BEFORE

THE STATE OF CALIFORNIA

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY (Cal/EPA)

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT (OEHHA)

COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON

OEHHA's APRIL 23, 2015 NOTICE OF INTENT TO LIST ALOE VERA, WHOLE LEAF EXTRACT AND GOLDENSEAL ROOT POWDER

June 9, 2015

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1.0 Background

California's Office of Environmental Health Hazard Assessment (OEHHA) on April 23, 2015 issued a Notice of Intent to List two herbal ingredients, Aloe vera, whole leaf extract, and goldenseal root powder, as known to the state of California to cause cancer under the state's Safe Drinking Water and Toxic Enforcement Act of 1985 (Proposition 65). The notice states these actions are being proposed pursuant to the so-called "Labor Code" listing mechanism, and that OEHHA has determined that these chemicals meet the criteria for listing by this mechanism.

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry. AHPA is comprised of domestic and foreign companies doing business as growers, processors, manufacturers and marketers of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs. Many AHPA members do business in California and thus are subject to Proposition 65, and these comments are submitted on their behalf.

OEHHA states in its April 23, 2015 notice that it is providing this opportunity to comment as to whether the chemicals identified above meet the requirements for listing as causing cancer specified in Health and Safety Code section 25249.8(a) and Labor Code section 6382(b)(1). OEHHA further asserts that these are "ministerial listings" and as such states that all comments should be limited to whether the International Agency for Research on Cancer (IARC) has identified the specific chemical or substance as a known or potential human or animal carcinogen. In the April 23, 2015 notice OEHHA also asserts that it "cannot consider scientific arguments concerning the weight or quality of the evidence considered by IARC when it identified these chemicals and will not respond to such comments if they are submitted."

AHPA cannot accept this limitation on the content of its comments and believes it is unlawful for OEHHA to ignore such comments. OEHHA's implementation of the so-called Labor Code listing mechanism grants enormous authority -- rulemaking authority -- to an entity that is not under the control of any California state entity and that can make decisions without any due process safeguards, in violation of the United States and California Constitutions as well as well-established principles of government and public policy. Specifically, with respect to the proposed listing of goldenseal root powder, OEHHA's policy will cause the agency to overlook errors in IARC's process and flaws in the faulty document that served as the primary scientific basis for IARC's review of animal carcinogenicity, which was the main factor in its classification decision. As

discussed below, OEHHA can only implement Proposition 65 consistent with law and with sound public policy by reviewing these errors and reconsidering the proposed listing of goldenseal root powder.

2.0 Comments on *Aloe vera*, whole leaf extract

2.1 Comments of the IASC

AHPA is aware that the International Aloe Science Council (IASC) has filed comments in the matter of OEHHA's April 23, 2015 notice of intent to list "Aloe vera, whole leaf extract" as known to the state to cause cancer under Proposition 65.

AHPA joins these IASC comments in their entirety, incorporates the IASC comments by reference in the present comments, and calls particular attention to the following requests contained therein:

- That the aloe vera material be identified as "*Aloe vera*, non-decolorized whole leaf extract."
- That OEHHA clarify in the listing that the only relevant route of exposure is the oral route.
- That the listing specifically identify as excluded from the listing the same aloe vera-derived ingredients that are identified in the April 23, 2015 notice as excluded from this proposed listing, so that the listing does not cover *Aloe vera* decolorized whole leaf extract, *Aloe vera* decolorized leaf juice; *Aloe vera* gel; *Aloe vera* gel extract, or *Aloe vera* latex.

2.2 Use of the name *Aloe barbadensis* Miller

OEHHA states in the April 23, 2015 notice that *Aloe vera* "is also known as *Aloe barbadensis* Miller" and that whole leaf extract of *Aloe vera* "is a natural constituent of the *Aloe barbadensis* Miller plant."

It is literally accurate that *Aloe vera* "is also known as *Aloe barbadensis* Miller," but the latter name is currently considered by all authoritative botanical references to be a "synonym" for this plant, for which the currently "accepted" name is *Aloe vera* (L.) Burm. f.[1] Under the rules of botanical nomenclature, a synonym is not interchangeable with an accepted name, and although use of a synonym may not be strictly considered

[1] See for example The Plant List, a collaboration between the Royal Botanic Gardens, Kew and Missouri Botanical Garden (http://www.theplantlist.org/tpl1.1/record/kew-298116); and the GRIN database, maintained by the U.S. Department of Agriculture, Agricultural Research Service (http://www.ars-grin.gov/cgi-bin/npgs/html/taxon.pl?2518); both accessed June 7, 2015.

to be an error, only use of accepted taxonomic names can ensure that any potential confusion is minimized.

It is unclear how OEHHA came to call this plant by its synonymous name and not its accepted name. The April 23, 2015 notice takes the position that certain substances identified by the International Agency for Research on Cancer (IARC) are required to be listed as known to the state of California to cause cancer, and the notice provides two references to IARC's 2013 review of a nondecolorized whole leaf extract of *Aloe vera*. But the first such cited reference (IARC, 2015) identifies only "*Aloe vera*, whole leaf extract" and the other (Grosse *et al.*, 2013) includes the synonym only in citing a prior publication that used the synonym rather than the accepted name.

AHPA therefore requests that OEHHA clarify that *Aloe vera*, nondecolorized whole leaf extract "is a natural constituent of the *Aloe vera* (L.) Burm. f. plant."

3.0 Comments on goldenseal root powder

3.1 IARC failed to consider all relevant research

As part of its process to prepare for its meetings, IARC issues a call for data that may be relevant to the substances that will be the subject of an upcoming meeting. Thus, in advance of the June 2013 IARC meeting at which goldenseal root powder (*Hydrastis canadensis*) was considered, IARC issued such communication and expressed interest in locating studies that are relevant to the carcinogenicity of the agents that would be reviewed.

In response to this request, AHPA communicated to IARC to identify scientific articles published in scientific journals,[2] as follows:

- Dunnick JK *et al.* 2011. Investigating the potential for toxicity from long-term use of the herbal products, goldenseal and milk thistle. *Toxicol Pathology* 39:398-409.
- Karmaker SR, SJ Biswas, and AR Khuda-Bukhsh. 2010. Anti-carcinogenic potentials of a plant extract *(Hydrastis canadensis)*: I. Evidence from in vivo studies in mice *(Mus musculus)*. *Asian Pac J Cancer Prevent* 11:545-551.

[2] AHPA also identified a publicly available doctoral thesis for review: Garrett SM. 2009. Anticancer properties of research-grade *Hydrastis canadensis* (goldenseal) and characterization of its effect on the *mdr1*-encoded phosphoglycoprotein efflux pump. In describing its criteria for identifying research for review IARC states it will "exceptionally" consider "doctoral theses and other material that are in their final form and publicly available…." IARC Monographs Vol. 108 at p. 10, 2015.

The first of the two above-identified articles (Dunnick *et al.* 2011) summarizes two separate research projects sponsored by NTP, including one on goldenseal root powder that reported as its primary finding "an increase in liver tumors in rats and mice." AHPA's communication to IARC also noted that an unpublished document, a Technical Report issued by NTP itself in April 2010, titled "NTP Technical Report on the toxicology and carcinogenesis studies of goldenseal root powder (*Hydrastis canadensis*) in F344/N rats and B6C3F1 mice (feed studies)" (NTP TR 562) could also be of interest at the June 2013 IARC meeting; this report concludes that under the conditions of two-year feeding studies and based on increased incidences of hepatocellular adenomas (and adenomas and carcinomas combined in the case of male rats) there was "clear evidence of carcinogenic activity" in male and female rats and "some evidence of carcinogenic activity" in male mice.

The latter article (Karmaker *et al.* 2010), published in a peer-reviewed scientific journal, records research conducted on a crude ethanolic extract of goldenseal root in which inbred strain of Swiss albino mice (*Mus musculus*) were fed for up to 4 months either a low-protein diet (the control); the same diet along with two hepatocarcinogens, p-DAB (p-dimethylaminoazobenzene) and phenobarbitol; or the same diet mixed with the hepatocarcinogens at the same daily dose plus the goldenseal extract. This research found "clear evidences of the Hydrastis [i.e., goldenseal] extract providing protective action to different sub-cellular organelles like mitochrondria, golgibodies, endoplasmic reticulum etc." It also reported that feeding of the goldenseal extract "resulted in less number of mice showing liver tumors, or slower tumor growth in mice that showed tumors … [and there was] less damage in the liver tissue of the [goldenseal] fed mice or better recovery."

The references listed in the IARC monograph on goldenseal[3] do not include either of the above listed scientific articles (i.e., neither Dunnick *et al.* 2011 nor Karmaker *et al.* 2010) that were published in peer-reviewed journals, although the NTP Technical Report (NTP TR 562) is included in this reference. It is obvious in reading the IARC monograph on goldenseal that the only reference considered in developing the monograph's section 5.3 on animal carcinogenicity data was the NTP TR 562. All of the information in that section is drawn directly from only the studies addressed in that report, which drew conclusions of hepatocellular harm (increased hepatocellular adenomas and carcinomas). But IARC had been provided by AHPA with another published study which

[3] IARC Monograph Vol. 108 – Goldenseal. 2015.

indicated exactly the opposite conclusion and provided evidence of protection against hepatocellular cancer.

IARC describes its policy in selecting literature for review in its monograph development, stating, "Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals [though] those judged inadequate or irrelevant to the evaluation may be cited but not summarized." IARC also states that in considering relevant data "only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. … Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed."[4]

When OEHHA references any finding in an IARC monograph it must assume that IARC considered all relevant data in drawing the conclusions presented in each monograph. It is obvious, however, that although IARC considered the data in NTP TR 562, and by extension the data in the related Dunnick article, it completely ignored the exact opposite conclusions draw in the Karmaker article (as well as the data on goldenseal's anti-cancer properties reported in the Garrett doctoral thesis referenced in footnote 2 of these comments, which could have been "exceptionally" included).

OEHHA should therefore consider the IARC monograph to be inadequate to support its own findings, and certainly inadequate to support listing of goldenseal root powder as "known to the state of California to cause cancer."

3.2 A single carcinoma in a single test animal should not result in a Proposition 65 listing

The 2-year goldenseal root powder feeding study conducted by NTP identified just one carcinoma in just one F344/N male rat, and this occurred only at the highest dosage of goldenseal, 25,000 ppm (i.e., 2.5 percent; between 1,194 and 1,939 mg/kg bodyweight at different life stages) fed daily over essentially the test animal's entire lifetime. This level would equate to between about 72,000 and 116,000 milligrams per day for a 60 kilo human, while the standard dose of goldenseal is 2 grams daily and the herb is used only sporadically.

The historical background rate of hepatocellular carcinomas in male F344/N rats reported in the literature range from 0-2% and averages 0-0.3%[5] (Tennekes *et al*., 2004;

[4] IARC Monograph Vol. 108 – Preamble at pp. 9-10, 2015.
[5] Tennekes, H; Gembardt, C; Dammann, M; van Ravenzwaay, B. 2004. The stability of historical control data for common neoplasms in laboratory rats: Adrenal gland (medulla), mammary gland,

Chandra and Frith, 1992). Thus the single hepatocellular carcinoma found in male rats in the NTP goldenseal study , which was 2% (1 out of 50 animals), was within the range of historical background rates.

Yet NTP drew its conclusion of "clear evidence of carcinogenic activity" in male F344/N rats under the conditions of its study "based on the increased incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined)." This single carcinoma, within the historical range, should not have been considered in NTP's analysis. Because it is impossible to consider how NTP's conclusion may have changed had this background norm been acknowledged, its conclusion for male rats should be subjected to further review.

3.3 Other flaws in conclusions drawn from the NTP 2-year feeding studies

NTP TR 562 concludes that under the conditions of two-year feeding studies and based on increased incidences of hepatocellular adenomas (and adenomas and carcinomas combined in the case of male rats) there was "clear evidence of carcinogenic activity" in male and female rats and "some evidence of carcinogenic activity" in male mice.

These classifications, however, are not appropriate, because the one significant increase in carcinomas observed in the entire study (one hepatocellular carcinoma at the high dose in a male rat), is within historic control incidence. In addition, while increased incidences of hepatocellular adenomas were observed in both sexes of rats and in male mice, the adenomas were not associated with carcinomas. Elevation of adenomas without an associated increase in carcinomas, as compared to mere tumorigenicity, is much weaker evidence of carcinogenicity. For goldenseal, there are no excess hepatocellular carcinomas in mice, despite excess adenomas, casting doubt on the general presumption that the liver adenomas observed can progress to carcinomas. Thus the classifications of carcinogenic activity (based on liver neoplasms), are made without any compelling elevation in liver carcinomas.

3.4 NTP's 2-year study on goldenseal also identified protective outcomes

The 2-year feeding studies conducted by NTP as reported in NTP TR 562 also reported certain protective outcomes in the test animals under the conditions of this study and found decreased incidences of many endpoints other than liver effects. For example, incidence rates of pancreatic islets adenoma, pancreatic islets adenoma or carcinoma,

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liver, endocrine pancreas, and pituitary gland. *Regul Toxicol Pharmacol.* 40(1):18-27; also Chandra, M; Frith, CF. 1992. Spontaneous neoplasms in aged control Fischer 344 rats. *Cancer Lett.* 62:49-56.

thyroid gland adenoma, and thyroid gland adenoma or carcinoma decreased in male rats exposed to goldenseal at all doses. Additionally, incidence rates of a number of neoplasms were decreased at all doses in female rats exposed to goldenseal (e.g., mononuclear cell leukemia, clitoral gland carcinoma, all categories of mammary gland tumors, thyroid gland adenoma, and benign and/or malignant neoplasms in all organs). Some endpoints had a significant decrease at all doses and a significant negative trend, as well (e.g., mammary gland fibroadenoma; mammary gland fibroadenoma, adenoma, or carcinoma). Male mice had decreased incidences of Harderian gland adenoma and carcinoma, and alveolar/bronchiolar carcinoma. Although there were some increased incidences of neoplastic events in the rat liver, there were many cases of decreased neoplastic effects, including carcinogenic effects, in multiple organs. These findings suggest that goldenseal has protective effects with respect to neoplastic effects including cancer.

Moreover, non-neoplastic effects were also decreased in various organs with exposure to goldenseal. For example, decreased cardiomyopathy was detected in both male and female rats. Decreased incidence of cellular infiltration of histiocytes in the lung in male rats, as well as decreased cyst in pars distalis of the pituitary gland in female rats were found. These results add further support for goldenseal having a protective role for some endpoints.

There is no mention in the IARC goldenseal root powder monograph of any of these potentially protective effects, which may indicate that IARC did not consider this data. AHPA cannot speculate as to whether consideration of this data would have altered the conclusions of IARC's review of goldenseal, but OEHHA must assume that IARC considered all relevant data in drawing the conclusions presented in each monograph. Absent certainty that IARC did, in fact, review all relevant data, OEHHA should again consider the IARC monograph to be inadequate to support its own findings, and certainly inadequate to support listing of goldenseal root powder as "known to the state of California to cause cancer."

4.0 Comments on the Labor Code mechanism

4.1 Restatement of support for "Coalition" comments

AHPA is aware that the California Chamber of Commerce and 22 other organizations (the Coalition) filed comments on May 15, 2015 in the matter of OEHHA's April 21, 2015 notice of additional changes to the proposed regulation regarding the procedure and

criteria OEHHA uses to list and de-list chemicals via the so-called "Labor Code" listing mechanism of Proposition 65. AHPA was a party to the Coalition and incorporates herein by reference the points communicated in the May 15, 2015 comments on this matter. A copy of the May 15, 2015 comments is attached hereto as an exhibit.

4.2 Additional concerns on OEHHA's use of the Labor Code mechanism

AHPA has previously raised with OEHHA its concerns about the agency's over-reliance on the so-called Labor Code listing mechanism. OEHHA's statement in this proposed listing that it must blind itself to science is remarkable. AHPA believes that OEHHA's implementation of the so-called Labor Code listing mechanism constitutes an abdication of the authority delegated to the agency by the voters in enacting Proposition 65 and an interpretation of the statute that improperly delegates law-making authority to an unelected, undemocratic, and only quasi-governmental international body that convenes ad hoc groups of scientists, chosen in a non-transparent process, to review and summarize scientific research and make extremely consequential decisions, without even taking public comment.

Not surprisingly, IARC explicitly disavows any policy- or law-making role, and does not intend its determinations to carry the force of law:

> The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.[6]

It is all the more inappropriate for OEHHA to rely on the determinations of IARC -- or, rather, the small group of individuals appointed by IARC to review any individual substance -- to make decisions that have the effect of placing chemicals on the Proposition 65 list following only a "ministerial" process.

This abdication by OEHHA of any substantive role rests on an interpretation of Proposition 65 that improperly delegates the People's authority to an entity without any safeguards for due process, public involvement, or control by the People's representatives. This constitutes an unlawful delegation of power to make laws that

[6] IARC Monograph Vol. 108 – Preamble at p. 9, 2015.

govern conduct of people doing business in California, in violation of the United States and California Constitutions. *See, e.g., Carter v. Carter Coal Co.*, 298 U.S. 238, 310 (1936) (striking down law that empowered industry associations to draw up regulatory codes that carried the force of law); *Natural Resources Defense Council v. EPA*, 464 F.3d 1, 9 (D.C. Cir. 2006) ("[A]ssigning law-making functions to international bodies . . . would raise serious constitutional questions in light of the nondelegation doctrine, numerous constitutional procedural requirements for making law, and the separation of powers."); *Carson Mobilehome Park Owners' Assn. v. City of Carson*, 35 Cal. 3d 184, 190 (1983) ("An unconstitutional delegation of authority occurs only when a legislative body (1) leaves the resolution of fundamental policy issues to others or (2) fails to provide adequate direction for the implementation of that policy."); *Bagley v. City of Manhattan Beach*, 18 Cal. 3d 22, 26-27 (1976) (employing non-delegation doctrine to invalidate voter initiative that would have allowed wages to be set by an arbitrator, and holding that "the city possessing no power under existing state statute to provide for arbitration of wage rates, such power cannot be created by local initiative"); *Int'l Assn. of Plumbing & Mech. Officials v. Cal. Bldg. Standards Comm'n*, 55 Cal. App. 4th 245, 253-54 (1997) ("IAPMO") (upholding delegation of authority to the California Building Standards Commission, a governmental entity, to adopt as law model codes prepared by private entities, but only because the Commission was vested with discretion subject to adequate safeguards and was not required to adopt the standards approved by a private entity).

In particular, IARC can change its procedures at any time. It need not consider any comments. It could appoint patently unqualified scientists, with undisclosed conflicts of interests or from backgrounds biased against certain industries or fields. It could act by majority vote, or by dictate of those appointed by governments who provide the organization with the most funding. It could be controlled by the chemical industry, or by activists with any number of agendas. Because there are zero safeguards on IARC's processes, OEHHA's unwillingness even to review IARC's scientific determinations and consider comments on them only furthers the injury to the democratic process and to the use of sound science in regulatory decision-making. OEHHA has a responsibility to interpret and implement Proposition 65 in a manner that carries out the voters' mandate consistent with the U.S. and California Constitutions, and OEHHA's unwillingness to consider comments shirks that responsibility.