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National Organic Standards Board
USDA-AMS-NOP
1400 Independence Ave. SW.,
Room 2648-S, Mail Stop 0268
Washington, DC 20250-0268

Re. CS: Laminarin and Seaweed Extracts

These comments to the National Organic Standards Board (NOSB) on its Fall 2015 agenda are submitted on behalf of Beyond Pesticides. Founded in 1981 as a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to bridge the interests of consumers, farmers and farmworkers, Beyond Pesticides advances improved protections from pesticides and alternative pest management strategies that reduce or eliminate a reliance on pesticides. Our membership and network span the 50 states and the world.

Beyond Pesticides opposes the proposal of the Crops Subcommittee (CS) to classify laminarin as nonsynthetic. We support the proposal of the CS to classify seaweed extracts as synthetic and to deny the petition for listing on §205.601. We believe that the same reasoning applies to both. The CS has not explained its reasoning for differentiating between the use of sodium hydroxide in laminarin and potassium hydroxide in seaweed extracts for determining the classification.

Classification: Laminarin and seaweed extracts are synthetic.

Laminarin and seaweed extract must be classified as synthetic substances if they are extracted as described in the petitions. Sulfuric acid is added during the extraction process. It is neutralized with sodium or potassium hydroxide in a later step. While the reaction of sulfuric acid and sodium/potassium hydroxide neutralizes the acid, thus "removing" that effect, it does not remove the sulfur. Sodium or potassium is also added. Thus, sodium sulfate or potassium sulfate is a net addition. No later step in the process removes the sodium/potassium sulfate. It is the remaining material at levels that are of technical concern or that have technical effect that requires the classification of this material as a synthetic. Removal is not the same thing as eliminating the function while creating an added substance in the material.

In comments submitted before the spring 2014 NOSB meeting, the Organic Materials Review Instititute (OMRI) stated something similar:

> Sodium hydroxide does in fact neutralize sulfuric acid; however, it does so by reacting together to produce water and sodium sulfate. Therefore, sodium sulfate, a synthetic, is still apparently present in the final laminarin extract after manufacturing is complete (although in small quantities). OMRI would consider the resulting sodium sulfate to need additional review for compliance to the organic regulations.

In comments presented at the spring 2014 meeting in San Antonio, Lindsay Fernandez-Salvador of OMRI cautioned about finding that the sodium sulfate is found at "insignificant levels" because it would be the first time that the NOSB has used such reasoning since the publication of the new guidance on the classification of materials.[1]

Unfortunately, there is some uncertainty about which classification guidelines to use. The NOSB has adopted classification guidelines, and the NOP has proposed draft guidelines that are still incomplete. In the following, the important difference between the two is that according to the NOSB guidelines, a substance is synthetic if there are **significant** residues of a synthetic added during extraction, while according to the draft NOP guidelines, a substance is synthetic if any synthetic added during extraction is **not removed so that it has no technical or functional effect**. A key defect in both of these sets of guidelines is the failure to define the critical terms "significant" and "technical or functional effect." Regardless of the definition, however, there is a synthetic material that remains in the material after it is extracted, and it is this chemical that would not occur naturally that requires the board's review. Without an NOSB determination that laminarin is synthetic because of this remaining unnatural material, it would not have the opportunity to evaluate its acceptability in organic production.

In the case of laminarin or seaweed extract, there is a residue of two synthetic substances added during extraction. Is that residue "significant"? Does it have a "technical or functional effect"? The minority report of spring 2014 performed some calculations estimating the residues of <u>added</u> sulfate at 624 parts per million (ppm) and <u>added</u> sodium at 299 ppm. The uncertainties in the calculation make it likely that these are <u>underestimates</u>.

While the majority is correct in stating that the technical/functional effect of acidity has been removed, it has not addressed the effects of the additions of sulfate and sodium in removing the acidity. In fact, these concentrations are significant within the laminarin. Like the 2014 minority opinion, we do not claim that they would be a significant addition to the crop plants.

The CS says,

> The reaction and filtration steps result in a purified laminarin in which the sodium and sulfate ions do not have a technical or functional effect. This is quite different than the listing for aquatic plant extracts that are classified as synthetic for crop production at

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[1] Transcript of spring 2014 meeting, p. 577.

205.601(j)(1). In those the extracting agents such as potassium hydroxide does leave behind enough potassium to have a functional effect as a fertilizer. In laminarin, neither the sodium (at 0.001%) nor the sulfate ions (at 0.0034%) have a functional effect for disease suppression.

The fact that sodium and sulfate ions do not affect disease suppression does not mean that they have no technical or functional effect. We do not know what other technical or functional effects the sulfate and sodium/potassium might have on laminarin. Are they preservatives? Sodium sulfate is used as a viscosity modifying agent in cosmetics. The scientific literature review *Safety Assessment of Inorganic Sulfates as Used in Cosmetics* performed by Cosmetic Ingredient Review[2] (CIR) states that sodium sulfate is used as a viscosity-control agent. Does the concentration found in laminarin perform this effect? Table 3 of the CIR report (attached) indicates that the answer is "yes."

Some issues raised in the TR are red herrings.

The TR says,[3] "According to the manufacturing process described in the petition, it is expected that some synthetic sulfate (SO_4^{-2} as well as some HSO_4^-) and sodium are present in ionic form in the final solution with the extracted laminarin. However, because the final product is in aqueous form, the sodium and sulfate ions would not be expected to react or precipitate as solid sodium sulfate." The fact that the sodium sulfate is in solution is not relevant to its existence as a synthetic material with a technical and functional effect.

The TR also says,[4]

> The EPA typically requires any component of a pesticide formula greater than or equal to 0.1% to be declared on the Confidential Statement of Formula (CSF), including impurities from acid-base reactions such as those described in this technical report. There can be no exceptions for listing on the CSF where 'Impurities of Toxicological Significance' are concerned (Pfiefer 2015). Based on theoretical calculations in Question 3, sulfate ions could conceivably comprise 0.0034% of a final commercial laminarin product, and sodium consists of .001%. Therefore, these residual by-products from the acid-base reaction would not likely be declared on the CSF, even as impurities.

This also is not relevant to the classification issue, where the issue of the impurities is not their "toxicological significance," but (according to the draft classification guidance) their presence in an amount that produces a "technical or functional effect." Only if a synthetic determination is made by the board would the board consider whether the chemical represents a harm. Since

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[2] Cosmetic Ingredient Review, 2013. *Safety Assessment of Inorganic Sulfates as Used in Cosmetics*, http://www.cir-safety.org/sites/default/files/inorgs032014slr.pdf (The 2013 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.)

[3] Lines 298-301.

[4] Lines 382-388.

"technical or functional effect" has not been defined in the draft guidance, we must take it to be defined broadly, as in the minority report from spring 2014.

Why do we care about the classification of laminarin and seaweed extracts?

Laminarin and fucoidan are extracted from seaweed. Laminarin is also found in fungi. They work by amplifying natural plant defenses. (The petition for seaweed extracts is less specific about the mechanisms by which they "increase plant strength.") Why, then, should we care whether there are small residues of synthetic that causes laminarin and seaweed extracts to be classified as synthetic? There are two general reasons, as well as some specific concerns.

1. Determining as nonsynthetic substances formulated with high levels of sulfuric acid resulting in high levels of sulfate sets a bad precedent for future synthetic-nonsynthetic decisions.
2. With no board oversight of materials deemed nonsynthetic, given USDA's new position that NOSB recommendations are only binding for synthetic materials –and no assurance of NOP consultation—decisions such as these are critical to board oversight and compliance with the Organic Foods Production Act (OFPA). For instance, if the board wanted to designate a natural material with an annotation that certain formulations are not allowed, USDA's announced policy would not require that annotation to be attached to the 602 listing.

Concerns about laminarin and seaweed extracts can be addressed with a synthetic classification.

Given that we believe laminarin and seaweed extracts as described in the petitions are synthetic materials, the board should be aware that there are health concerns that we believe deserve some consideration. With the benefit of a complete technical review, these issues could be addressed and the public could be assured of the material's acceptability under OFPA standards. The health concerns –and possibly ecological concerns—arise from the mode of action of these materials –increasing the plant's own defenses. While this appears to be a good thing on the surface, many plants produce toxins when stimulated by herbivores or disease organisms. EPA has not evaluated these impacts, and if laminarin is judged to be nonsynthetic, it will be used in organic production without <u>anyone</u> evaluating it fully. In addition, because of NOP's ruling, any board recommendation on restricting or annotating a nonsynthetic material will be left entirely to the discretion of USDA. We attach an appendix that identifies issues that should be investigated.

Overharvesting of seaweed for both laminarin and seaweed extract pose threats to the biodiversity of oceans.

Kelp forests are important ecologically. "They are complex three-dimensional structures providing habitat, food and shelter for various species and are characterised by high productivity and a high diversity of associated flora and fauna. They also form important reproduction and nursery grounds for fish."[5] Although kelp itself recovers from intensive harvesting,[6] kelp harvesting can have significant impacts on other members of the ecosystem.[7]

Brown seaweed extract is a fertilizer

The CS notes that although seaweed extract is petitioned as a plant strengthener, products are labeled as a 0-0-3 or 0-0-1 fertilizer. Since brown seaweed extract is synthetic, it is a synthetic fertilizer and should not be permitted.

Conclusion

A definition of "synthetic" that depends on effects of synthetic additives –using terms like "significant" or "technical or functional effect," for example– is problematic to the decision making process. The definition of "synthetic" should be based on the method by which the material is made, and the effects are something to be determined afterwards. This is just one problem with relying on the incomplete draft materials classification guidance.

The NOSB is left without clear guidance on the classification of materials. NOSB efforts were abandoned when the NOP issued draft guidance. That draft is incomplete and has never received a complete hearing by the NOSB. Based on that incomplete draft guidance, the CS has reached the conclusion that laminarin is nonsynthetic and the very similarly made seaweed extracts are synthetic. We (and a minority of the CS in 2014) have reached the conclusion that both are synthetic. Given the uncertainties in the application of guidance that is both incomplete and in draft form, we believe that the NOSB should follow a precautionary approach and classify both as synthetic. In the appendix below, we present possible consequences of failing to take a precautionary approach.

Thank you for your consideration of these comments.

Sincerely,

Terry Shistar, Ph.D.
Board of Directors

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[5] Werner, A., & Kraan, S. (2004). Review of the potential mechanisation of kelp harvesting in Ireland. Marine Environment and Health Series, No. 17, 2004. Marine Institute.

[6] Rothman, M. D., Anderson, R. J., & Smit, A. J. (2006). The effects of harvesting of the South African kelp (Ecklonia maxima) on kelp population structure, growth rate and recruitment. *Journal of applied phycology*, *18*(3-5), 335-341.

[7] Lorentsen, S. H., Sjøtun, K., & Grémillet, D. (2010). Multi-trophic consequences of kelp harvest. *Biological Conservation*, *143*(9), 2054-2062.

Attachment: Table 3 from Cosmetic Ingredient Review, 2013. *Safety Assessment of Inorganic Sulfates as Used in Cosmetics*
Appendix: Risk Analysis of Laminarin and Seaweed Extracts

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[9,10]

	Sodium Sulfate # of Uses	Conc. (%)	**Zinc Sulfate** # of Uses	Conc. (%)
		Exposure Type		
Eye Area	11	0.000046-0.0064	NR	NR
Incidental Ingestion	NR	0.00015-0.83	NR	0.05
Incidental Inhalation-Sprays	38	0.00015-2	10	NR
Incidental Inhalation-Powders	34	0.005	10	NR
Dermal Contact	272	0.00001-96.8	45	0.057-1
Deodorant (underarm)	2	0.0001-0.0027	NR	NR
Hair - Non-Coloring	76	0.00095-2	16	0.44
Hair-Coloring	209	1-2.7	NR	NR
Nail	11	0.001-9.1	NR	NR
Mucous Membrane	190	0.00015-96.8	2	0.057
Baby Products	7	0.29	NR	NR
		Duration of Use		
Leave-On	74	0.00001-9.1	23	0.07-1
Rinse off	458	0.00015-8	30	0.057
Diluted for (bath) Use	42	0.14-96.8	NR	NR
Totals/Conc. Range	612	0.00001-96.8	63	0.057-1

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses;
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Note: the calculated concentration of sulfate in laminarin is approximately 624 ppm = 0.000624 = 0,0624%. The petition for seaweed extracts says the concentration of potassium sulfate is a maximum of 1740 ppm, of which 55%, or 957 ppm = 0.000957 = 0.0957% is sulfate.

Laminarin and Seaweed Extract Risk Analysis

As we all know, "natural" does not mean safe. One of the most toxic pesticides we know –the predator poison sodium fluoroacetate or 1080— occurs naturally as an anti-herbivore metabolite in various plants.

Laminarin acts by increasing the concentration of anti-herbivore and anti-fungal metabolites in plants. Although humans do not consume the species containing 1080, we do consume plants that contain compounds that would be toxic in larger quantities and whose relatives are considered poisonous. Solanaceous plants, including tomatoes, potatoes, and eggplants, with relatives poisonous nightshades, are examples. Some people are more sensitive than others to the toxic components in the Solanaceae.

These points lead us to question whether laminarin and seaweed extracts might result in levels of exposure to plant-defensive chemicals that could prove toxic to consumers. Might they also result in levels of exposure that are toxic to pollinators? The petition considers the toxicity of laminarin and seaweed extracts *per se*, but not the toxic properties induced in plants as they might affect humans, pollinators, or other non-target organisms. The issue of the toxicity induced by laminarin and seaweed extracts is one that would be considered by the NOSB in a decision to list laminarin and seaweed extracts as synthetic inputs, but is not considered in this decision. Not only do we believe that the manufacturing process qualifies this material as a synthetic material, there are sufficient issues of health and safety that the Board should evaluate as it moves forward in determining whether these materials should be recommended for allowance in organic production. In order to give the NOSB a better sense of the problems that could arise, we have performed a preliminary risk analysis of the use of laminarin. As stated earlier, the petition for seaweed extracts is much less specific about the mechanisms by which the substance acts, but since the extracts contain laminarin, this analysis applies to them as well.

Plant Immunity –Defenses against pathogens and herbivores

Over millions of years of association and coevolution with organisms that consume them –both animals and microorganisms—plants have developed means of defense appropriate for those who cannot run away or hide. These defenses may be **constitutive** or **inducible**. Constitutive defenses are present regardless of the presence of herbivores or disease, and include barriers such as cell walls, waxy epidermal cuticle, and bark. In addition to protecting the plant, they also play a structural role. In addition to constitutive defenses, virtually all living plant cells can detect invading pathogens and respond with inducible defenses. Inducible defenses include the production of toxic chemicals, pathogen-degrading enzymes, and deliberate cell suicide. Due to the high energy and nutrient cost of producing toxic chemicals and defensive proteins, plants often wait until pathogens are detected before producing them.[8]

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[8] Freeman, B.C. and G.A. Beattie. 2008. An Overview of Plant Defenses against Pathogens and Herbivores. *The Plant Health Instructor*. American Phytopathological Society. http://www.apsnet.org/edcenter/intropp/topics/Pages/OverviewOfPlantDiseases.aspx

Plants can recognize damage by herbivores and pathogens –by the quality and quantity of leaf damage, chemicals in insect oral secretions, oviposition fluids, and specific proteins, lipopolysaccharides, and cell wall components commonly found in microbes.[9] When they recognize an attack, they may initiate several lines of defense. The first line of defense is **basal resistance**, which fortifies plant cells against attack. If pathogens are able to suppress the basal resistance, plants may respond with a **hypersensitive response**, which is characterized by deliberate plant cell suicide at the site of infection, as well as other defenses like **RNA silencing** (digesting foreign RNA or DNA) and the production of defensive chemicals, known as phytoalexins.[10] The inducible response to insect (and other) herbivory includes **direct** and **indirect defenses.** Direct responses are those that inherently affect the susceptibility of the plant to insect attacks. Indirect defenses attract predators or parasites of the insect herbivore.[11]

Direct defenses against insect herbivores may be either anti-nutritional (barriers to access, including cell wall strengthening and repellents, and reducing the nutritional value to herbivores and pathogens by either removing essential nutrients or inhibiting digestive enzyme) or toxic (causing either physical or chemical damage).[12]

The anti-nutrition defenses may make the plant tissues less digestible to human consumers as well as insect herbivores. They may result in tougher vegetables that require more cooking, other processing, or chewing in order to extract nutrients. Plants may also use chemical defenses that injure or damage herbivores. Some cause physical damage to the insect, such as proteases, which digest proteins in the insect, causing physical damage to the gut and surrounding tissues. Other chemicals are toxic, inhibiting vital processes and possibly killing the insect.[13] The most important of these are low molecular weight compounds called **plant secondary metabolites**.[14] Breeding for plant secondary metabolites (PSMs) with repellent or toxic properties against herbivores and/or pathogens is important for the development of crops

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[9] Fürstenberg-Hägg, J., Zagrobelny, M., & Bak, S. (2013). Plant defense against insect herbivores. *International journal of molecular sciences*, *14*(5), 10242-10297.
Freeman, B.C. and G.A. Beattie. 2008. An Overview of Plant Defenses against Pathogens and Herbivores. *The Plant Health Instructor*. American Phytopathological Society. http://www.apsnet.org/edcenter/intropp/topics/Pages/OverviewOfPlantDiseases.aspx

[10] Freeman, B.C. and G.A. Beattie. 2008. An Overview of Plant Defenses against Pathogens and Herbivores. *The Plant Health Instructor*. American Phytopathological Society. http://www.apsnet.org/edcenter/intropp/topics/Pages/OverviewOfPlantDiseases.aspx
Ferrari, S. (2010). Biological elicitors of plant secondary metabolites: Mode of action and use in the production of nutraceutics. In *Bio-Farms for Nutraceuticals* (pp. 152-166). Springer US.

[11] Chen, M. S. (2008). Inducible direct plant defense against insect herbivores: a review. *Insect science*, *15*(2), 101-114.

[12] Chen, M. S. (2008). Inducible direct plant defense against insect herbivores: a review. *Insect science*, *15*(2), 101-114.

[13] Chen, M. S. (2008). Inducible direct plant defense against insect herbivores: a review. *Insect science*, *15*(2), 101-114.

[14] Both "phytoalexin" and "plant secondary metabolite" are used in a restrictive sense and a general sense to include all induced plant defensive chemicals. Here "phytoalexin" refers to a chemical used in defense against disease, "plant secondary metabolite" refers to a chemical used in defense against insect and other herbivores and "plant defense chemicals" refers to all induced plant defensive chemicals.

resistant to insects and disease. PSMs may be expressed constitutively, but are often activated or synthesized as a result of infection or herbivory. Both phytoalexins and PSMs are often made and/or stored in strategic plant tissues –those adjacent to an infection site or valuable for reproduction and survival (e.g., flowers, fruits, seeds, roots, or tubers.)[15] Breeding for insect and disease resistance based on PSMs and phytoalexins can produce crops that are toxic to humans.

Indirect defenses involve the attraction, feeding, and protection of other organisms that feed on the herbivores. This includes the production of volatile organic chemicals, extrafloral nectar, other food, and nesting or refuge sites.[16] Since the volatile organic chemicals and extrafloral nectar are possibly toxic, they will be considered below.

Plant Defensive Chemicals

As mentioned above, plant defensive chemicals (PDCs) have attracted the attention of plant breeders because of their protective function. Although it is generally believed that the main function of PDCs in plants is protection from herbivores, they often serve other purposes as well. For example, PSMs containing nitrogen are often stored in legume seeds and the nitrogen used in seedling metabolism during germination.[17]

Thousands of chemicals have been identified as PDCs, including alkaloids, benzoxazinoides, cyanogenic glucosides, glucosinolates, non-protein amino acids, phenolics, and terpenoids.[18] In addition to the large number of chemicals, many plants contain complex mixtures of plant protective chemicals, which may provide synergistic effects.[19]

There is a large diversity of PDCs known across many plant families, but the most studied have been in Solanaceae, Fabaceae, and Brassicaceae, all of which include food crops.[20] Following are some examples. Some PDCs found in Brassicaceae are spirobrassinin, cyclobrassinin, rutalexin, rapalexin A, Brassinin, brassilexin.[21] Most species in the Brassicaceae produce one or more indole glucosinolates.[22] Solanaceous plants contain glycoalkaloids including α-solanine

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[15] Acamovic, T., & Brooker, J. D. (2005). Biochemistry of plant secondary metabolites and their effects in animals. *Proceedings of the Nutrition Society*, *64*(03), 403-412.

[16] Fürstenberg-Hägg, J., Zagrobelny, M., & Bak, S. (2013). Plant defense against insect herbivores. *International journal of molecular sciences*, *14*(5), 10242-10297.

[17] Wink, M. (1988). Plant breeding: importance of plant secondary metabolites for protection against pathogens and herbivores. *Theoretical and Applied Genetics*, *75*(2), 225-233.

[18] Fürstenberg-Hägg, J., Zagrobelny, M., & Bak, S. (2013). Plant defense against insect herbivores. *International journal of molecular sciences*, *14*(5), 10242-10297.

[19] Howe, G. A., & Jander, G. (2008). Plant immunity to insect herbivores. *Annu. Rev. Plant Biol.*, *59*, 41-66.

[20] Jeandet, P., Hébrard, C., Deville, M. A., Cordelier, S., Dorey, S., Aziz, A., & Crouzet, J. (2014). Deciphering the role of phytoalexins in plant-microorganism interactions and human health. *Molecules*, *19*(11), 18033-18056. (See especially Table 1.) Ahuja, I., Kissen, R., & Bones, A. M. (2012). Phytoalexins in defense against pathogens. *Trends in plant science*, *17*(2), 73-90.

[21] Ahuja, I., Kissen, R., & Bones, A. M. (2012). Phytoalexins in defense against pathogens. *Trends in plant science*, *17*(2), 73-90.

[22] Agerbirk, N., De Vos, M., Kim, J. H., & Jander, G. (2009). Indole glucosinolate breakdown and its biological effects. *Phytochemistry Reviews*, *8*(1), 101-120.

and α-chaconine.[23] Sesquiterpene phytoalexins of the Solanaceae include rishitin, lubimin and solavetivone; and the polyacetylenic phytoalexins are falcarinol and falcarindiol.[24]
Capsidiol is found in pepper fruits.[25] Substantial amounts of nicotine are found in eggplant and sometimes tomatoes.[26] PDCs found in legumes include proteinase inhibitors, tannins, phytates, phytohemagglutinins,[27] and non-protein amino acids.[28]

Chemicals Involved in Indirect Defenses

Volatile Organic Chemicals

Plants release more than 1000 volatile organic chemicals (VOCs) to attract pollinators and predators or repel herbivores. These VOCs are mostly 6-carbon aldehydes, alcohols, esters, and terpenoids. They may be release in huge amounts when the plant is attacked by herbivores. Different feeding patterns (chewing vs. sucking) lead to the synthesis and release of different VOCs, and roots produce different chemicals from leaves.[29]

Extrafloral Nectar

Extrafloral nectar (EFN) is secreted on leaves and shoots to attract predators and parasitoids, but also serves as a repellent. Crops producing EFN include cotton, *Prunus* species (almond, cherry, peach and plum), and most legumes. EFN consists mainly of about 90% sugars, with amino acids, lipids, proteins, antioxidants, mineral nutrients and chemicals such as alkaloids, phenolics and VOCs, the composition varying widely among species and different types of nectar within the same species. EFN is not always toxic, and EFN toxic to one insect species might not affect others. The production of EFN is increased by herbivory, as well as in response to VOCs from herbivore-damaged plants.[30]

Value to humans

In addition to their value in protecting crops, humans have found PDCs to be valuable in other ways. They provide the flavor in many spices and vegetables. Herbal medicine is based on

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[23] Hopkins, J. (1995). The glycoalkaloids: naturally of interest (but a hot potato?). *Food and Chemical Toxicology*, *33*(4), 323-328.
[24] Charles, M. T., Tano, K., Asselin, A., & Arul, J. (2009). Physiological basis of UV-C induced resistance to Botrytis cinerea in tomato fruit. V. Constitutive defence enzymes and inducible pathogenesis-related proteins. *Postharvest Biology and Technology*, *51*(3), 414-424.
[25] Ahuja, I., Kissen, R., & Bones, A. M. (2012). Phytoalexins in defense against pathogens. *Trends in plant science*, *17*(2), 73-90.
[26] Domino, E. F., Hornbach, E., & Demana, T. (1993). The nicotine content of common vegetables. *New England Journal of Medicine*, *329*(6), 437-437.
[27] Sathe, S. K., Salunke, D. K., & Cheryan, M. (1984). Technology of removal of unwanted components of dry beans. *Critical Reviews in Food Science & Nutrition*, *21*(3), 263-287.
[28] Dixon, R. A., & Sumner, L. W. (2003). Legume natural products: understanding and manipulating complex pathways for human and animal health. *Plant Physiology*, *131*(3), 878-885.
[29] Fürstenberg-Hägg, J., Zagrobelny, M., & Bak, S. (2013). Plant defense against insect herbivores. *International journal of molecular sciences*, *14*(5), 10242-10297.
[30] Fürstenberg-Hägg, J., Zagrobelny, M., & Bak, S. (2013). Plant defense against insect herbivores. *International journal of molecular sciences*, *14*(5), 10242-10297.

PDCs.[31] They are considered valuable phytonutrients, providing antioxidant, anti-inflammatory, and immune system support functions. It has been suggested that because of higher levels of PSMs, "[O]rganic plant foods may in fact benefit human health more than corresponding conventional ones."[32] The evidence that consumption of Brassica vegetables, (broccoli, cabbage, kale, mustard greens, Brussels sprouts, and cauliflower) reduces the risk of several types of cancer, is attributed to the presence of several PDCs.[33] The recognition of the many values of PSMs has led to attempts to produce them using cell cultures, stimulated by elicitors.[34]

Toxicity to humans

Despite their value in food and medicine, many PDCs are toxic to humans.[35] A number of food plants are poisonous, but generally people consume non-poisonous parts (tomatoes, rhubarb, brassicas), or process the crop in a way to remove the poison (cassava, beans). However, some PDCs occur in food crops at levels that border on human toxicity and may actually be fatal under some conditions.

Potatoes contain significant quantities of the glycoalkaloids α-solanine and α-chaconine.[36] The glycoalkaloids are produced in response to stress, which may include exposure to light, mechanical damage, improper storage conditions, either as a tuber or after partial food processing, sprouting,[37] infection with disease,[38] and insecticide exposure.[39] Glycoalkaloids in potatoes are known to have resulted in many cases of human poisoning, sometimes fatal, from the consumption of greened or damaged tubers.[40] Selection for potatoes resistant to Colorado potato beetle resulted in potatoes that were poisonous to humans.[41] Thus PDCs in potatoes are close to the threshold of human toxicity.

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[31] Bourgaud, F., Gravot, A., Milesi, S., & Gontier, E. (2001). Production of plant secondary metabolites: a historical perspective. *Plant science*, *161*(5), 839-851.

[32] Brandt, K., & Mølgaard, J. P. (2001). Organic agriculture: does it enhance or reduce the nutritional value of plant foods? *Journal of the Science of Food and Agriculture*, *81*(9), 924-931.

[33] Jahangir, M., Abdel-Farid, I. B., Kim, H. K., Choi, Y. H., & Verpoorte, R. (2009). Healthy and unhealthy plants: The effect of stress on the metabolism of Brassicaceae. *Environmental and Experimental Botany*, *67*(1), 23-33.

[34] Bourgaud, F., Gravot, A., Milesi, S., & Gontier, E. (2001). Production of plant secondary metabolites: a historical perspective. *Plant science*, *161*(5), 839-851.

[35] See a short of poisonous plants and their toxic PSMs list at http://www.ansci.cornell.edu/plants/php/plants.php?action=display&ispecies=human

[36] Hopkins, J. (1995). The glycoalkaloids: naturally of interest (but a hot potato?). *Food and Chemical Toxicology*, *33*(4), 323-328.

[37] World Health Organization. Solanine and chaconine. WHO Food Additive Series 30.

[38] Ahuja, I., Kissen, R., & Bones, A. M. (2012). Phytoalexins in defense against pathogens. *Trends in plant science*, *17*(2), 73-90.

[39] Zarzecka, K., Gugala, M., & Mystkowska, I. (2013). Glycoalkaloid contents in potato leaves and tubers as influenced by insecticide application. *Plant, Soil and Environment*, *59*(4), 183-188.

[40] World Health Organization. Solanine and chaconine. WHO Food Additive Series 30.

[41] Wink, M. (1988). Plant breeding: importance of plant secondary metabolites for protection against pathogens and herbivores. *Theoretical and Applied Genetics*, *75*(2), 225-233.

Other Solanaceous plants contain PDCs that are toxic to humans. Eggplants contain a significant amount of nicotine, and tomatoes a smaller amount.[42] Solanaceous vegetables have been implicated in debilitating cases of arthritis.[43] One medical researcher summarized,

> The Solanaceae cause at least two known health problems. They contain cholinesterase inhibiting glycoalkaloids and steroids including, among others, the drugs solanine in potato and eggplant, tomatine in tomato, nicotine in tobacco, and capsaicin in garden peppers. When these inhibitors accumulate in the body, alone or with other cholinesterase inhibitors such as caffeine or food impurities containing systemic cholinesterase inhibiting pesticides, the result may be a paralytic-like muscle spasm, aches, pains, tenderness, inflammation, and stiff body movements. These symptoms may dissipate in a few hours or days if ingestion is stopped; people vary in sensitivity. The second problem is the ability of the Solanaceae (those species analyzed) to develop naturally the very active metabolite of vitamin D_3 (1a25 dihydroxycholecalciferol) that results in calcinosis of soft tissues, ligaments, and tendons, mineralization in walls of major arteries and veins, and osteopetrosis and related pathology in livestock. In time, there is progressive lameness and extended uselessness, with eventual death of livestock. [44]

In Fabaceae (legumes), some varieties of lima beans contain cyanogenic glycosides equivalent to more than 2000 ppm hydrogen cyanide, causing some countries to prohibit import of lima beans with levels over 200 ppm.[45] Excessive consumption of legumes in the genus Lathyrus (chickling peas or grass peas) causes the neurological disease known as lathyrism as a result of 3-N-oxalyl-L-2,3-diaminopropanoic acid (ODPA), a non-protein amino acid in the peas.[46]

Finally, although many PDCs are found in the Brassicaceae, the most prevalent are the glucosinolates, found in most members of the family. The distribution of specific glucosinolates varies among Brassica vegetables. Some glucosinolates are responsible for the health-giving features of the cabbage family, such as protection against cancer.[47] However, others are toxic to humans and livestock.[48] For example, progoitrin is degraded to goitrin, a potent goitrogen

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[42] Domino, E. F., Hornbach, E., & Demana, T. (1993). The nicotine content of common vegetables. *New England Journal of Medicine*, *329*(6), 437-437.
[43] N.F. Childers, Ph.D. and M.S. Margoles, M.D. (1993). An Apparent Relation of Nightshades (*Solanaceae*) to Arthritis Journal of Neurological and Orthopedic Medical Surgery 12:227-231.
[44] N.F. Childers, Ph.D. and M.S. Margoles, M.D. (1993). An Apparent Relation of Nightshades (*Solanaceae*) to Arthritis Journal of Neurological and Orthopedic Medical Surgery 12:227-231.
[45] Fenwick, G. R. (1986). The natural toxicants of common foods for animals and man. In *Proc. Nutr. Soc. Aust* (Vol. 11, pp. 11-23).
[46] Dixon, R. A., & Sumner, L. W. (2003). Legume natural products: understanding and manipulating complex pathways for human and animal health. *Plant Physiology*, *131*(3), 878-885.
[47] Jahangir, M., Abdel-Farid, I. B., Kim, H. K., Choi, Y. H., & Verpoorte, R. (2009). Healthy and unhealthy plants: The effect of stress on the metabolism of Brassicaceae. *Environmental and Experimental Botany*, *67*(1), 23-33.
[48] Zukalová, H., & Vasak, J. (2002). The role and effects of glucosinolates of Brassica species-a review. *Rostlinna Vyroba*, *48*(4), 175-180.

that binds to iodine, preventing its uptake by the body.[49] Goitrin can also be nitrosated if in contact with nitrites in the gastrointestinal tract, producing the mutagenic compound N-nitrosooxazolidone.[50] Jahangir et al conclude, "The effects of specific glucosinolate degradation products on individual organisms vary and are not always known. If used in excessive quantity, many of these compounds can be highly toxic."[51]

Elicitors of Plant Immunity

Elicitors are chemicals from various sources that induce plant defenses, including phytoalexins and PSMs. They include VOCs released by plants as well as materials like laminarin, salicylic acid, and chitosan that may applied to plants.[52] All of these can elicit a cascade of events, resulting in direct defense responses, including the accumulation of PDCs.[53] The plant defenses modulated by laminarin depend on plant genotypes rather than the degree of innate resistance.[54]

The crops for which laminarin is currently registered include some of the vegetables examined above –tomatoes, eggplant, and cole crops (Brassicaceae). The discussion above touches on some of the PDCs that are toxic to humans that could be elicited by use of laminarin on these crops. A technical review of laminarin could reveal others, and to some extent remove some of the uncertainty around which PDCs are increased by application of laminarin and by how much. However, as indicated above, there is still much uncertainty.

Laminarin is not currently registered for use on potatoes, which would be the most problematic use because of the already low margin of safety. Legumes are also not currently included. However, potatoes and legumes are susceptible to diseases that could benefit from an increase in resistance.[55] Since EPA's review of laminarin did not examine the toxicity of the plant

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[49] Zukalová, H., & Vasak, J. (2002). The role and effects of glucosinolates of Brassica species-a review. *Rostlinna Vyroba*, *48*(4), 175-180.

[50] Jahangir, M., Abdel-Farid, I. B., Kim, H. K., Choi, Y. H., & Verpoorte, R. (2009). Healthy and unhealthy plants: The effect of stress on the metabolism of Brassicaceae. *Environmental and Experimental Botany*, *67*(1), 23-33.

[51] Jahangir, M., Abdel-Farid, I. B., Kim, H. K., Choi, Y. H., & Verpoorte, R. (2009). Healthy and unhealthy plants: The effect of stress on the metabolism of Brassicaceae. *Environmental and Experimental Botany*, *67*(1), 23-33.

[52] Zhao, J., Davis, L. C., & Verpoorte, R. (2005). Elicitor signal transduction leading to production of plant secondary metabolites. *Biotechnology advances*, *23*(4), 283-333.

[53] Ferrari, S. (2010). Biological elicitors of plant secondary metabolites: Mode of action and use in the production of nutraceutics. In *Bio-Farms for Nutraceuticals* (pp. 152-166). Springer US.

[54] Desender, S., Klarzynski, O., Potin, P., Barzic, M. R., Andrivon, D., & Val, F. (2006). Lipopolysaccharides of Pectobacterium atrosepticum and Pseudomonas corrugata induce different defence response patterns in tobacco, tomato, and potato. *Plant Biology*, *8*(5), 636-645.

[55] Wu, G., Shortt, B. J., Lawrence, E. B., Levine, E. B., Fitzsimmons, K. C., & Shah, D. M. (1995). Disease resistance conferred by expression of a gene encoding H2O2-generating glucose oxidase in transgenic potato plants. *The Plant Cell*, *7*(9), 1357-1368. Miklas, P. N., Kelly, J. D., Beebe, S. E., & Blair, M. W. (2006). Common bean breeding for resistance against biotic and abiotic stresses: from classical to MAS breeding. *Euphytica*, *147*(1-2), 105-131.

defenses induced by laminarin,[56] it is not unreasonable to assume that laminarin might sometime be registered on these crops as well, as are seaweed extracts.[57]

The application of elicitors has outpaced the science. There are many benefits to using elicitors of plant immunity, but there are also some severe risks. Many of the secondary metabolites produced in response to laminarin or other seaweed extracts, while possibly toxic to insects and pathogens, will be innocuous to humans. In many cases, they may increase the nutritional value of the crop. However, the science needs to ensure that its use will not result in the overproduction of secondary metabolites like poisonous glycoalkaloids found in Solanaceous crops and toxic glucosinolates in brassicas before their use in organic production is allowed.

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[56] EPA, p. 34 of Laminarin application (Biopesticide Registrayion Action Document, p. 4): "Because Laminarin is considered to be "toxicologically innocuous," no residue studies are required to support an exemption from the requirement of a tolerance. Laminarin's low toxicity profile notwithstanding, another justification for an exemption from the requirement of a tolerance is the minimal likelihood of residues for this biochemical pesticide."

[57] See, for example, Sharma, H. S., Fleming, C., Selby, C., Rao, J. R., & Martin, T. (2014). Plant biostimulants: a review on the processing of macroalgae and use of extracts for crop management to reduce abiotic and biotic stresses. *Journal of applied phycology*, *26*(1), 465-490.