



Genetically Engineered Oil Seed Crops and Novel Terrestrial Nutrients: Ethical Considerations

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Abstract

Genetically engineered (GE) organisms have been at the center of ethical debates among the public and regulators over their potential risks and benefits to the environment and society. Unlike the currently commercial GE crops that express resistance or tolerance to pesticides or herbicides, a new GE crop produces two bioactive nutrients (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) that heretofore have largely been produced only in aquatic environments. This represents a novel category of risk to ecosystem functioning. The present paper describes why growing oilseed crops engineered to produce EPA and DHA means introducing into a terrestrial ecosystem a pair of highly bioactive nutrients that are novel to terrestrial ecosystems and why that may have ecological and physiological consequences. More importantly perhaps, this paper argues that discussion of this novel risk represents an opportunity to examine the way the debate over genetically modified crops is being conducted.

Keywords Ethics · Genetic engineering · Environmental risk · Oil seed crops · Long-chain polyunsaturated fatty acids · EPA · DHA

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Introduction

The State of the Debate on Genetically Engineered Foods and Crops

Among all forms of biotechnology to have entered the public eye over the last several decades, genetically engineered (GE) organisms stand apart for the amount of controversy they have engendered. Advocates argue that experimenting with genetic modification of foodstuffs is at least ethically permissible, and perhaps ethically required because our burgeoning human population is placing increasing demands on our planet to supply us with needed nutrients, pharmaceuticals, and industrial chemicals (see, e.g., Borlaug 2000; Giri and Tyagi 2016). Critics argue that such experimentation is unethical (see, e.g., Center for Food Safety 2016; MacDonald 2018; Trillium Asset Management 2018). Underpinning at least part of this ethical debate is a scientific and technological debate. Advocates of GE crops believe that developing such crops is relatively safe, and promises to help humanity grow more and better quality food with fewer inputs (Francis et al. 2017). Critics worry that GE crops pose risks to normal ecosystem functioning, reduce biodiversity, impoverish farmers in developing countries, pose risks to human health, and perhaps constitute a violation of the natural order (Carpenter 2011; Bawa and Anilakumar 2013; Lucht 2015). Of course, it must be acknowledged that the style and degree of advocacy and critique varies enormously; there are cautious advocates just as there are moderate critics.

Forming a reasoned ethical opinion about this issue requires some familiarity with the current scientific consensus. To begin, what does science say about the safety of genetically engineered foods for human consumption? The broad consensus among scientists is that genetically engineered foods per se pose no special risks for human consumption (for an overview, see National Academy of Sciences 2016). Certain risks—such as allergenicity (Marsteller et al., 2016) resulting from inserting genes from species known to be allergenic, such as the peanut—have been documented, and the approval processes for novel foods in countries such as Canada (Canada Food Inspection Agency and Health Canada; CFIA 2016) and the US (Food and Drug Administration; FDA 2017) require documentation that such risks have been taken into consideration and that steps have been taken to avoid them. Such exceptions aside, the broad if not quite unanimous (see Hilbeck et al. 2015) scientific consensus is that GE foods are safe to eat, in that they pose no greater intrinsic risk than foods that have been genetically altered by traditional selective breeding and hybridization or by other modern techniques, such as targeted genome modifications (Chen and Gao 2014).

The other category of potential risks that must be examined consists of a range of possible environmental and ecological repercussions. Such risks include possible negative effects on other species from exposure to, and/or consumption of, GE crops (e.g. monarch butterfly larvae and stream dwelling caddisfly in relation to Bt corn pollen and corn byproducts, respectively; Losey et al. 1999 and Rosi-Marshall et al. 2007, respectively), the risk of cross-pollination with (and hence “pollution” of) other wild and domesticated plant species (Snow 2002; Warwick

et al. 2008), and the risk that GE crops bred to be hardy in a variety of ways may ultimately result in “superweeds” (either directly or through cross pollination) (Kling 1996).

What about the benefits of GE crops? It is easier at this point to describe the benefits *sought* via various instances of genetic engineering. These range from genetic modifications that aim to benefit farmers (e.g., herbicide- and drought tolerance) through to genetic modifications that aim to benefit suppliers and consumers (e.g., apples that do not oxidize when their flesh is exposed to air; Cressey 2013) to genetic modifications that aim to benefit nearly everyone along the value chain (such as greater crop yield). However, the extent to which such benefits have been realized remains stubbornly controversial (See Kathage and Qaim 2012; Klümper and Qaim 2014; National Academies of Sciences, Engineering, and Medicine 2016).

Evidence for documented benefits from GE crops is mixed, in part because there are different ways to measure such benefits. For example, when rice is modified to express higher levels of beta-carotene in order to combat blindness associated with Vitamin A deficiency (Ye et al. 2000), do we best measure success chemically, nutritionally, or epidemiologically? When a crop species is modified to tolerate a herbicide such as Glyphosate (Shah et al. 1986), do we demonstrate success by reasoning that this will allow lower rates of use of herbicides “in theory,” or by seeking to demonstrate it under laboratory conditions, or in test fields, or over years of practice by hundreds of farmers? In this regard, we note that Powles (2008) has suggested that the introduction of Glyphosate resistant crops has resulted in more, rather than less, Glyphosate being used. On the other hand, even if more Glyphosate is used, that may be a substitute for other, more toxic herbicides such as atrazine (see Coupe and Capel 2016).

Some have argued that the value of GE crops lies not just in their present characteristics, but also in the implied trajectory for further crop improvement (e.g., enhancing drought tolerance in crops in anticipation of climate change; Franks et al. 2015). The reasoning is that even if present day genetic modifications have resulted in relatively limited success, this does not mean that success will never come. Advocates argue that these are still early years, and better things lie down the road. For example, initial efforts, during the 1990’s, at modifying rice to contain more beta-carotene (“golden rice”) met with only modest success; in 2015, “Golden Rice 2” was announced, featuring a level of beta-carotene an order of magnitude higher and clearly at nutritionally significant levels (Jacchia et al. 2015). Yet Golden Rice is, at time of writing, still not being grown commercially for its intended purpose (Everding 2016). Indeed, production of Golden Rice has only recently—in early 2018—been approved by the governments of Canada, Australia, New Zealand, and the United States (Coghlan 2018).

It is also worth noting the ethical asymmetry between evidence of risk and evidence of benefit. In a society that values freedom, the absence of substantial evidence of risk associated with a given activity may license undertaking that activity, even in the absence of substantial evidence for benefit. Of course, absence of evidence of risk does not generally constitute evidence that there is no risk, especially not in a context in which too little effort has been expended in seeking appropriate information. And while considerable effort has been expended in establishing the

safety of genetically engineered foods for human consumption (but see Diels et al. 2011), considerably less effort has gone into examining the potential for GE organisms to have broader ecological effects. Further, even where there are known risks, the activities producing those risks may still be ethically justified if the benefits of those activities are sufficiently large, and if the distribution of risks and benefits is reasonably fair. Ethical assessment of risks, in other words, is complex.

It is worth mentioning a mistake that both advocates and critics have committed from time to time when attempting to characterize the benefits and hazards of GE crops per se. Anyone familiar with the debate over GE crops and GE foods will have witnessed many instances in which an advocate blithely proclaims that ‘GE crops produce greater yield’ (even though not all are designed to do so!), along with many instances in which a critic casually states that ‘GE crops reduce genetic diversity’ as if that applies to every GE variety or to GE crops as such. It is worth reminding ourselves that risks and benefits are generally associated with specific traits (or perhaps to specific instantiations of traits) rather than more broadly to an entire species or to GE crops as a whole.

Finally, it should be pointed out that not all ethical controversies regarding GE crops or GE foods pertain to risks and benefits and, such being the case, a consequentialist focus on risks and benefits is not the only way of framing an ethical question such as this one. An alternative is to frame ethical issues in terms of rights and duties. Thus, some critics have argued not that GE foods are unsafe, but that consumers have a ‘right to know what they are eating.’ But as MacDonald and Whellams (2007) argue, while such rights claims often have substantial rhetorical force, it is much harder to specify just what those claims are *grounded* in—that is, what compelling interest such a proposed right is intended to honor and protect. MacDonald and Whellams further argue that the right to know the genetic provenance of one’s food is not in any obvious way ethically akin to other instances of the ‘right to know,’ such as the right of the accused to know what they are accused of, and the right of patients to know their medical diagnoses. Rights must be grounded in a compelling interest, and such a compelling interest can be hard to identify in the case of GE foods.

Perhaps as a result of the above debates, the public and regulators are often deeply divided over the ethics of GE crop introductions. A substantial proportion of consumers in both North America and Europe have adopted a strongly anti-GE stance, while many others seem to consider it a non-issue. In addition, European regulators have generally imposed relatively strict regulations, whereas regulators in North America have adopted a relatively permissive stance (Ishii and Araki 2016). One issue may be that the private sector has exerted increasing dominance in advancing new biotechnologies, and the public sector has had to invest a significant share of financial resources in enhancing biotechnological capacities in public institutions, in order to evaluate and respond to the challenges posed by the private sector in attempts to generate revenue (Altieri and Rosset 1999). The problem is that research at public institutions increasingly reflects the interests of private funders at the expense of research for the public good, such as research into biological control, sustainable production systems and general agro-ecological techniques, and due-diligence research, such as risk assessments of developing technologies. In response,

Krimsky and Wrubel (1996) and Altieri and Rosset (1999) argue that the public must therefore request more research on alternatives to biotechnology by universities and other public organizations.

The Hixson et al. Result

A recent study by Hixson and colleagues (2016)¹ provides initial evidence of an entirely new category of risks related to the proliferation of GE crops. In brief, they found that two specific nutrients (the omega-3 [or n-3], long-chain, polyunsaturated fatty acids or LC-PUFAs, namely EPA [eicosapentaenoic acid; 20:5n-3] and DHA [docosahexaenoic acid; 22:6n-3]) present in certain GE oilseed plants caused growth defects in a common moth species. This is significant because a number of efforts are underway to genetically modify crop plant species (e.g., camelina and canola) to manifest high concentrations of EPA and DHA; these crops are being developed primarily, at least at the outset, for use in finfish aquaculture feeds.

In the study carried out by Hixson and colleagues, canola oil was replaced with pure algal EPA and DHA in artificial diets for the cabbage white butterfly (*Pieris rapae*). Increasing levels of EPA and DHA, up to a maximum (which mimicked EPA + DHA contents that could be found in a GE oilseed crop plant), resulted in progressively heavier adults, with smaller wings and a higher frequency of wing deformities, i.e., wilted, folded, underdeveloped, and/or non-functioning wings. From these preliminary results the authors concluded that further studies are warranted in order to more fully understand the impacts of these highly bioactive fatty acids on herbivorous terrestrial insects and, in particular, on those that may consume relevant tissues of GE oilseed plants.

LC-PUFAs such as EPA and DHA are essential to the health of both aquatic and terrestrial organisms. However, they are far more abundant in aquatic environments—indeed, they are virtually (but not entirely: e.g., they are found in some mosses) absent in terrestrial primary producers (Colombo et al. 2017; Hixson et al. 2015; Twining et al. 2016). Efforts to genetically engineer oilseed crops to be rich in LC-PUFAs like EPA and DHA are grounded in the commercial importance of LC-PUFA, particularly for the production of aquaculture feeds. The aquafeed industry consumes in excess of 750,000 metric tons of fish oil per year (Hixson 2014). Quotas to protect wild fish stocks have been set at an annual global harvest of fish oils of ~ 1 million metric tons, of which <20% is used for direct human nutrition (Henriques et al. 2014) and approximately 75% used for aquafeeds (Tacon and Metian 2015). As an oilseed crop, camelina can yield 0.75 metric tons of oil per hectare (Napier et al. 2015). In order to fully replace fish oil with GE camelina oil in aquafeeds, about 1 million hectares would be required globally to satisfy the demand. In comparison, the current annual Canadian sowing of related oilseeds such as canola is in excess of 9 million hectares (Statistics Canada 2017). This is important, because it suggests the possibility that very large quantities of crops manifesting very high levels

¹ Stefanie Colombo, a co-author on this paper, was known as Stefanie Hixson in previous publications.

of EPA and DHA could be grown in the foreseeable future in an attempt to offset reductions in fish oil harvests. This implies the introduction of very high levels of these bioactive substances to terrestrial ecosystems—ecosystems, again, in which they currently occur only at very low levels.

Novel Category of Risk

While there are multiple examples of nutritionally and pharmacologically-enhanced crops, for the most part such enhancements are the result of conventional plant breeding and selection. However, it is increasingly common for GE crops to be developed that feature enhanced nutrient profiles (e.g., golden rice) or that produce vaccines and chemotherapeutants, although most of these have not reached commercialization and industrial scale production (Newell-McGloughlin 2008). But importantly, traits such as enhanced nutrient levels are not normally entirely novel to terrestrial plants, as the same nutrients are found in other terrestrial plants. For example, the beta-carotene manifested by Golden Rice is not abundant in other strains of rice, but it is abundant in many other food crops. In contrast, the oilseed crops containing EPA and DHA amount to a new category of GE crop because these bioactive compounds are not known to be produced by terrestrial crop plants. These two LC-PUFAs are known to be critically involved in key physiological functions in invertebrates and vertebrates (including humans); and, in particular, EPA and DHA are known for their generally positive effects on vertebrate cardiovascular and neurological health (reviewed by Bazinet and Laye 2014; Calder 2015; Mozaffarian and Wu 2012). But, as previously noted, EPA and DHA, which are abundant in aquatic ecosystems, are not known to be produced by any current terrestrial crops (Colombo et al. 2017; Hixson et al. 2015; Twining et al. 2016). The resulting fatty acid profile of the seed oil produced by the GE crop, compared to the wild-type cultivar, is closer to that of fish oil, because it contains EPA and DHA at levels similar to fish oil. This is crucial commercially as a viable terrestrial source of EPA and DHA would significantly reduce dependency on wild fisheries.

These facts help to clarify the significance of the Hixson and colleagues study. If that study can be replicated, what it implies is not just the discovery of a novel concern with regard to a specific GE crop, or even with regard to GE crops in general. Instead, it is the discovery of an entirely new *category* of risk related to GE crops. The Hixson and colleagues study provides tentative serendipitous confirmation of a problem that could in principle have been foreseen, but which the authors of that study were not in fact working on. That problem lies in the fact that growing oilseed crops engineered to produce EPA and DHA means introducing to a terrestrial ecosystem a pair of highly bioactive nutrients that are, for the most part, foreign to terrestrial ecosystems at the level of primary producers and their herbivorous insect consumers. The potential ecological and evolutionary consequences of introducing these GE crops, including potential effects on terrestrial insects, outcrossing and crop gene flow, and broad effects on terrestrial ecosystems, has been discussed in a recent review (Colombo et al. 2018).

The introduction of EPA and DHA into terrestrial ecosystems at the level of primary producers would be less worrisome were it not for two factors. First, EPA and DHA are known to be highly bioactive molecules in ways that generally enhance the fitness of both invertebrates and vertebrates. Aquatic invertebrates, for example, demonstrate increased growth rates and reproductive success when they have access to omega-3 LC-PUFAs like EPA and DHA (Arendt et al. 2005; Müller-Navarra et al. 2000; Wacker et al. 2002). Similarly, vertebrates, such as fish (e.g., Izquierdo et al. 2001; Watanabe 1993) and birds (e.g. Dodson et al. 2016; Twining et al. 2016), exhibit optimal growth and reproduction when they have access to adequate amounts of EPA and/or DHA in their diets. Second, EPA and DHA are *virtually* absent from terrestrial ecosystems—that is, absent in any significant quantities. In fact, EPA and DHA are the main drivers of the differences in fatty acid content observed between aquatic and terrestrial primary producers (Colombo et al. 2017; Hixson et al. 2015). However, as mentioned above, small quantities are found in certain moss species (e.g. *Physcomitrella patens*; Beike et al. 2014), and both EPA and DHA can be synthesized, from 18-carbon omega-3 fatty acid precursors, in small quantities by animals (including humans). In summary, the quantities of EPA and DHA in other terrestrial sources is trivial when compared to the concentration of those substances in the oilseed crops currently being engineered to express them.

To some extent, the risk here is comparable to the risks posed by attempts to produce pharmaceuticals in GE crop plants. This practice—variously known as “pharming” or “biofarming”—involves engineering a crop plant (for example, tobacco) to manifest, in its leaves for example, a valued pharmaceutical product, such as insulin or the cancer drug Trastuzumab (the generic name for Herceptin). Not surprisingly, such attempts have been subject to substantial scrutiny. The primary concern in such cases has been the possibility of pharmaceutical-laden vegetable matter making its way into the human food chain.

In some cases, pharming means introducing an entirely new substance (such as Trastuzumab, a monoclonal antibody) into the environment. However, pharming has generally been aimed at producing novel substances in relatively small *laboratory* quantities, rather than in *industrial* quantities. In contrast, companies now seeking to grow GE oilseed crops aim ultimately to harvest very large quantities in order to supply EPA and DHA on an industrial scale, whether for use in food stock for the aquaculture industry or for use in human nutritional supplements (Craze 2016).

Introducing EPA and DHA into the terrestrial ecosystem is perhaps even more worrisome than introducing GE plants containing proteins such as Trastuzumab might be. For one thing, EPA and DHA are highly bioactive and are implicated in the metabolic processes of a very large number of terrestrial vertebrates and invertebrates. The introduction and transfer of these novel bioactive fatty acids into the agro-ecosystem may have cascading effects throughout terrestrial food webs. For example, in aquatic invertebrates, dietary EPA and DHA are well known to stimulate growth and reproduction (Arts et al. 2009). If the same effects of EPA and DHA occur in terrestrial invertebrates as are observed in aquatic invertebrates, then the growth rate, reproductive success, and/or survivability of crop pests may increase, for example. Further, in aquatic ecosystems EPA and DHA are transferred from the bottom of the food chain to the top and selectively retained, as these fatty acids are

conserved for specialized physiologically-related functions (Colombo et al. 2017; Hixson et al. 2015; Kainz et al. 2004). Production of EPA and DHA by terrestrial crops thus has the potential to impact not only primary consumers (e.g., herbivorous insects, rodents, birds), but also their secondary consumers (e.g., insectivorous birds, bats, and insects etc.), and tertiary consumers (e.g., foxes, predatory birds, etc.).

Indeed, the fact that EPA and DHA play such an important (and generally positive) role in invertebrate biology was central to Hixson and colleagues' motivation to carry out their experiments in the first place.

Does GE Matter Here?

It is crucial to note that the problem described here lies in the fact that EPA and DHA are being produced by terrestrial crops, *and not in whether or not they are the result of GE*. The results of the study by Hixson and colleagues (2016) suggests that introducing EPA and DHA to terrestrial ecosystems could have significant impacts, regardless of whether the source was a GE crop, a hybrid crop, or a crop developed through radiation mutagenesis. In fact, the worry would be the same were humans—for whatever reason, and however implausibly—to simply decide to spray large quantities of EPA and DHA across the landscape.

The potential danger lies in the introduction of novel bioactive nutrients; the fact that GE crops are a potential *source* is interesting here, but not essential. Hence the present paper should not be seen as a criticism of GE crops or of genetic engineering in general. Indeed, it is more accurately read primarily as a warning regarding the introduction (by whatever means) of a novel bioactive nutrient or nutrients. The present paper is only secondarily a note of caution regarding the possibility that GE could be one *mechanism* for introducing such novel, and potentially worrisome, bioactive nutrients.

More to the point, the fact that these genetically engineered oilseed crops contain EPA and DHA is only incidentally connected to the specific mechanism used to achieve this result, namely insertion of foreign transgenes into the genome of crops to express traits or phenotypes that produce certain qualities or nutrients. What matters is that these plants *now have that trait*. It is the trait that is potentially worrisome, not the genetic modification per se.

Recommendations

For Scientists

The most obvious need here is for additional scientific study. The addition of this trait (EPA and DHA synthesis by terrestrial oil-seed crop plants) significantly enhances the nutritional value of the seed. In a basic sense, EPA and DHA are critically involved in maintaining structure and fluidity in cell membranes (Arts and Kohler 2009) and EPA is a precursor of anti-inflammatory eicosanoids. This has

key effects on physiological functions in both invertebrates and vertebrates, in particular the overall positive effects that EPA and DHA have on vertebrate cardiovascular and neurological health. In aquatic invertebrates, EPA and DHA are known to enhance growth, reproduction rates, and overall survival. With regard to terrestrial animals that do not normally have access to these fatty acids, we need to understand the potential physiological effects caused by the consumption of EPA and DHA. To begin with, attempts must be made to replicate the Hixson and colleagues study of the effects of EPA and DHA ingestion on the growth and development of *Pieris rapae* and more importantly in other herbivorous insects that consume seeds exclusively from oilseed crops. In addition, it is important also to ascertain whether EPA and DHA are produced in plant tissues other than the seed of GE crops, which would determine whether only seed-specialists would consume these fatty acids, or if all pests of this crop (that forage on leaves, stems, roots, and shoots) would be subject to consuming EPA and DHA. Second, tests should be carried out using the GE crops, if those can be obtained, rather than the artificial diets that Hixson and colleagues were relegated to using. Eventually, studies should be designed to examine cross-trophic-system effects—e.g., by feeding invertebrates raised on GE oilseed plants to vertebrates. Ideally, studies could be conducted with GE canola and camelina, along with a variety of their insect pests, in an insect quarantine facility. This would provide more realistic data that would help clarify the real risk.

For Regulators

Given the need for evidence-based regulation, it seems clear that regulators should encourage scientists, by whatever mechanisms available to them, to engage in the kinds of science that would provide the relevant information. In the meantime, given the information already available, caution is warranted with regard to crops genetically engineered to express EPA and DHA, even if future studies fail to replicate the Hixson and colleagues result. Enough is already known about the biological role and likely effects of EPA and DHA to allow the formulation of an informed hypothesis about the potential impact of allowing massive quantities of those substances to be introduced to terrestrial ecosystems for the first time. The Hixson and colleagues result was, from one perspective, merely the stimulus that served to raise questions about the wisdom of introducing a novel bioactive nutrient, in large quantities, into the terrestrial ecosystem. Even without that result, there would be sufficient reason to worry about the introduction of a novel, bioactive nutrient into the terrestrial ecosystem.

In particular, caution is appropriate in the approval of field tests of crops genetically engineered to express long-chain omega-3 polyunsaturated fatty acids. In principle, it would be safer initially to require trials to be conducted in greenhouse environments until science can provide reasonable reassurance that such fatty acids are unlikely to have substantial deleterious effects in terrestrial ecosystems.

The foreseeable risks here, while still hypothetical, are considerable. And while they are not likely to be direct risks to human health, they may have considerable

human impact nonetheless. After all, ecological effects stand to have an impact on agriculture, which in turn can have massive economic effects.

For the Public

At present, there is no reason for the public to be alarmed about the issues discussed here. To begin, the Hixson and colleagues study is but a single, small study (see the recommendation above regarding the need for further studies.) And even if that result is replicated and found to be robust, the fact that genetically engineered oil-seed has deleterious developmental effects on one or more species of invertebrates does not immediately signal any risk to human health. The public would be well advised to await further insight from scientists and regulators.

Post Script: The Politicization of Science

Finally, it is worth noting the way that public and scholarly *discussion* of the Hixson and colleagues study exemplifies the extreme polarization of discussion of GE crops more generally. The paper by Hixson and colleagues is appropriately cautious: it presents results from a very small trial, admits methodological limitations, and suggests that the results warrant additional study. But upon publication, the study was immediately taken up by advocates and critics alike for their respective political purposes. Critics of GE crops (Robinson 2016) held up the study as evidence of the grave dangers of meddling with nature. Advocates, on the other hand, immediately criticized the study and hypothesized that the authors themselves had a secret agenda (Lynas, 2016). And indeed, this is quite typical of the tone of much of the debate regarding biotechnology generally, and genetic engineering of crops more specifically, in recent years. This sort of polarization is regrettable, to say the least. Mampuy and Brom (2015) point out that much of the debate over genetically modified crops follows a consistent pattern, one that begins with the publication of a scientific study:

Discussions following the publication of an alarming study roughly follow the same pattern. After publication, the discussion starts within the scientific community with detailed arguments about the research design and methodologies used. Soon however, the audience widens and the discussion drifts off towards arguments about GMOs in general and their role in agricultural practice... Finally, prejudices, personal attacks and accusations about conflicts of interest start to increasingly influence the debate that ends in a deadlock without a definitive outcome. (pp. 907–908)

Discussion of the Hixson and colleagues paper has followed this pattern quite closely. And this is quite obviously a shame. The paper is far from alarmist, but nor are Hixson and colleagues apologists for the bio-agriculture industry. It is an attempt to add one, admittedly small, piece to a much larger puzzle. It ought to be welcomed as such by both sides of the debate.

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