Memorandum

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Subject Regulatory status and review of available information pertaining to *Amanita muscaria*: lack of general recognition of safety for its use in foods.

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Keywords: *Amanita muscaria*; *A. muscaria*; Amanita mushrooms; Fly Agaric; Fly Amanita; muscimol; CAS# 2763-96-4; ibotenic acid; CAS# 2552-55-8; muscarine; CAS# 300-54-9

The Division of Food Ingredients' (DFI) toxicology review team was asked to review whether any food use of the mushroom, *Amanita muscaria*, meets the statutory criteria for general recognition of safety. This memorandum considers the pertinent scientific information and concludes that the use of *A. muscaria, A. muscaria* extracts and its currently known pharmacologically active constituents (muscimol, ibotenic acid, and muscarine)[1] in food does not meet the criteria for general recognition of safety. There is inadequate scientific data and information demonstrating the safety of their consumption. Furthermore, the information that is available indicates that the use of *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and muscarine in food may be harmful.

[1] For purposes of this memorandum, we refer to these three constituents as the constituents of *A. muscaria*.

GRAS Provision in the Statutory Definition of a Food Additive

As defined in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 321(s)], the term "food additive" refers to any substance the intended use of which results in it becoming a component of any food, unless the substance is generally recognized as safe (GRAS) among qualified experts under the conditions of its intended use or unless an enumerated exception applies [see section 201(s)(1)-(6) of the FD&C Act]. There is no prior sanction for *Amanita muscaria*, its extracts, muscimol, ibotenic acid, or muscarine under 21 CFR part 181, and none of the other exceptions listed in section 201(s)(1)-(6) of the FD&C Act apply to their use in conventional food.

As there is no food additive regulation establishing safe conditions of use for *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, or muscarine as ingredients in food, and because the use of these substances in conventional food is not excepted from the food additive definition under section 201(s)(1)-(6) of the FD&C Act, this memorandum considers the applicability of the GRAS criteria for the use of *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and muscarine as an ingredient in food.[2]

GRAS Criteria

A conclusion that a substance is GRAS under the conditions of its intended use requires both general recognition of safety and evidence of safety. FDA has defined “safe” (21 CFR 170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use.

General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use.

FDA's regulations in 21 CFR Part 170 describe the eligibility criteria for classification of a substance added to food as GRAS.[3] Under 21 CFR 170.30(a)-(c), general recognition of safety must be based on the views of qualified food safety experts. The basis of such views may be either through: (1) scientific procedures; or (2) in the case of a substance used in food prior to January 1, 1958, experience based on common use in food.

FDA's regulations in 21 CFR Part 170 define "common use in food" and establish eligibility criteria for classification as GRAS through experience based on common use in food. Under 21 CFR 170.3(f), common use in food means "a substantial history of consumption of a substance for food use by a significant number of consumers."

FDA's regulations in 21 CFR Part 170 define "scientific procedures" and establish eligibility criteria for classification as GRAS through scientific procedures. Under 21 CFR 170.3(h), scientific procedures “include the application of scientific data (including, as appropriate, data from human, animal, analytical, or other scientific studies), information, and methods,

[2] GRAS status is not applicable to dietary ingredients in dietary supplements. The GRAS provision is a clause in the FD&C Act’s food additive definition [FD&C Act section 201(s); 21 USC 321(s)]. Dietary ingredients in dietary supplements are excepted from the food additive definition in the Act [FD&C Act section 201(s)(6); 21 USC 321(s)(6)].
[3] These criteria are discussed more fully in the GRAS final rule (81 FR 54960; August 17, 2016).

whether published or unpublished, as well as the application of scientific principles, appropriate to establish the safety of a substance under the conditions of its intended use." Under 21 CFR 170.30(b), general recognition of safety based upon scientific procedures "shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive." Section 170.30(b) further states that general recognition of safety through scientific procedures is ordinarily based upon published studies, which may be corroborated by unpublished scientific data, information, or methods.

General recognition of safety through scientific procedures must be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods. The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. Mechanisms to establish the basis for concluding that there is common knowledge throughout the expert scientific community about the safety of a substance are more varied. Most often, publication of data in a peer-reviewed scientific journal on a test substance has been used to establish common knowledge throughout the expert scientific community in addition to general availability.

Overview of *A. muscaria*

Amanita muscaria, commonly referred to as the fly agaric or fly amanita, is a toxic mushroom species found in temperate forest regions throughout the Northern hemisphere. The fruiting body of *A. muscaria* is easily distinguished by its red coloration and white spots. Consumption of *A. muscaria* is associated with adverse effects on the central nervous system (CNS), including hallucinations, drowsiness, and delirium, with reports of seizure, coma, and possible death in severe poisoning cases. The principle pharmacologically active constituents of *A. muscaria* with reported psychotropic effects include the isoxazole compounds ibotenic acid, muscimol, and muscarine (Jo et al., 2014). Neither *A. muscaria*, *A. muscaria* extracts, nor its constituents ibotenic acid, muscimol, or muscarine are approved drugs in the United States.

Regulatory Status of *A. muscaria*

Insufficient Evidence of GRAS Status Based on Common Use in Food Prior to 1958:

FDA is unaware of any evidence that *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, or muscarine were intentionally added to food prior to 1958. In order to determine if *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, or muscarine was used in food prior to 1958, a search was conducted in three databases– PubMed[4], Web of Science Core Collection[5], and *FDA's Scientific Terminology and Regulatory Information (STARI)*[6]

[4] PubMed, https://pubmed.ncbi.nlm.nih.gov/, Evidence Based on Common Use in Food Prior to 1958 search query publication date through June 26, 2024.
[5] Web of Science, http://www.webofknowledge.com/, Evidence Based on Common Use in Food Prior to 1958 search query publication date through June 26, 2024.
[6] The data contained within STARI dates back to the 1970s. It includes primarily chemical substances (including substances/organisms used as chemicals) and associated identifying and regulatory information, but also any scientific term that may have been of interest to CFSAN. There are currently over 198,000 terms (preferred terms, synonyms) accessed through STARI, including over 50,000 CAS numbers, over 44,000 CERES IDs, over 17,600 UNII codes, and over 1500

database. The PubMed database has literature dating back to about 1951, and in some cases, even earlier literature is available. The Web of Science Core Collection consists of six online databases with indexing coverage from the year 1900 to the present. The PubMed and Web of Science databases were searched using the search terms "*Amanita muscaria"* AND "food", "fly agaric" AND "food", "muscimol" AND "food", "ibotenic acid" AND "food", or "muscarine" AND "food". Because STARI generally contains only food-related substances, we queried STARI using the search terms "*Amanita muscaria*", "muscimol", "ibotenic acid", or "muscarine" only.

The STARI searches returned no matching records. The PubMed and Web of Science searches yielded several literature results describing certain purported non-food uses, including cultural/ritual uses, ethnopharmacological uses, or recreational use of *A. muscaria* for intoxicating and entheogenic effects, and a traditional preparation of *A. muscaria* in milk to catch flies (Lumpert & Kreft, 2016).[7] The only purported consumption of *A. muscaria* mushrooms as a food source was by certain indigenous/cultural populations in Europe, Russia, and Japan (Rubel & Arora, 2008). The authors suggested that "knowledgeable processing" by parboiling of *A. muscaria* was necessary for detoxification and removal of water soluble ibotenic acid and muscimol constituents. A study by Tsunoda et al. (1993) noted reduced ibotenic acid and muscimol content following *A. muscaria* preparation by boiling or soaking in water (Tsunoda et al., 1993). However, the same study noted, that *A. muscaria* toxic components were still present at measurable levels after boiling and might not be deactivated by cooking. Currently, there are no internationally recognized food standards or specifications to support the safe processing and consumption of *A. muscaria* as a food.

The results indicate that use of *A. muscaria* as a food is very limited, which does not support a substantial history of consumption of *A. muscaria*, its extract, or its constituents for use in food by a significant number of consumers prior to 1958. Taken together, the information identified in our search does not constitute a history of common use in food and does not demonstrate safe use as a food ingredient by general population prior to 1958. Rather, the search results identify safety concerns with such prior use, including intoxication and adverse effects on the CNS associated with *A. muscaria* consumption. We find insufficient evidence of safety for the use of these substances in conventional food to be recognized as safe by qualified experts.

Accordingly, *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and muscarine do not meet the "common use in food" criterion for GRAS status. Therefore, any eligibility for classification as GRAS would need to be established on the basis of "scientific procedures." In other words, adequate technical evidence of safety must exist, and this technical evidence must be generally known and accepted by qualified food safety experts to demonstrate the safety of the intended use.

Insufficient Evidence of GRAS Status Based on Scientific Procedures (Technical Evidence of Safety):

Regulations (primarily 21 CFR Parts 73-189 and 40 CFR Parts 180-186) with over 11,000 connections to specific substances. Accessed June 26, 2024.

[7] In contrast to hallucinogenic mushrooms containing psilocybin, *A. muscaria* and its constituents are not scheduled as controlled substances in the United States.

A search of the scientific literature published through June 26, 2024 was conducted in two databases – PubMed[8] and Web of Science Core Collection[9] - using the search terms "*Amanita muscaria*", *"Amanita muscaria"* AND "Toxicity", *"Amanita muscaria"* AND "Safety", "Fly Agaric", "Muscimol" AND "Safety", "Ibotenic Acid" AND "Safety", and "Muscarine" AND "Safety". The results of this search are summarized in Table 1. Selection criteria included the terms "safety" and/or "toxicity" to narrow the scope of results to publications germane to the *A. muscaria*, ibotenic acid, muscimol, and muscarine safety evaluations and exclude publications irrelevant to establishing safety to support a GRAS conclusion.

Table 1: Summary of literature search terms and results.

Search Terms	Database	Search Results (Number)
"Amanita muscaria"	PubMed	192
	Web of Science (Core Collection)	492
"Amanita muscaria" AND "Toxicity"	PubMed	17
	Web of Science (Core Collection)	20
"Amanita muscaria" AND "Safety"	PubMed	1
	Web of Science (Core Collection)	9
"Fly Agaric"	PubMed	52
	Web of Science (Core Collection)	75
"Muscimol" AND "Safety"	PubMed	31
	Web of Science (Core Collection)	31
"Ibotenic Acid" AND "Safety"	PubMed	9
	Web of Science (Core Collection)	13
"Muscarine" AND "Safety"	PubMed	5
	Web of Science (Core Collection)	10

Based on these search criteria, 604 unique results related to *A. muscaria*, muscimol, ibotenic acid, and/or muscarine were identified; however, none support the safe use of *A. muscaria* or its pharmacologically active constituents as an ingredient in food.

The identified literature generally consisted of publications and reviews describing *A. muscaria* biology and ecology of mushrooms, as well as numerous studies focused on the bioaccumulation of trace contaminants and heavy metals in *A. muscaria* (Falandysz & Lipka,

[8] Pubmed, https://pubmed.ncbi.nlm.nih.gov/, Evidence Based on Scientific Procedures search query publication date through June 26, 2024.
[9] Web of Science, http://www.webofknowledge.com/, Evidence Based on Scientific Procedures search query publication date through June 26, 2024.

2003; Falandysz et al., 2007; Falandysz et al., 2018). Amavadin, an organic vanadium compound, was identified as a constituent of *A. muscaria* (Bayer & Kneifel, 1972; Bayer et al., 1987; Braeuer et al., 2021; Falandysz & Lipka, 2003; Falandysz et al., 2007; Falandysz et al., 2018). Additionally, several publications highlighted analytical methods for the detection and quantification of muscimol, ibotenic acid, and muscarine in mushroom tissues, and human plasma and urine samples (Avila & Guevara-Pulido, 2020; Chen et al., 2015; Cunningham & Kelleher, 1973; Deja et al., 2014; Gennaro et al., 1997; Ginterová et al., 2014; Merová et al., 2008; Merová et al., 2011; Stríbrny et al., 2012; Tsujikawa et al., 2007; Xu et al., 2020).

Numerous publications highlighted information pertaining to evidence of cultural, religious, and/or traditional uses of *A. muscaria*. Several publications denote ritual and narcotic use of *A. muscaria* by indigenous populations in Russia (Dunn, 1973; Saar, 1991a, 1991b). Other reports highlight the historical use of *A. muscaria* and ibotenic acid as a house fly attractant (Härkönen, 1998; Lumpert & Kreft, 2016; Muto & Sugawara, 1965; Takemoto et al., 1964). Importantly, such uses do not support the safety of *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and/or muscarine for use as an ingredient in food. Rather, the search results identify safety concerns pertaining to the psychoactive and entheogenic properties of *A. muscaria*.

The identified literature consisted of publications and reviews describing the reported pharmacologic and physiologic effects of *A. muscaria*, muscimol, ibotenic acid, and muscarine. Several publications denote the utility of muscimol research and mechanistic information supporting the development of novel γ-aminobutyric acid (GABA) neurotransmitter uptake inhibitors (Krogsgaard-Larsen et al., 2000). Additionally, studies reporting anticonvulsant and potential therapeutic effects of intracerebral muscimol infusion for treatment drug-resistant epilepsy were noted (Collins, 1980; Heiss, Argersinger, et al., 2019). A query of clinicaltrials.gov identified an additional small-scale study investigating the safety and efficacy of muscimol infusions into the subthalamic region of the brain for treatment of Parkinson's disease symptoms (NINDS, 2009). Studies designed to investigate purported therapeutic effects or benefits of *A. muscaria, A. muscaria* extracts, or its pharmacologically active constituents are inadequate to characterize and evaluate safety and therefore are not relevant to the determination of safety for use in food. Moreover, the recent literature contained numerous clinical case reports detailing severe adverse health effects and mortality related to *A. muscaria* poisoning events.

The FDA "Bad Bug" book[10] identifies *A. muscaria* and its constituents muscimol, ibotenic acid and muscarine as toxic agents that cause poisoning following ingestion, which also raises serious safety concerns.

Additionally, muscimol, ibotenic acid, and muscarine may be marketed as specific ionic salts which incorporate different counterions. Such salts are anticipated to disassociate into its muscimol, ibotenic acid, or muscarine (active) and counterion components when consumed. Therefore, in the absence of sufficient scientific evidence to demonstrate otherwise, all safety concerns identified in our reviews related to use or presence of muscimol, ibotenic acid, or muscarine in foods are pertinent to all salt forms of muscimol, ibotenic acid, and muscarine.

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[10] FDA Bad Bug Book (2nd Edition). Accessed June 26, 2024. https://www.fda.gov/food/foodborne-pathogens/bad-bug-book-second-edition.

Lack of Sufficient Data to Establish Safety in Food Use

Findings in the publicly available literature raise concerns regarding the safety of *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and muscarine. Summarized below are relevant records retrieved from our literature search and additional information relevant to our review of *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and muscarine.

- *Cramer Toxicity Classification*

Based on the toxic hazard decision tree criteria set forth by Cramer et al. (1978), muscimol, ibotenic acid, and muscarine would be classified as Class III substances (Cramer et al., 1976). This classification indicates high toxicological potential based on the chemical structure and available metabolism data.

- *Background and Purported Biological Activity/Mode of Action*

A. muscaria is a basidiomycete in the genus *Amanita* and is typically recognized due to its distinguishable fruiting body, with a red coloration and white spots. *A. muscaria* mushrooms are native to conifer and deciduous forests throughout the Northern hemisphere. Numerous publications and mycological field guides denote that *A. muscaria* is a poisonous mushroom species, and that it may not be rendered edible by cooking. The hallmarks of "pantherine-muscarine" poisoning syndrome mimic that of anticholinergic toxidrome, and include flushing, fever, pupillary dilation, vomiting, diarrhea, hallucinations, and psychoactive effects (Caffrey & Lank, 2018). Neurologic effects of *A. muscaria* intoxication can alternate between observations of sedation and severe agitation due to concomitant GABA and glutamate signaling activity (Satora et al., 2005). The *A. muscaria* toxidrome is predominantly associated with its pharmacologically active constituents muscimol and ibotenic acid (Michelot & Melendez-Howell, 2003).

Muscimol is considered a likely toxicologic determinant of major clinical signs associated with *A. muscaria* poisoning events (Puschner, 2007). Muscimol is an isoxazole constituent, with a conformationally similar structure to the inhibitory neurotransmitter, GABA (Brehm et al., 1997; Brehm et al., 1972). Muscimol is found in *A. muscaria* cap and stem tissues at levels of 46-1203 ppm and 82-292 ppm, respectively (Tsujikawa et al., 2006). Muscimol has been definitively characterized as a selective agonist at inotropic GABA receptors (Benkherouf et al., 2019; G. A. R. Johnston, 2014). Specifically, muscimol is a potent agonist of $GABA_A$ receptors, and partial agonist of $GABA_C$ receptors. Intracerebral injection of muscimol is a common model in neurobehavioral studies as a means to reversibly inactivate targeted brain regions (Edeline et al., 2002; Majchrzak & Di Scala, 2000). Notably, GABA receptor agonists are a known drug class commonly used as anticonvulsants, sedatives, and anxiolytics (Allen et al., 2024).

Ibotenic acid is an isoxazole constituent present in *A. muscaria* cap and stem tissues at levels of 182-1839 ppm and 627-1998 ppm, respectfully (Tsujikawa et al., 2006). Ibotenic acid is characterized as an excitatory amino acid, similar to the neurotransmitter glutamate, due to its agonist activity upon ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors (G. A.

Johnston et al., 1968; Peredy & Bruce, 2014). Glutamate is considered a major excitatory neurotransmitter in the mammalian central nervous system. Intracerebral injection of ibotenic acid is a well characterized brain lesioning method used in neurobehavioral research (Coyle & Schwarcz, 2020). Ibotenic acid causes perikaryal-specific, axon-sparing, spherical lesions regardless of the targeted brain region, and without induction of convulsant effects (Schwarcz et al., 1979). Research suggests that spontaneous decarboxylation of ibotenic acid to muscimol may occur *in vivo* following consumption of *A. muscaria* (Clarke & Crews, 2014; Curtis et al., 1979; Stebelska, 2013).

Muscarine is a neurotoxic quaternary ammonium alkaloid. Numerous muscarine containing mushrooms are considered poisonous, including several species in the genera *Inocybe* and *Clitocybe* (Clarke & Crews, 2014; Patocka et al., 2021). Muscarine binds to muscarinic-type acetylcholine receptors of the parasympathetic autonomic nervous system producing symptoms of cholinergic toxicity, including diarrhea, diaphoresis, urination, miosis, bronchorrhea, bradycardia, bronchoconstriction, emesis, lacrimation, and salivation (Chew et al., 2008; Peredy & Bradford, 2014). Muscarine has been determined to be a minor constituent of *A. muscaria* at levels around 3 ppm (Lurie et al., 2009).

Developmental exposure to *A. muscaria*, muscimol, ibotenic acid, or muscarine would raise serious safety concerns based on the psychoactive properties of these substances. A balance between inhibitory and excitatory signaling is necessary for generation of functional neuronal networks during ontogenesis. In the developing vertebrate brain, GABAergic signaling is initially excitatory, but becomes inhibitory (as it is in the adult brain) due to a shift in the reversal potential for chloride ions (Ben-Ari, 2002; Simeone et al., 2003). Prescribed drugs that act as $GABA_A$ receptor agonists, including benzodiazepines and barbiturates, are often contraindicated for use during pregnancy (Bounds & Patel, 2024; Creeley & Denton, 2019). NMDA glutamate receptor signaling also plays a major role in brain development, specifically refining the axonal and dendritic arbors of a developing neuron and maturation of glutamatergic synapses (Ewald & Cline, 2009). Acetylcholine signaling supports neuromodulatory roles in the developing and mature brain, including development of the neural plate, cortical plasticity, and synapse formation (Galvin et al., 2018; Sam & Bordoni, 2024). Aberrant GABAergic, glutaminergic, and/or cholinergic signaling by *A. muscaria* or its pharmacologically active constituents may perturb the coordination of excitatory and inhibitory signaling potentially causing adverse effects on neurodevelopment.

- *Absorption, Distribution, Metabolism, and Excretion (ADME)*

The available literature did not provide sufficient details to characterize the ADME profile of *A. muscaria* and its principal toxic constituents, muscimol, ibotenic acid, and muscarine. Based on the time of symptom onset following consumption of *A. muscaria*, rapid absorption of psychoactive constituents is suspected (Puschner, 2007). The general literature reports that ibotenic acid is decarboxylated to form muscimol, and that both constituents are able to readily cross the blood-brain barrier (Nielsen et al., 1985). Ott et al. (1975) reports that following muscimol and ibotenic acid administration in mice, both constituents are detected in urine within 1 h of exposure (Ott et al., 1975).

- *Toxicity Studies*

No toxicity studies sufficient to establish the safe use of *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and muscarine as ingredients in food were identified in our search of the generally available literature. The studies that were identified using the search parameters described above were generally intended to assess relative psychoactive effects of *A. muscaria* and its principal toxic constituents, muscimol, ibotenic acid, and muscarine, and case reports of accidental ingestion of *A. muscaria* in canines. Such studies do not support the safety of a food ingredient,[11] which may be consumed by the entire population over a lifetime; assurance of safety for a food ingredient requires an evaluation of potential effects of long-term use within various segments of the population, with consideration of vulnerable subpopulations such as pregnant individuals/conceptus/fetus, infants, and young children, if appropriate. What follows is a brief description of the studies identified.

A study by Dearolis and colleagues evaluated the effects of muscimol administration on cerebral electrical activity, and spontaneous and conditioned behaviors in rats, rabbits, and cats (Decarolis et al., 1969). Muscimol produced distinct effects on brain electrical signaling in rabbits and rats as measured by electroencephalogram. Based on their observations, the authors concluded that muscimol produces potent effects on the CNS. Intraperitoneal administration of muscimol in male mice was associated with clinical observations of sedation, impaired motor coordination, ptosis, antinociception, and catalepsy (Löscher, 1982). Median neurotoxic (TD50) and lethal (LD50) doses for muscimol were reported as 0.65 mg/kg bodyweight (BW) and 8.1 mg/kg bw, respectively.

Several identified publications focused on potential therapeutic applications of targeted intracerebral infusions of muscimol in non-human primates (Heiss, Walbridge, et al., 2019; Heiss et al., 2010; Heiss et al., 2005; Ludvig et al., 2012; Ludvig et al., 2015). Administration of higher levels of muscimol (8.8 mM) into the bilateral subthalamic nuclei of adult rhesus monkeys induced severe bilateral hyperkinesia, hemiballismus, and interspersed periods of somnolence (Heiss, Walbridge, et al., 2019). While such studies support proof-of-concept investigations of the use of intracerebral muscimol injections as therapeutic agents for treatment of medically intractable epilepsy, they are not sufficient to support the safe use of muscimol in food **(see footnote 11)**.

Rossmeisl et al. describes a case report detailing *A. muscaria* toxicosis in two dogs following accidental ingestion (Rossmeisl et al., 2006). The canines presented with somnolence, gastroenteritis, hypersalivation, miotic pupils, and generalized seizures. The owners in both cases reported growth of *A. muscaria* near their respective enclosures, and exposure was confirmed by evaluation of urinary and serum ibotenic acid and muscimol levels. Other publications denote instances of fatal *A. muscaria* poisoning events in dogs (Lindberg & Holmgren, 2012; Romano et al., 2019). A retrospective evaluation of canine mushroom

[11] For example, the design and endpoints of these studies were not sufficient to provide pivotal safety information on *A. muscaria* and its principal toxic constituents, muscimol, ibotenic acid, and muscarine, when consumed as an ingredient in food. Further, the studies were not designed to support a determination of a no observed adverse effect level (NOAEL) and derivation of an acceptable daily intake (ADI) level. For further information on FDA's recommendations for food safety assessments, see Guidance for Industry and Other Stakeholders, Toxicological Principles of the Safety Assessment of Food Ingredients, Redbook 2000 (2007), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-and-other-stakeholders-redbook-2000.

ingestions reported to the Norwegian Poison Information Center from 2011 to 2022 identified 17 cases associated with exposure to isoxazoles (muscimol and ibotenic acid), and 2 lethal cases related to ingestion of *A. muscaria* (Seljetun & Kragstad, 2023).

- *Human Studies and Case Reports*

Numerous case reports detailing serious adverse events related to *A. muscaria* intoxication following accidental or intentional ingestion were identified in the review of the literature. The clinical manifestation of *A. muscaria* intoxication is well documented with onset of symptoms occurring within 30 min to 2 hours following consumption, and often characterized by CNS symptoms such as disorientation, fatigue, and visual and auditory hallucinations (Michelot & Melendez-Howell, 2003; Rampolli et al., 2021; Satora et al., 2005). In more severe cases, *A. muscaria* intoxication can induce coma, seizures, respiratory depression, and death (Meisel et al., 2022; Rampolli et al., 2021). In some cases, clinicians report alternating states of CNS stimulation/excitation and depression (Amaducci et al., 2020). Additionally, cholinergic or anticholinergic effects, possibly related to muscarine content, have also been reported (Buck, 1963; Hohn & Schoenemann, 2000).

Meisel et al. (2022) described two case reports of severe *A. muscaria* intoxication, including a fatality (Meisel et al., 2022). In one case, a 75-year-old man presented to the emergency clinic with nausea, visual and auditory hallucinations, and lethargy following accidental consumption of a single *A. muscaria* mushroom cap. The patient required intubation and symptomatic care, and was able to make a full recovery. *A. muscaria* intoxication was confirmed by assessment of muscimol and ibotenic acid in collected mushroom samples and patient blood. In the second case, a 44-year-old man presented to the emergency department unresponsive in a state of cardiac arrest following ingestion of 6-10 dried *A. muscaria* mushrooms. The patient showed no improvement following 9 days of symptomatic care and died following removal of life support. Notably, drug screenings and autopsy results did not identify any alternative explanation for the cause of death. A notice published in the Centers for Disease Control (CDC) Morbidity and Mortality Weekly report series detailed a case of *A. muscaria* intoxication in a middle aged man in Minnesota (Taylor et al., 2019). The subject presented to the emergency department with altered mental status, emesis, incontinence, diarrhea, diaphoresis, and excessive salivation and required symptomatic care, endotracheal intubation, and mechanical ventilation due to respiratory failure. The subject recovered and was discharged after 8 days. The identity of the mushroom as *A. muscaria* was confirmed based on the patient's description of the mushroom consumed, and examination of a remaining specimen in the area of collection by a mycologist. Another case report detailed onset of coma and generalized seizures in a 21-year-old male following ingestion of *A. muscaria* mushrooms (Mikaszewska-Sokolewicz et al., 2016). Duration and severity of clinical effects likely vary with the magnitude of exposure. Rampolli et al. described a case of prolonged coma (72 h) requiring intubation in a 44-year-old male subject after reportingly consuming a half a kilogram of *A. muscaria* mushrooms (Rampolli et al., 2021). Other case reports highlight prolonged CNS effects, including delirium, hallucinations, paranoid psychosis lasting up to five days following *A. muscaria* ingestion (Amaducci et al., 2020; Brvar et al., 2006). Another publication and conference abstract highlight additional cases of *A. muscaria* toxicity reported in children, including observations of coma and respiratory arrest (Benjamin, 1992; Hoegber et al., 2008).

A retrospective review of regional poison control center data (Oregon and Alaska) from 2022

identified 23 cases related to *A. muscaria* exposure, and three major categories of symptoms, including gastrointestinal effects, CNS depression related to muscimol, and CNS excitation related to ibotenic acid. (Moss & Hendrickson, 2019). Another retrospective study identified two cases of *A. muscaria* poisoning presentations at an emergency department in Bern, Switzerland between 2001 and 2017 (Keller et al., 2018).

A query of the CFSAN Adverse Event Reporting System (CAERS)[12] database identified seven adverse event reports using the search term "*Amanita muscaria*", "*A. muscaria*", "muscimol", "ibotenic acid", and/or "muscarine" occurring between May 9, 2023 and June 15, 2024. The reports highlight serious safety concerns related to use of products containing *A. muscaria* or its pharmacologically active constituents as ingredients, including purported incidences of CNS depression, somnolence, seizures, and hospitalization. Moreover, a query of America's Poison Center's National Poison Data System (NPDS)[13] was conducted using the following criteria: available generic/product codes for "Group 2 mushrooms: muscimol and ibotenic acid", "Mushrooms, Processed Preparations: Amanita Containing", or containing a product code applicable to "muscimol", "'mushrooms-muscimol/ibotenic acid", and "Mushrooms-muscarine/histamine", and a case occurrence date between 1/1/2023 and 6/30/2024. NPDS searches related to "Group 2 mushrooms: muscimol and ibotenic acid", "Mushrooms, Processed Preparations: Amanita Containing", or containing a product code applicable to "muscimol", "'mushrooms-muscimol/ibotenic acid", and "Mushrooms-muscarine/histamine", identified 695, 57, and 155 cases, respectively. The cases highlight subject hospitalization, intubation, and critical care associated with exposure, and reported adverse clinical effects of hallucinations, hypertension, tachycardia, seizures, CNS depression, coma, respiratory depression, and death, among others.

On June 27, 2024, Prophet Premium Blends announced a voluntary recall of all Diamond Shruumz brand Infused Cones, Chocolate Bars, and Gummies (Micro- and Mega/Extreme-Dose)[14]. Prophet Premium Blends publicly identified muscimol as the causative agent in the outbreak. As of July 9, 2024, the FDA has received 58 case reports of illness related to the recalled products, including 30 hospitalizations, and one potentially associated death under investigation[15]. Severe symptoms, including seizures, central nervous system depression (loss of consciousness, confusion, sleepiness), agitation, abnormal heart rates, hyper/hypotension, nausea, and vomiting have been reported. To date, no conclusions have been reached by the FDA regarding the cause of the illnesses, and no ingredient has been definitively determined to be the source.

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[12] CAERS is a database that contains information on adverse event and product complaint reports submitted to FDA for foods, dietary supplements, and cosmetics. The database is designed to support CFSAN's safety surveillance program. Adverse event reports for a given product in CAERS reflect only original information reported to the FDA and do not represent any conclusion by FDA about whether the product was causal to the adverse events. https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers

[13] The National Poison Data System (NPDS) is the data warehouse for the United State's 55 poison centers. Each poison center submits de-identified case data to NPDS after providing necessary poison exposure management and information services to callers. https://poisoncenters.org/national-poison-data-system. NPDS query conducted July 3, 2024.

[14] Prophet Premium Blends Announcement of Voluntary Recall. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/prophet-premium-blends-recalls-diamond-shruumz-products-because-possible-health-risk. Accessed July 9, 2024.

[15] FDA issued advisory. Investigation of Illnesses: Diamond Shruumz-Brand Chocolate Bars, Cones, & Gummies (June 2024). Content current as of July 9, 2024. https://www.fda.gov/food/outbreaks-foodborne-illness/investigation-illnesses-diamond-shruumz-brand-chocolate-bars-cones-gummies-june-2024

Trends in recreational use of novel psychoactive substance have been reportedly increasing. We note that the use of a substance in food to induce intoxication raises safety concerns. In an article published in the American Journal of Preventative Medicine, Leas et al. described the growing need for a public health response to the unregulated sale of *A. muscaria* mushrooms and products containing isolated muscimol (Leas et al., 2024). The authors noted clear safety concerns and that there exists no publicly available information indicating that FDA had received a GRAS or New Dietary Ingredient (NDI) notification for such ingredients.

- *Firm's GRAS Conclusion is Not Supported by the Scientific Evidence*

During our review, FDA/DFI identified two press releases issued by Psyched Wellness Ltd.: (1) a press release dated March 8, 2022[16] announcing its GRAS conclusion for its "proprietary extract" of Amanita Muscaria, and (2) a press release dated February 15, 2022, [17] asserting that a "90-day oral toxicity study of Amanita Muscaria (AME-1) reveals no adverse effects."

The March 2022 press release states: "The panel of experts concluded that AME-1 is safe for a variety of finished conventional food products, including for use in the general adult population 18 years and over, except pregnant women and lactating mothers." The press release also states that it would be included in dietary supplements. The press released stated: "The successful GRAS certification allows Psyched to legally sell its AME-1 products in the United States." However, this statement is false as the firm failed to meet its burden in demonstrating that this use is GRAS. Upon review of the data cited by the company in its press releases it is evident that the safety information does not support a conclusion for reasonable certainty of no harm nor is there evidence of general recognition by qualified experts of safety for use in food of *A. muscaria* and its constituents. We note that the company did not submit a GRAS notification to FDA regarding its conclusion. Furthermore, any "approval" or "certification" by a GRAS panel does not mean that the criteria for GRAS have been met. The outcome of a GRAS panel's deliberations does not create or confer GRAS status of the use of an ingredient. Rather, it could provide evidence supporting the proponent's contention that there is general acceptance based on generally available information among relevant scientific communities. Other information relevant to best practices for convening a GRAS panel, including assessing conflicts of interest, can be found in our final guidance[18].

According to the firm's press releases, the safety of the Psyched Wellness Ltd's *A. muscaria* extract is based on the results of a 90-day oral toxicity study and an independent review by a panel of scientific experts. The firm stated in its February 2022 press release that a No Observed Adverse Effect Level (NOAEL) was determined in the study on the basis that no adverse effects were detected with regard to standard assessed subchronic toxicity study

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[16] Psyched Wellness Ltd Press Release, Self-GRAS Affirmation of *A. muscaria* extract. Published March 8, 2022. https://www.proactiveinvestors.com/companies/news/976112/psyched-wellness-receives-gras-approval-for-amanita-muscaria-extract-gets-green-light-to-bulk-produce-market-products-in-the-us-976112.html

[17] Psyched Wellness Ltd Press Release. Published February 15, 2022. https://www.proactiveinvestors.com/companies/news/974140/psyched-wellness-says-90-day-oral-toxicity-study-of-amanita-muscaria-ame-1-reveals-no-adverse-effects-974140.html

[18] FDA Guidance for Industry: Best Practices for Convening a GRAS Panel. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-best-practices-convening-gras-panel

parameters, including clinical signs, mortality, bodyweight, clinical chemistry, hematology, gross necropsy and organ weights. However, at the time of our assessment, the aforementioned study had still not been published in a reputable peer-reviewed scientific journal, nor was it available for review by subject matter experts. Because the study is unpublished and not generally available/accepted, it cannot be considered pivotal information that would form the basis of a GRAS conclusion to establish a safe use in food.

Furthermore, based on the limited information presented in the press releases, and known physiological effects of *A. muscaria*, and its constituents muscimol, ibotenic acid, and muscarine; the briefly mentioned 90-day subchronic oral toxicity study, even if published, would be insufficient to support that there would be reasonable certainty of no harm in the minds of competent scientists that the intended use of *A. muscaria* extracts in food could be safely consumed by the general population, including vulnerable subpopulations such as pregnant individuals/conceptus/fetus, infants, and young children, considering lifetime exposure. Specifically, this study did not evaluate necessary safety endpoints relevant to potential neurotoxicity, developmental toxicity, or chronic toxicity that would be paramount given the known mechanism of action of these substances. The press release also does not address necessary information such as study design, compliance with established testing guidelines, nor endpoints that are key components of standard 90-day oral toxicity studies, such as comprehensive histopathological evaluations.

The firm specified that the GRAS conclusion for the use of their *A. muscaria* extract would be specific to an intended population which encompassed the general adult population 18 years and older, except pregnant women and lactating mothers. However, already discussed, the lack of safety data precludes GRAS status for *A. muscaria* extract for the general population of all ages. Furthermore, given the identified safety concerns, any warning statements would not be sufficient to support any safe use of *A. muscaria* or its pharmacologically active constituents in conventional food.

Overall Conclusions

Overall, the available data are insufficient to support the safety of *A. muscaria, A. muscaria* extracts, or its currently known pharmacologically active constituents, muscimol, ibotenic acid, and muscarine, for use as food ingredients that will be consumed by the general public. Moreover, the available information underscores their potential for serious harm and adverse effects on the central nervous system. Therefore, there is no basis to conclude that the use of *A. muscaria, A. muscaria* extracts, or its currently known pharmacologically active constituents, muscimol, ibotenic acid, and muscarine, or their salts or conjugates, in food is GRAS.

The available data and information in the scientific literature do not support the safe use of *A. muscaria*, *A. muscaria* extracts, or its currently known pharmacologically active constituents, muscimol, ibotenic acid, or muscarine in food, and therefore the addition of *A. muscaria, A. muscaria* extracts, or its pharmacologically active constituents, muscimol, ibotenic acid, or muscarine to food does not meet the statutory criteria for classification as GRAS. Furthermore, there is no consensus among qualified experts that *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and muscarine are safe for use as food ingredients based on either common use in food (prior to 1958) or technical evidence of safety.

There is no food additive regulation establishing safe conditions of use of *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, or muscarine. The use or intended use of *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, and muscarine in conventional foods is not eligible for a listed exception to regulation as a food additive [Section 201(s)(1)-(6) of the FD&C Act].

Accordingly, when *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, or muscarine is added or intended for addition to conventional food, it is an unapproved food additive and is deemed an unsafe food additive within the meaning of Section 409(a) of the FD&C Act. Food that is, bears, or contains an unsafe food additive, such as *A. muscaria*, *A. muscaria* extracts, muscimol, ibotenic acid, or muscarine, is adulterated under 402(a)(2)(C)(i) of the FD&C Act. Introducing or delivering for introduction an adulterated food into interstate commerce is a prohibited act under Section 301(a) of the FD&C Act.

[redacted]

___ [redacted], Ph.D. ___

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