential mechanisms by which a single drink of alcohol can increase transdermal absorption of topically applied chemicals. "Ethanol induced changes in lipid peroxidation and TEWL demonstrate that drinking alcohol induces transdermal absorption of xenobiotics." [21]

Can Alcohol-Based Hand-Rub Solutions Cause You To Lose Your Driver's License? Comparative Cutaneous Absorption of Various Alcohols. " ETOH may be absorbed during intensive use, either via transcutaneous absorption or inhalation of fumes in closed areas." [22]

Permeability of commercial solvents through living human skin. The following permeability rated (g/m[2]h) of single solvents were measured…ethanol 11.3" [23]

Isoeugenol

Isoeugenol is an important contact allergen; can it be safety replaced with isoeugenol acetate? "The prevalence of contact allergy to the fragrance mix in individuals with eczema is up to 10%. Within the mix, isoeugenol (CAS 97-54-1) is an important individual allergen." [24]

Synergistic Effects

Allergens in combination have a synergistic effect on the elicitation response: a study of fragrance-sensitized individuals. "It was found that the combination of two allergens in individuals allergic to both substances had a synergistic effect on the elicitation response evaluated by all three methods. The 1:1 mixtures of the two allergens elicited responses as if the doses were three to four times higher than those actually used, which is significantly more than expected if an additive effect had been present." [25]

There have been numerous complaints that fragrances tend to linger in the air, "Simulated exposure studies were conducted on 3 surrogate products consisting of 9 ingredients for their toxicity, volume of use, chemical structure, volatility", 4 of which are incorporated into Angel (Eugenol, Linalool, d-Limonene, Hexyl Cinnamal).

There data showed "behavior of different materials due to volatilities and responses to airflow in exposure chamber, similar to real life. D-Limonene long lasting: high concentrations at 5 ft distances demonstrates effect of air movement on a volatile, not seen with less volatile materials. The data shows die-away phase of each material suggesting that after several hours, measurable fragrance material is reduced by more than an order of magnitude, although concentrations of more volatile materials remained high."

There are so many complaints about the respiratory effects of fragrances: "Analysis shows small particle size increasing the likelihood of inhalation and the intended stimulation of the olfactory system. At 1.5 ft. ht the variation in the concentration of each material resulted from volatilization of particles they become lighter and remain suspended.

While airborne levels of the nine fragrances were reproducible, the physiological interpretation concentration is unknown at this time. One possible starting point for the biological significance of these results could be the ACGIH guidelines for Particulates Not Otherwise Classified of 10 mg/m^3 for inhalable particles and 3 mg/m^3 for respirable particles. These data provide an understanding of modeling for standard exposure conditions and show that any assessment of exposure from different fragranced product forms is influences by the product form. The information will be useful in the design of future clinical studies in normal and sensitive subpopulations to assess the potential effects of inhaled fragrance materials." **Exhibit 13.**

Evaluation of phototoxic properties of fragrances. Fragrances are widely used in topical formulations and can cause photoallergic or phototoxic reactions. Moderate UVA-induced haemolysis (5-11%) was found with … alpha-amyl cinnamic aldehyde ... Moderate UVB-induced haemolysis was induced by hydroxy citronellal, cinnamic alcohol, cinnamic aldehyde, alpha-amyl cinnamic aldehyde ... Assessment of the correlation of the clinical effects of these findings could lead to improved protection of the skin from noxious compounds.[26]

CONCLUSION:

The NTEF requests that the Commissioner of the FDA exercise his authority predicated on this petitioners request and publish for comment:

Chapter I Subchapter G (Title 21 CFR- Food and Drug -Subpart A 740.1(b)
Sec. 740.1

> *"(b) The Commissioner of Food and Drugs, either on his own initiative or behalf of any interested person who has submitted a petition, may publish a proposal to establish or amend, under subpart B of this part, a regulation prescribing a warning for a cosmetic. Any such petition shall include an adequate factual basis to support the petition, shall be in the form set forth in part 10 of this chapter, and will be published for comment if it contains reasonable grounds for the proposed regulation.*"

Angel needs to be declared misbranded as it does not comply with any of the labeling requirements, it's importation into the country because of the non-compliance regarding labeling and the incorporation of a drug into it's finished products warrants the immediate reclassification of this product.

Fragrances are volatile organic compounds which are easily disbursed into the ambient air readily inhaled affecting the lungs and thru dermal contact of the molecules from casual contact. The lingering effects have been demonstrated with the industry's mannequins confirming the long lasting effects of certain fragrance ingredients along with the physiological interpretations for concentrations are unknown. The Research Institute for Fragrance Materials, **Exhibit 13,** clearly stated that they needed to design studies to assess the potential effects of inhaled fragrance materials.

There has been no provided studies by Clarins for the normal and subpopulation regarding their effects from their finished product, Angel.

Ethanol is a skin penetrator in conjunction with geraniol and eugenol which are also skin permeators. Angel is an ethanol based product into which Coumarin is dissolved and studies have confirmed it's ability to be absorbed and introduced into the vascular system. People who are on anti-coagulants could have their blood levels becoming influenced by the application of this product. Coumarin is a known precursor to the drug Warfin.

Most women use more than one fragranced product and the multi-application of Angel containing products will increase the absorption of the Coumarin by the consumer.

The introduction of Coumarin into the body has proven to affect the developing fetus. Coumarin's effect upon the brain that leads to mild neurological dysfunctions, behavioral favorable task-oriented and social-emotional behavior, along with being an anticoagulant precursor clearly demonstrates that Angel is a drug.

Chapter IX Subchapter II (21`U.S.C. Subchapter II Section 321(g)(1)(B)(C))

Sec. 321

"*(g)(1) The term ``drug'' means (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals"*

There exists an inherent risk of an imminent health hazard to both the developing fetus and those on anticoagulant drugs predicated on the aforementioned studies and disclosure of ingredients by Clarins. Under:

Chapter I Subchapter A (Title 21 CFR –Food and Drug –Subpart A Section 2.5 (a)(1)(2))

Sec. 2.5

"(a) Within the meaning of the Federal Food, Drug, and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists."

A preponderance of the ingredients in Angel are known skin sensitizers, respiratory and eye irritants in addition almost all of the ingredients toxicological

properties have not been fully evaluated. Their incorporation of known allergens which have a synergistic effect have not been fully studied.

The autoxidation of linalool and d-limonene are more potential than the pure forms of these chemicals.

The current research reveals phototoxic effects in almost half of the chemicals evaluated. Given the concern over the changes in our environment, this may also be something that should be taken into consideration when the FDA evaluates the safety of this fragrance and it's labeling requirements if allowed to return to the US marketplace shelves.

It appears from the confirmatory test results from Clarins own laboratory that Angel presents a clear and present danger to the viability of the ocular cells. These are legitimate concerns over the safety of the product that warrant stringent warnings on the packaging.

The intentional omission referencing the inherent danger to the eyes is to be construed as both active concealment (concealment by words or acts of something that one has a duty to reveal) or fraudulent concealment (affirmative suppression or hiding, with the intent to deceive or defraud, of a material fact or circumstance that is legally bound to reveal). This could also be in conjunction with affirmative misconduct (an affirmative act of misrepresentation of a material fact).

Petitioner respectfully requests that the perfume "Angel" be declared misbranded for the aforementioned violations along with restricting the importation for overt omissions of the required labeling as referenced above.

CERTIFICATION:

The undersigned certifies, that, to the best of their knowledge and the belief of the undersigned, this petition includes all information and views on which the petition

///
///
///
///
///
///
///

relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Thank you.

Respectfully submitted by:

The National Toxic Encephalopathy Foundation

_____	_____
Angel De Fazio, B.S.A.T.	Jack D. Thrasher, PhD.
President	Technical Consultant

_____
Nina B. Immers, MBA (Former RN in CA and TX)
Medical Research Consultant

Enc: Petition

Cc: Representative Shelley Berkley (D-NV)
Senator John Ensign (R-NV)
Senator Harry Reid (D-NV)
Representative Jon Porter (R-NV)