I am writing to provide comments to the California Office of Environmental Health Hazard Assessment ("OEHHA") regarding its April 23, 2015 Notice of Intent to List Chemicals By The Labor Code Mechanism: Aloe Vera, Whole Leaf Extract And Goldenseal Root Powder (the "Notice"). I am President of Steinberg & Associates, Inc., an independent consultant company dealing principally with the regulations of cosmetics and topical drugs. Among my many industry positions, I served as National President of the Society of Cosmetic Chemists and for over 18 years I wrote a regular column on cosmetic regulations for *Cosmetics & Toiletries* magazine. My CV is attached.

The Notice states that the intent to list Aloe vera is based on IARC's classification of Aloe vera, whole leaf extract, in Group 2B (the agent is "possibly carcinogenic to humans") and that there is "sufficient evidence of carcinogenicity in experimental animals" for Aloe vera, citing Grosse *et al.*, 2013 (the "Grosse Report").

The Grosse Report, published at www.thelancet.com/oncology, Vol. 14 August 2013, covered many chemicals, but only said this about Aloe vera:

> "From *Aloe vera* leaves, four products are processed: the whole leaf and decolourised whole leaf extracts, gel, and dried latex. Decolourisation by activated carbon removes the toxic anthraquinones from the latex in the whole leaf extract. Exposure data do not identify the type of product used by the many consumers. In a 2-year study in rats, drinking-water containing whole leaf extract induced, in both sexes, increased incidences of adenoma and carcinoma of the large intestine—tumours that occur rarely in rats.[11] The anthrone C-glycosides aloin A and aloin B, found in the latex, are converted to aloe-emodin-9-anthrone by bacteria present in the gastrointestinal tract of rats and humans, and sequentially oxidised to aloe-emodin, which is genotoxic and could be responsible for the reported tumours."

All of this information is based on footnote 11: National Toxicology Program. Toxicology and carcinogenesis studies of a nondecolorized whole leaf extract of aloe barbadensis miller (aloe vera) in F344/N rats and B6C3F$_1$ mice (drinking water studies). 2013 http://ntp.niehs.nih.gov/Ntp/About_Ntp/Trpanel/2011/April/DraftTR577.Pdf; 2013 (accessed July 2, 2013) (the "NTP Report").

This is the Abstract of the NTP Report:

> "*Aloe* barbadensis Miller, Aloe vera, has enjoyed a long history of lay acceptance as an herbal remedy and is perhaps the most popular herbal remedy in use today. In recent times, the oral consumption of Aloe vera has been promoted as a prophylaxis and treatment to alleviate a variety of unrelated systemic conditions. The National Cancer Institute nominated Aloe vera for study under the National Toxicology Program, because of its widespread human exposure and because components in Aloe vera may possess tumor-promoting activities. Male and female F344/N rats and B6C3F$_1$ mice were

exposed to freeze dried (max. 6% moisture) and gamma-irradiated extracts of Aloe vera plant leaves in drinking water for 14 days, 13 weeks, or 2 years."

Materials per NTP, pages 50-51.

"The Aloe vera leaf extracts used in these studies were from *Aloe barbadensis* Miller plants that were cultivated in Harlingen, Texas. Leaf weights were a minimum of 400 grams at harvest, and the time from harvest to lyophilization was a maximum of 6 h. The lyophilized (max. 6% moisture content) Aloe vera leaf extracts used in the 14-day, 13-week, and 2-year studies were obtained from Pangea Phytoceuticals, Inc. (Harlingen, TX). For the 14-day studies, extracts included *Aloe barbadensis* Miller Process A gel (Aloe vera gel), *Aloe barbadensis* Miller non-decolorized whole leaf (Aloe vera whole leaf), and *Aloe barbadensis* Miller decolorized whole leaf (Aloe vera decolorized whole leaf) extracts. The 13-week and 2-year studies used only the *Aloe barbadensis* Miller nondecolorized whole leaf (Aloe vera whole leaf) extract.

The Aloe vera gel extract used in the study consisted of the inner leaf gel of hand-filleted Aloe vera leaves with the pulp removed. No further treatments were performed on this material prior to lyophilization.

The Aloe vera nondecolorized whole leaf extract was produced by grinding the whole leaves of Aloe vera plants and treating the slurry with cellulase (23 mg/L) to reduce viscosity and maximize yields. The Aloe vera nondecolorized whole leaf extract (referred to as Aloe vera whole leaf extract in this technical report) contained the Aloe vera inner leaf gel and the Aloe vera latex, including the anthraquinones. Some Aloe vera latex anthraquinones are potent cathartic agents and induce laxation.

The Aloe vera decolorized whole leaf extract was produced in an identical manner as the Aloe vera whole leaf extract, with the exception that the slurry was further treated with activated carbon (1.0% wt/wt). Treatment of the whole leaf extract with activated charcoal removes the Aloe vera latex anthraquinone components from the extract.

The Notice seeks to list the following:

"Identity of chemicals: *Aloe vera*, also known as *Aloe barbadensis* Miller, is one of approximately 420 species of Aloe plants. Other common names of *Aloe vera* are Barbados aloe, Mediterranean aloe, True aloe, and Curaçao aloe. Whole leaf extract of *Aloe vera* is commonly referred to as whole leaf *Aloe vera* juice or Aloe juice. Whole leaf extract of *Aloe vera* is the liquid portion of the *Aloe vera* leaf (e.g., what remains after removal of fibrous material, such as lignified plant fibers), and is a natural constituent of the *Aloe barbadensis* Miller plant. *Aloe vera* whole leaf extract is not the same as *Aloe vera* decolorized whole leaf extract, *Aloe*

vera gel, *Aloe vera* gel extract, or *Aloe vera* latex, which would not be covered by this proposed listing." (OEHHA website.)

It is very clear from the NTP Report that the Aloe vera that OEHHA has nominated for Prop 65 is not what was tested and reported in the NTP Report.

As the chemicals listed in the Notice can be confusing, to simplify the subject, I will define the 4 different chemicals listed by simple letters:

A: This chemical refers to the whole leaf from the plant that is ground up and then chemically altered by the addition of cellulase. But the Notice does not indicate which type of the many major cellulase enzymes in commercial use was used in the process, the reaction time, end-points used, results tested for, etc. Without this information there is no way to reproduce or replicate their process.

B: This chemical is produced if product A is treated with activated carbon (although the length of the treatment is not disclosed).

C: This chemical refers to the inner gel which is obtained after removing the outer skin.

D: This chemical is the yellowish latex which is found between the gel and the skin.

There are major flaws in the NTP Report which cut against OEHHA's reliance on the Report to support the listing of any of these four chemicals on Prop 65.

First, *Aloe barbadensis* Miller is found in commercial production in many parts of Texas, Arizona, California, Florida, and all over the world where there is warm climate. The NTP Report used material only from Harlingen, Texas, and there was no attempt made to determine if the plant/leaves grown and obtained in that specific location in Texas have the same characteristics as plants/leaves found in other locations in Texas, let alone other regions of the world, whether the composition of the material used is the same for materials found elsewhere, and/or whether the results would be the same for plants/leaves sourced from different locations.

Aloe is clearly extremely complex and the A, B, C, and D chemicals described above all have significantly different compositions. The composition of the starting material varies depending on where it is grown (a fact totally ignored in the NTP Report), the age of the plant (plants usually don't reach maturity for 4 years and have a life span of 12 years), how much water was given to the plant during growing, how the plant was held from the cutting to freeze drying (Aloe is very unstable after it is cut from the plant, with degradation starting almost immediately), whether the plants where grown alone or with trees, as sunlight affects the composition, and temperature changes, especially possible freezing temperatures. The NTP Report concedes that composition varies (see pages 18, 24, 25, 128, and 248), but failed to test for those variations or perform feeding studies of the same plant grown elsewhere and under all the different growing conditions cited.

A second major flaw with the NTP Report is the way in which it treated the Aloe vera plants/leaves. The material used was from leaves weighing at least 400 g, which then underwent lyophilization for up to 6 hours. Lyophilization, or freeze drying, is a technique used to remove water. However, it also removes water soluble chemicals when the frozen water is sublimed. They tested the reconstituted material for malic acid, aloin A and anthraquinones. Malic acid, however, is not found in Aloe, rather *esters* of malic acid have been found. Anthraquinones are a class of naturally occurring phenolic compounds based on the 9,10-anthraquinone skeleton with different safety issues. Nor does the NTP Report account for the fact that treatment of the starting material with cellulase produces a totally different composition than the starting material. Thus, it is far from clear that the Aloe vera tested for the NTP Report is the same as the chemicals listed in the Notice, and there is no assurance that the testing of other Aloe vera plants/leaves would yield the same results.

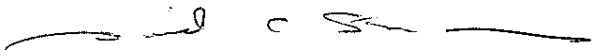
Another problem with relying on the NTP Report as support for listing Aloe vera is that the Aloe leaf is 99+% water (NTP Report, page 17). Only by freeze drying and then adding water to the resulting powder, can you create the 1%, 1.5%, 2%, and 3 % solutions used in the drinking water fed to the mice and rats used in the studies. This concentration of solids does not occur in the actual chemical which OEHHA is considering adding to Prop 65, which is Aloe vera, whole leaf extract, without regard to whether it is freeze dried or otherwise treated. It is also important to note that the "clear evidence of carcinogenic activity" (NTP Report, page 14) is only based on the 2% and 3% concentration studies conducted for 2 years in rats; similar studies in mice did not show this finding.

Another important limitation of the NTP Report is the fact that the studies were based on the ingestiom of freeze dried solutions; neither the tests nor the Report address the topical application of Aloe vera. Thus, there is no basis upon which to conclude that the topical application of Aloe vera, through the use of cosmetics or skin care products, would produce the same results or pose the same risks, if any.

There are many major peer reviewed publications that show what has been found in Aloe barbadensis plants. These include: Molecules 2008, 13 1599-1616 (from South Africa); Int. J of Chemical & Biochemical Sciences, 3 (2013) 29-33 (from Pakistan); and the Int. J, Biol Medical Res. 2011, 2 (1) 466-71 (Iran and Turkey). The fact that the plants are all different chemically raises the question as to whether the lumping of all Aloe barbensis Miller, regardless of location and the lack of any studies indicating possible carcinogenic activity, can be justified by OEHHA.

In conclusion, the studies relied upon by OEHHA via IARC via Lancet via NTP are seriously flawed and do not support the listing of Aloe vera on Prop 65. If OEHHA nonetheless decides to list Aloe vera, then the listing should be restricted to the Aloe vera plant/leaf used in studies upon which OEHHA relies, specifically "the whole leaf of the *Aloe Barbedenis* Miller leaf, weighing a minimum of 400 g and obtained from Harlingen, Texas." The listing should also indicate that the Aloe vera plant/leaves must be treated by the addition of cellulase, freeze dried, and then reconstituted to a minimum concentration of 2%. The only exposure that would trigger Prop 65 would be from drinking Aloe vera and any topical application is exempt from Prop 65

requirements. Any other listing would exceed the scope of the extremely limited studies upon which OEHHA relies and cannot be supported. OEHHA should also insist that the OAG strictly enforce this limited listing and sanction any entity that seeks to impose Prop 65 requirements, including by issuing a Prop 65 Notice, on any product that does not meet this precise definition.



David C. Steinberg, FRAPS

Curriculum Vitae

David C. Steinberg

Education:

BS Chemistry, Drexel University, 1965
MBA Management, Pace University, 1969

Occupation:

1995 Founded Steinberg & Associates, Inc.
A consulting firm for the Cosmetic industry-
Specializing in the Chemistry of Cosmetic Ingredients, Preservatives and preservation, International and US regulations, domestic and international labeling of cosmetics and cosmetic drugs; and marketing of ingredients. Expert witness in patent, business issues and injury cases dealing in the personal care area.

In 2006, founded the Cosmetic Preservative Council and is the Executive Director

In 2008, founded Report Reaction. LLC to assist clients in complying with new FDA OTC labeling requirements

Academia:

Fairleigh Dickinson University
Founder, Master's Degree Program in Cosmetic Sciences
Adjunct Assistant Professor of Chemistry, 1982 to 2000
Graduate School of Chemistry
"Skin Care Raw Materials"
"Hair Care Raw Materials"
"Chemistry of Cosmetic Raw Materials"

Center For Professional Advancement
" Cosmetic Preservation"
" Cosmetic Product Stability"
" Critical Components of Skin Products"
" Drug versus Cosmetic Regulations"
" Sunscreens" (Director)
" Labeling Over-The Counter Drugs" (Director)
" Ingredients For Cosmetics " (Director)

Society of Cosmetic Chemist, Continuing Education Program,
"Cosmetic Raw Materials"
"Preservatives for Cosmetics"
"International Cosmetic Regulations"
"The New Cosmetic Regulations of the European Union"

Center for Professional Innovation and Education
"Pharmaceutical Skin Product Development"
"Cosmetic Skin Product Development"

Memberships:

American Chemical Society
Regulatory Affairs Professionals Society
Society of Cosmetic Scientists
Society of Cosmetic Chemists
Offices: New York Chapter Chair, 1979
National Treasurer, 1987-8
National President, 1991

Praesidium: International Federation of Societies of Cosmetic Chemists, Honorary Auditor, 1992-5
Scientific Committee, 1995-7

Honors:

Society of Cosmetic Chemists, Merit Award, 1985
Society of Cosmetic Chemists, Fellow, 1987
Eminent Visiting Scholar, Virginia State University, 1987
Paper of the Year, 1988, Australian Society of Cosmetic Chemists
IFSCC Sponsored Speaker, Brazil 1996, 2000
IFSCC Sponsored Speaker, Croatia, 2010
IFSCC Sponsored Speaker, Columbia, Chile, 2011
California Chapter Paper of the year 2006, 2014
Regulatory Affairs Professionals Society, Fellow, 2009

Miscellaneous:

Columnist on International Cosmetic Regulations, *Cosmetics & Toiletries Magazine,* 1995 to 2013

Analyst, *Kosmet* Data Base 1995-97

Advisory Board, *Cosmetics & Toiletries Magazine* 1995 to present

Board of Directors, J. W. Hanson Company, Inc. 1998

Board of Directors, ICMAD, 1999 to present

Board of Directors, Zenitech, 2003-10

Strategic Planning Advisory Board, Renaissance Pharmaceutical Company 1995-7

Editorial Committee *Journal of Cosmetic Science,* 1998, 2008-10

Editorial Board *Journal of Applied Cosmetology,* 1998

Chairman, Preservatech Conference, 1998, Paris, France

Chairman, Preservatech Conference, 1999 Chicago, IL

Books:

Preservatives For Cosmetics, Allured Publishing, 1996; Second Edition 2005, Third Edition 2012

A Guide to European Cosmetic Regulations, ICMAD, 1997; Second Edition 2007, Third Edition 2012

Primary Ingredients, Hansotech Publication, 1998

FDA OTC Label Requirements Guidelines, Hirschhorn & Young, 2000

Oils of Nature, Allured Publishing, 2008

Chapters:

Advanced Technology Conference 1996, Cosmetics & Toiletries, Chapter on Cosmeceuticals: An American Perspective

Transdermal and Topical Drug Delivery Systems, Co-Author of Chapter: Topical Protective and Cosmetic Products, Interpharm Press, 1997

Sun Products, Co-Author of Chapter: Encyclopedia of UV Absorbers for Sunscreen Products , Allured Publishing, 1998

Sunscreen Regulations: US, Europe, Australia and Japan, Co-Author of Chapter: Cosmetic Regulations in a Competitive Environment, Marcel Dekker, 2000

Antiperspirants and Deodorants, Author of Chapter: Regulations of Underarm Antiperspirants and Deodorants, Marcel Dekker, 1999

Formulation Science Volume I, Author of Chapter: Personal Care Product Stability, Association of Formulating Chemists, 1998

The Chemistry and Manufacture of Cosmetics, Author of Chapter: Cosmetic Microbiology and Preservation, Allured Publishing Corp., 2000

Fundamentals of EU Regulatory Affairs, Author of Chapter: Cosmetics, RAPS, 2002; 2004, 2006, 2008

Regulations of Sunscreens worldwide, Author of Chapter, Sunscreens Regulations and Commercial Development 3rd Edition, Taylor & Francis, 2005

Cosmetic Microbiology, 2nd Edition, Author of Chapter, Global Regulation of Preservatives and Cosmetic Preservatives. Taylor & Francis Group, 2006

Cosmetic and Drug Microbiology, Author of Chapter, Global Preservative Systems, Informa Healthcare, 2006

Regulatory Accomplishments:

Testified before the FDA (at their request) on Sunscreen Regulations, and Regulations of Over-The-Counter Drugs.

Authored the change in US regulations of OTC Drugs on the acceptance of foreign data for US approvals.

Submitted and had approval from the European Union on moving three prohibited ingredients in cosmetics, to being allowed under restricted conditions. This was the first time in the history of the EU cosmetic regulations that this was achieved (2001-2).

Submitted information to allow the use of three ingredients prohibited in Canada to now be allowed for their intended purpose. 2004

Submitted and had approval from the European Union on allowing a Category 3 carcinogen, to be used in cosmetics, 2008. Submitted and achieved the same result in 2014.