AMERICAN HERBAL PRODUCTS ASSOCIATION

September 2, 2024

United Kingdom Food Standards Agency
Floors 6 and 7, Clive House
70 Petty France
London SW1H 9EX

Via electronic submission to: ashwagandha-callforevidence@food.gov.uk

RE: Comments to the United Kingdom Food Standards Agency's Call for Evidence for Ashwagandha

The following submission was prepared by the American Herbal Products Association (AHPA), the U.S.-based trade association and voice of the herbal products industry. AHPA is comprised of domestic and foreign companies doing business as growers, collectors, processors, manufacturers, marketers, importers, exporters and distributors of herbs and herbal products. Among AHPA's members are companies that market products that consist of ashwagandha (*Withania somnifera*) as a botanical raw material or ingredient or that contain ashwagandha as an ingredient in a finished product.

AHPA has prepared this submission in response to the July 8, 2024 United Kingdom Food Standards Agency's (FSA) Call for Evidence for ashwagandha.[1] With respect to the "Evidence Required" as listed in the consultation, AHPA's submission is focused on the request for "any available information/data on the safety assessment of food supplements containing ashwagandha, including toxicological testing and relevant toxicological data." AHPA has notified relevant members about the Call for Evidence and the FSA may receive information on other types of evidence from AHPA members and others in the herbal products industry.

AHPA Botanical Safety Handbook 2nd Ed. (On-line version) – *Withania somnifera* entry
AHPA's Botanical Safety Handbook 2nd Ed. (2013) provides safety information on over 500 species of herbs, derived from data compiled from clinical trials, pharmacological and toxicological studies, medical case reports, and historical texts, as well as the corresponding literature citations. Each entry provides an overall safety classification and an interactions classification. All entries are reviewed by an Expert Advisory Council that includes some of the most renowned herbal and integrative medicine experts in the United States. It is available in hard-copy format, as well as an on-line version that undergoes periodic revision to incorporate new safety information.

AHPA most recently updated the ashwagandha entry in 2023 based on an extensive literature search and review of the relevant safety information available at that time (April 2023). As of the publication of the 2023 update, ashwagandha is categorized in Safety Class 1 and Interactions

[1] Accessible at https://www.food.gov.uk/news-alerts/consultations/ashwagandha.

Class A, which are defined as follows in the Introduction to the AHPA Botanical Safety Handbook:

> **Safety Class 1:**
> Herbs that can be safely consumed when used appropriately.
> - History of safe traditional use
> - No case reports of significant adverse events with high probability of causality
> - No significant adverse events in clinical trials
> - No identified concerns for use during pregnancy or lactation
> - No innately toxic constituents
> - Toxicity associated with excessive use is not a basis for exclusion from this class
> - Minor or self-limiting side effects are not bases for exclusion from this class
>
> **Interactions Class A:**
> Herbs for which no clinically relevant interactions are expected
> - No case reports of suspected interactions with probability of causality
> - No clinically relevant interactions in human pharmacological studies, if any

The full text of the AHPA BSH entry for ashwagandha is provided as a separate document for FSA review.

Liver toxicity assessment

At the request of some of its members, and as part of the updating of the AHPA BSH entry for ashwagandha, AHPA staff have analyzed several case reports in the published literature linking the consumption of ashwagandha products to hepatotoxicity. This analysis includes consultation with a medical professional in hepatoxicity regarding 12 of the cases. These reports include 14 distinct patients documented in nine publicly available references. AHPA's analysis of these cases included the following:

- In nine of the patients, the identification of the specific ashwagandha product was incomplete, and botanical testing to confirm the identification of ashwagandha was not reported.
- Due to the low level of botanical identification across the case reports, it is not possible to ascertain whether different ashwagandha plant parts play a role in hepatotoxicity.
- The dosage of ashwagandha being taken by the patient was unknown in seven of the cases.
- In six of the cases, the patients reported taking other drugs or food in addition to the ashwagandha.
- Two cases reported on the patient's alcohol usage.
- The case reports are inconsistent in approaches used to screen for potential causes of hepatotoxicity, such as viral infections and other disease states.
- Inconsistent approaches were used to assess the potential for identifying ashwagandha as the causative agent in each of the cases.

Ashwagandha use has grown rapidly on a global scale in a relatively short period of time, for example market data from the U.S. mainstream multi-outlet channel shows ashwagandha first

made an appearance in the top 40 herbs in 2018 at number 34, and in just five years ashwagandha leapt to number 5 on that list with over 15-fold increased sales volume in that channel.[2] AHPA also notes that emergence of case reports follows the general trend of increased usage of ashwagandha products, leading to the observation of what is perceived to be more incidents of potentially idiosyncratic cases of hepatotoxicity.

Abortifacient classification

Another area of recent regulatory concern for ashwagandha is the potential for reproductive toxicity, and whether ashwagandha has a history of use as an abortifacient. At least some of this concern has been prompted by the "Risk assessment of the root of *Withania somnifera*" published by the DTU Food Institute in Denmark in 2020 (DTU report),[3] which resulted in the Danish government banning ashwagandha food supplements in that country.

This risk assessment, and others such as one compiled by the German Federal Institute for Risk Assessment (BfR),[4] reference the World Health Organization (WHO) ashwagandha monograph[5] as the source for the potential abortifacient use of ashwagandha. The WHO monograph in turn references the American Herbal Pharmacopoeia (AHP) monograph as the source of this information.

Both AHP and the AYUSH Institute of the Indian government have recently issued public statements regarding the WHO monograph's incomplete representation of the information presented in the AHP monograph regarding this issue. The AHP public statement[6] noted the following:

> "However, the WHO monograph, in an example of what is known in medical literature as citation distortion, did not fully articulate the AHP review which stated the following: 'There are conflicting reports regarding the use of ashwagandha in pregnancy. Large but undefined doses have been reported to possess abortifacient activity (Chadha 1976; Svoboda 1992). Of several ayurvedic practitioners consulted, none reported having observed an abortifacient activity clinically. Conversely, ashwagandha has, traditionally and in modern ayurvedic practice, been used to prevent miscarriage and stabilize the fetus (Tirtha 1998).'"

In addition to the WHO monograph, the DTU report cites an ethnobotanical survey conducted in Jordan[7] as evidence of the abortifacient potential for ashwagandha, which the DTU report characterizes as "all plant parts are known to cause toxic effects such as abortion or sterility."

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[2] Smith et al. 2019, HerbalGram 123:62-73; Smith et al. 2023, HerbalGram 139:52-63.

[3] DTU, 2020b. Risk assessment for *Withania somnifera*. Danish Technical University.

[4] Klenow S, Latté KP, Wegewitz U, Dusemund B, Pöting A, Appel KE, Großklaus R, Schumann R, Lampen A (2012) Risk assessment of plants and herbal preparations. Federal Institute for Risk Assessment, Risk Communication Department, Berlin. BfR-Wissenschaft 01/2012 ISSN 1614-3841 (Internet): 83-99.

[5] WHO (2009) Radix Withaniae. WHO monographs on selected medicinal plants. Volume 4: 373-394.

[6] Full text available at https://herbal-ahp.org/wp-content/uploads/2024/07/Press-Release-Ashwagandha-Abortifacient-Assessment_06-24-2024.pdf

[7] Al-Qura'n S (2005) An ethnobotanical survey of folk toxic plants in southern part of Jordan. Toxicon 46: 119-129.

However, the ethnobotanical survey is based on responses from local residents in the area in which the plants were surveyed, and does not present any scientific evidence that ashwagandha has documented abortifacient activity.

AHPA's BSH has evolved in the classification of ashwagandha as more research has been published and reviewed for inclusion in this publication. A potential for an abortifacient effect was similarly reported in the Botanical Safety Handbook 1st Ed. (McGuffin et al. 1997), which categorized ashwagandha as Safety class 2b: Not to be used in pregnancy unless otherwise recommended by a qualified health care practitioner, together with a "Notice" as an abortifacient. The 2b classification remained in the BSH 2nd. Ed. when published in 2013, but the Notice as an abortifacient was removed due to the lack of scientific primary literature that such an action existed. When the entry was further reviewed in 2021, the Safety class: 1 was assigned, again due to a lack of substantive scientific documentation that indicated a risk of reproductive harm during pregnancy.

AHPA has also consulted with a noted ethnobotanist, Dr. Thomas Brendler, regarding the conflicting informational record on the abortifacient activity of ashwagandha. Dr. Brendler shared the following with AHPA from his investigation of this topic:

> The purported abortive effect of ashwagandha can be traced back to a singular source, *Punjab Plants* (Stewart, 1869), where he writes, "At least one case has occurred in the Punjab in which the root was used with a view to effect criminal abortion, and I learned that in Sind this practice is not uncommon." No such claims are made in the preceding literature, but subsequently, this is taken up randomly throughout the literature to this day, often without reference. This historical claim, apart from being hearsay, could easily be attributed to taxonomic confusion as there is a stronger ethnobotanical indication for abortifacient activity associated with other Solanaceae native to the region. Some more recent ethnobotanical surveys repeat the claim which, however, raises the suspicion that this may be author bias based on the literature interpreting a reported uterotonic activity as abortive.

Comprehensive evaluation of all relevant evidence is required

AHPA is aware that since the release of the DTU report, other European countries have used that report as the basis for issuing their own regulatory concerns or restrictions on ashwagandha food supplements. The DTU report is the only citation for ashwagandha in the recent First Report of the Head of Agencies Working Group "Food Supplements"[8] in which ashwagandha is identified as one of several food supplement ingredients of possible safety concern. While the DTU report is now over four years old, it is being used as the basis for ongoing regulatory scrutiny without seemingly any independent assessment of its conclusions. It is also notable that while the DTU report is indicated to be an assessment of ashwagandha root, some of the safety concerns outlined in the report are associated with studies performed using derivatives of ashwagandha leaf or other plant parts that are not typically consumed as food supplements.

[8] Heads of Food Safety Agencies, 2024. First report of the HOA working group – "Food Supplements." Federal Office of Consumer Protection and Food Safety (BVL).

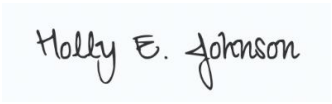
The DTU report noted a lack of toxicity studies beyond 28 days in length, however one 90-day study was published at the time of the DTU report (Antony et al., 2018)[9] and at least two additional 90-day studies have since been published (Al-Awar, 2022)[10] and Kalaivani et al., 2023[11]). A recent publication by Indian Ayurvedic medicine experts also disputes several of the findings of the DTU report and suggests additional scientific information that should be considered in assessing the safety of ashwagandha.[12]

Regulatory actions such as the one taken in Denmark should allow for the ongoing evaluation of new data that may impact risk management decisions, especially ones as drastic as prohibitions on access to well-researched botanicals. Ashwagandha is one of the most researched botanicals with a long history of use in traditional Ayurvedic medicine as well as in contemporary food supplement products. Regulatory actions should be based on a weight of evidence approach that fairly considers all relevant information for the intended end use of the product.

Summary statement

AHPA is appreciative of the opportunity to provide this input in response to the FSA's Call for Evidence regarding ashwagandha. Our members are committed to working towards reasonable regulatory oversight of food supplement ingredients and products in a transparent and scientifically supported fashion. Please contact us with any questions you may have about this submission or if AHPA can provide additional information relevant to this public consultation.

Respectfully submitted,



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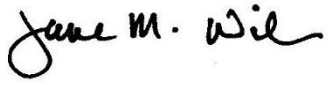

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[9] Antony, B., Benny, M., Kuruvilla, B. T., Gupta, N. K., Sebastian, A., & Jacob, S. (2018). Acute and sub chronic toxicity studies of purified withania somnifera extract in rats. *International Journal of Pharmacy and Pharmaceutical Sciences, 10*(12), 41-46. doi:10.22159/ijpps.2018v10i12.29493.

[10] Al-Awar, M. S. A. (2022). Acute and Sub-Acute Oral Toxicity Assessment of Mixed Extract of Trigonella Foenum-Graecum Seeds and Withania Somnifera Root in Rats. *Jordan Journal of Pharmaceutical Sciences, 15*(4), 493-506. doi:10.35516/jjps.v15i4.673.

[11] Kalaivani, P., Siva, R., Gayathri, V., Langade, D., Lash, P. L. H., & Patil, D. D. Y. (2023). Ninety-day repeated dose toxicity of Ashwagandha (Withania somnifera) root extract in Wistar rats. *Toxicology Reports, 11*, 189 - 198.

[12] Bhushan Patwardhanetal, Journal of Ayurveda and Integrative Medicine, https://doi.org/10.1016/j.jaim.2024.101028.