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Submission I on the Assessment Report for **APPLICATION A1018 FOOD DERIVED FROM HIGH OLEIC ACID SOYBEAN DP-305423-1**

Submitted to Food Standards Australia/New Zealand (FSANZ)

by

Submitter: Centre for Integrated Research in Biosafety
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Summary of key findings

We conclude from the FSANZ Assessment of high oleic acid soybean DP-305423-1 that the preferred action is Option 1: reject, unless further information from both FSANZ and the Applicant can address the serious uncertainties in cost/benefit and safety identified in this submission[1].

The charges applied by FSANZ to access the scientific dossier of GM applications are prohibitive and prevent full and open consultation at least with this public Centre, and we believe with the public in general.

We found the FSANZ cost/benefit analysis to be flawed and devoid of quantification. FSANZ have inappropriately relied on labelling to preserve choice for consumers wishing to avoid GM soybeans and their products. Labelling does not extend to these products if they are used in restaurants, cafes and takeaways (which are the Applicant's priority markets), are used as feed for animals in the human food supply, or contaminate "GM-free" foods inadvertently up to a concentration of 1%. The costs to consumers avoiding this product, even using labelling to moderate their exposure, will in our estimation significantly exceed any hypothetical cost, both financially and qualitatively (as in product diversity), to Australia New Zealand consumers from application rejection.

FSANZ have not addressed several important health and safety issues with DP-305423-1, including the combinatorial or synergistic effects of both high oleic acid levels and unintended increases and decreases in other fatty acids. This may be of significance for those who suffer acute respiratory distress or are prone to it, because these elevated fatty acids are associated with the disease or its symptoms and when inhaled can irritate the lungs. Critically, FSANZ have not provided a convincing case for having either identified or analysed off-target effects of the novel dsRNAs used in soybean DP-305423-1, or other unintended or unanticipated metabolic changes because they have not required transcriptome or proteome profiling. This seems most surprising since FSANZ are already aware of several unanticipated metabolic changes and transcription anomalies.

Finally, FSANZ have not provided a convincing case for assuring those with concerns about allergenic effects, since the one empiracle study described would not in our view be capable of detecting effects that were special to, or more likely because of, soybean DP-305423-1.

Thus, we encourage FSANZ to change their preference from Option 2: accept to Option 1: reject unless and until the concerns of the INBI submissions are satisfied using appropriate data from economic and safety studies.

Introduction

This submission from the Centre for Integrated Research in Biosafety (INBI) is one of two. Our submissions were prepared in response to an invitation from Food Standards Australia/New Zealand to comment on application A1018. A1018 is an application to amend the Australia New Zealand Food Standards Code to allow foods derived from soybean line DP-305423-1

[1] See also accompanying INBI submission under Kurenbach et al.

into the human food supply. In this case, the *fad2-1* gene is silenced by expressing a partial duplicate (*gm-fad2-1*) which is sufficient to evoke an RNAi effect. Silencing of *fad2-1* inhibits conversion of oleic acid into linoleic acid, resulting in an accumulation of the former and lower levels of the latter.

Our submissions were built in large part using the Biosafety Assessment Tool (https://bat.genok.org/bat/) produced by the University of Canterbury and GenØk – Centre for Biosafety. This is a free-to-the-public resource for hazard identification and risk assessment of genetically modified organisms.

This submission is based on the Executive Summary of Application A1018 Food derived from high oleic acid soybean line DP-305423-1 Assessment Report (FSANZ, 2009a) and its Supporting Document 1 (referred to hereafter as SD-1 and cited as FSANZ, 2009b), prepared by FSANZ. This submission is in three parts which follow a list of recommendations in brief. The first part is an overview of the assessment process specific to A1018. The second part is an evaluation of impact, particularly the cost/benefit analysis used to distinguish between Option 1 (reject) and Option 2 (accept). The third part is an evaluation of the scientific data. Unfortunately, this evaluation by necessity is based solely on the FASNZ assessment documents (which are made freely available) and those relevant documents that are in the literature. *We consider the costs of accessing the public record for the scientific dossiers provided to FSANZ by the developers is prohibitively high and inhibitory to full and proper consultation from this Centre, and thus by extension to the public at large.* We reserve the right to amend or extend our analysis, therefore, if information that was not made freely available for the purposes of public consultation at this time becomes known to us in the future. We recommend that the charges to the public wishing to access the scientific dossiers of the public record be eliminated, preferably by transferring the costs of legitimate public consultations to the developer. The documents could easily be uploaded to the web for downloading by reviewers thus eliminating all postage and handling costs. The costs incurred through staff time to assure that no confidential information is inadvertently included should be transferred to the developer who is the sole beneficiary of this service.

Summary of recommendations

Following this summary is a detailed explanation of the recommendations.

1. The charges to the public wishing to access the scientific dossiers of the public record should be eliminated.
2. FSANZ should be able to indicate the value of additional benefit from introducing what appears to be another product with the same primary trait as those approved in 2000, and which have a history of being a commercialisation failure. FSANZ should include the cost of the application evaluation procedure and submitters time in considering this application as part of the ongoing public costs in their cost/benefit analysis.
3. FSANZ should address the impact of Option 2 (accepting the application) on New Zealanders who may encounter this food unlabelled in restaurants or regard the use of high oleic acid soybeans as an animal feed as a GM ingredient in their food and therefore may not be able to avoid this product even with labelling.
4. FSANZ should rigorously incorporate into the cost/benefit analysis the operational reality

that GM high oleic acid soybeans will contaminate conventional soya supplies, thus reducing options for, and increasing costs to, the significant number of consumers who are avoiding all exposure to this product, not just detectable quantities.

5. FSANZ should provide quantitative estimates of the hidden costs to the public to exercise their legitimate option to source GM-free food using labelling, and demonstrate that such costs are lower than the costs of rejecting this application.
6. FSANZ should rigorously pursue its right to request experimental data from the Applicant to answer the questions outlined in the INBI submissions, before concluding that a rejection would not be justified on the basis of safety.
7. FSANZ should request a full chemical compositional description of whole foods prepared under a range of normal cooking and processing conditions using oil derived from DP-305423-1 and compared to oil from the proper conventional comparator line. This should be followed by animal feeding studies using whole foods produced using these two sources of oil.
8. FSANZ should request information from the Applicant on the effects of oleic acid on environmental flora that may flow through to human food and the dietary effects on human flora, particularly the ability of increased exposure to select for resistance and cross-resistance to clinical antibiotics and antiseptics.
9. FSANZ should show how it was demonstrated that unintended or unanticipated dsRNAs—which may still be unknown—produced in the DP-305423-1 soybean or secondarily in human cells had no adverse effects.
10. FSANZ should require the developer to determine the cause of reduced *fad2-2* transcript levels rather than assume that *gm-fad2-1* is the cause.
11. FSANZ should request information from the Applicant on all RNA molecules unique to DP-305423-1, or at unique concentrations in DP-305423-1, all off-target changes to gene expression in DP-305423-1, and the potential for the novel molecules (or molecules at novel concentrations), and possible derivatives that may be made in human cells, to cause effects on human cells. Moreover, that information should be informed by appropriate high throughput sequencing methodologies.
12. FSANZ should indicate how they or the Developer will monitor ongoing nucleotide-level changes in the transgene and subsequent changes to the off-target effects of the dsRNA. In the absence of such monitoring, approval should be conditional and limited to a period of no more than three years.
13. FSANZ should restrict its evaluation of compositional differences to those of significance between the proper, isogenic and conventional comparator grown under identical conditions and at the same time as DP-305423-1, in multiple environments and over several years, and not "water down" their significance by including uncontrolled comparisons. FSANZ should consider the risks of the whole food rather than each significant difference in isolation.
14. FSANZ should require data from proper immunostimulation and allergenicity testing of DP-305423-1 including tests from diet and inhalation exposures. (Comparisons using immune sera from subjects sensitised to conventional soy are not capable of detecting immune responses unique to DP-305423-1.)
15. FSANZ should request information from the Applicant on the effects of DP-305423-1 inhalation in animals that are used as models of acute respiratory syndrome, compared with inhalation of the proper conventional comparator. This should include an analysis of allergenicity and toxicity.

Part 1: Overview

FSANZ may be tempted to address some of the concerns expressed in this submission by asserting that Australians and New Zealanders will use very little high oleic acid oil from soybeans. For example, FSANZ have said that "[d]ietary exposure assessments of the fatty acids contained in soybean indicate that the substitution of soybean oil with oil from soybean 305423 would have minimal effect on the intake of dietary significant fatty acids" (p. 6 FSANZ, 2009a). We encourage FSANZ to not dismiss our comments based on such reasoning. To do so would be a methodological mistake because FSANZ cannot foresee all kinds of future uses and quantities of exposures to this novel product based on historical uses of a fundamentally different plant—the "conventional" soybean—and FSANZ cannot anticipate what novel combination of chemicals can result from this new use of soybeans in applications that have traditionally used other plants, such as olives and canola, and their oils. Hazard identification is not simply a matter of considering each single significant difference between conventional and this genetically engineered soybean in isolation. Nor is it appropriate to seek other precedents for quantitatively equivalent exposures from different plants or animals.

We describe the methodological error of using assumptions of exposure to dismiss the issues we describe in detail below. To their credit, FSANZ in this case have provided a more detailed exposure analysis than they have in other assessments in which we have been involved. This exposure analysis, however, is limited by:

- assumptions of consumption by age of consumer and not by sex or ethnic group and
- substitution of only currently consumed amounts of conventional soybean oil with high oleic acid soybean oil, without regard to new applications that might adopt high oleic acid soybean oil,

and therefore does not capture all relevant groups and amounts for the exposure analysis.

First, there is no reason to expect that the Developer will only seek to replace conventional soybean oil at current levels of consumption. The Developer may attempt to market high oleic acid soybean oil in place of other conventional high oleic acid oils such as olive and canola. Moreover, with increases in production of DP-305423-1 oil, more solid soy foods might contain DP-305423-1. In any case, once approved for use FSANZ will not be able to bind the Developer to marketing only to "commercial producers that serve the food service and food processing industries" and prevent sales directly to households.

Second, FSANZ would be assuming that the average use of DP-305423-1 soybean oil in human food preparation is a representative exposure for all consumers within the age group. We are unaware of any objective evidence that all consumers have diets that would result in such low exposures. Some consumers may eat more soybean products than others (e.g., the lactose intolerant, coeliac disease patients, certain ethnic groups) or more fried foods, and thereby soybean oil, than others. For example, Chinese women may consume upwards of 80 times as much soy as Americans or Europeans (Keinan-Boker et al., 2002). It would be in our view inappropriate to use averages to downplay exposure without more thorough documentation of maximum exposures among subgroups in Australia and New Zealand. We saw no such consideration in the Assessment. Maximum exposure analysis is recommended by Codex

Alimentarius.

> "Information about the known patterns of use and consumption of a food, and its derivatives should be used to estimate the likely intake of the food derived from the recombinant-DNA plant. The expected intake of the food should be used to assess the nutritional implications of the altered nutrient profile both at customary and maximal levels of consumption. *Basing the estimate on the highest likely consumption provides assurance that the potential for any undesirable nutritional effects will be detected.* Attention should be paid to the particular physiological characteristics and metabolic requirements of specific population groups such as infants, children, pregnant and lactating women, the elderly and those with chronic diseases or compromised immune systems" (emphasis added to p. 19 Codex, 2003).

Third, the Developer clearly expects exposures to increase or they would not be going to the expense of producing a soy oil to replace or supplement existing sources of high oleic acid oils (e.g., olives). These supply-driven increases may also not be experienced uniformly by consumers, dramatically increasing the exposure of some consumers while having little effect on others.

Fourth, high oleic acid soybean must be "as safe as" conventional soybeans across the spectrum of food uses and normal food preparation practices. If it is not, then any differences may result in currently unanticipated hazards arising from the use of this product in future contexts, particularly in combination with future genetically modified foods. "As safe as" is critically different as a standard than "safe as" for use as human food. This is especially important for those who may be presently, or may in the future, wish to avoid dietary sources of oleic fatty acids for particular health reasons.

Food is a complex mixture of material treated in a way that differs from how animals are exposed to those same materials and therefore must be tested in this complex form, as a whole food under normal conditions. The modification of oil type and quantity will cause oil derived from this soybean to be used in ways, or at quantities, for which there is no history of safe use. According to Codex Alimentarius:

> "The potential effects of food processing, including home preparation, on foods derived from recombinant-DNA plants should also be considered" (p. 18 Codex, 2003).

Fifth, there are compositional changes to these soybeans that are unanticipated and unintended (p. 5 FSANZ, 2009a). Moreover, it is unlikely that the techniques used by the Developer would with confidence have detected all unanticipated differences. Hence, average soybean use statistics are not suitable for substitution for data that describe the complex of chemicals that may result from heating, particularly repeated heating, of the oil with other metabolite differences at concentrations unique to soybean oils.

Fortunately, Codex Alimentarius guidelines allow FSANZ to ask for specific data of the type we identify below, if indeed high quality data of this type has not been supplied in the original dossiers. FSANZ therefore may request this information without fear of a challenge from the World Trade Organisation, and without creating additional costs to the Australian or New Zealand public since such data are the burden of the company and not the public. While FSANZ

may believe that they have "considered" the effects of heating and home preparation in coming to the recommendation of accepting this application, we recommend that assumption-based reasoning not be substituted for scientific testing to bring certainty to the assessment.

As far as we are aware, there is not a single scientific study that shows any of the benefits associated with a "Mediterranean diet" (associated with foods rich in oleic acid) extended to the use of high oleic acid soybeans. In fact, we are unaware of studies that show sustained or actual benefits of high oleic acids in isolation; those benefits are in the context of a whole diet. That fact is obscured in the Assessment where FSANZ makes repeated reference to the benefits of oleic acids despite the lack of evidence of any benefit from the use of high oleic acid soybeans and their oil. Reducing the benefits of certain diets and lifestyles to particular chemical ingredients such as oleic acid may tempt FSANZ to reduce the assessment of risk to oleic acid in isolation, or in comparison to whole foods or plants that are compositionally different from soybeans. In our view, this would be a significant methodological mistake.

It may be appropriate to consider high oleic acid soybeans and oil as a food supplement in the same way as supplements such as folic acid. The manufacturer's claimed benefit to consumers who eat food fried in their oil rather than in oils that produce more trans fats[2] may create a marketing advantage for the manufacturer, but also takes choices away from those who wish to control their own diets by mixing whole foods with a history of safe use. It is noteworthy in this regard that requirements for folic acid incorporation into bread in New Zealand have been deferred so that those who may wish to avoid higher dietary sources may do so (NZHearld, 2009). Regardless of the merits of the folic acid decision, the action indicates that the trans-Tasman regulation of food by FSANZ may not be sensitive enough to differences between Australian and New Zealand cultures.

The solution to problems caused by trans fats is not remote engineering of the Australian/New Zealand food supply in overseas agroecosystems, but a commitment to providing good food and social programs to encourage good eating in our two societies. This particular juxtaposition of alternatives disappointingly was not addressed in the FSANZ cost/benefit analysis.

Part 2: Impact analysis and options

FSANZ have concluded that "Under option 2, the potential benefits to all sectors outweigh the costs associated with the approval" (p. ii FSANZ, 2009a). We find insufficient information to uphold this statement and our analysis does not corroborate this finding.

According to the Food Standards Australia New Zealand Act 1991:

> "In making a draft assessment of the application, the Authority must have regard to…(c) whether costs that would arise to bodies or persons from a food regulatory measure developed or varied as a result of the application outweigh benefits that would arise to the public from the measure or variation; and (d) whether there are any alternatives (available to the Authority or not) which are more cost-effective than a food regulatory measure developed or varied as a result of the

[2] "The Applicant claims that high oleic acid soybean oil may therefore be used for a number of food applications, including deep fat frying, while also potentially offering improved nutritional properties compared to conventional oil or partially hydrogenated oil" (p. 2 Assessment Report).

application…" (section 15.3).

FSANZ suggested that the cost of Option 1 (reject) could be a decrease in the diversity of products for consumers or the industry who use imported soybeans or foods/feed produced from soybeans if soya and derivatives had to be free of DP-305423-1. Could FSANZ provide the basis for this hypothetical cost? There are other GM plants for which such hypothetical costs have been suggested in the past. By now FSANZ should be able to quantify this assertion. For example, some European countries and New Zealand have not approved other kinds of GM plants at least for planting. What costs, either financial or otherwise, have these societies suffered as a result of efforts to ensure that seed is segregated before export to these countries? We certainly could find no research basis for this hypothetical cost to Australia/New Zealand. Likewise, we could find no objective basis for assigning a benefit to consumers or the industry from acceptance of this application.

In 2000, FSANZ approved for food use other high oleic acid soybeans from this same Applicant (FSANZ, 2000). In Table 7 of SD-1, FSANZ compare the products previously approved with soybean DP-305423-1. The GM soybeans approved in 2000 reportedly produce the amounts of oleic acid and linoleic acid listed in Table 1.

Nine years post approval, FSANZ should be able to indicate how many products included G94-1, G94-19 or G168 high oleic acid soybean and extrapolate from that market share to additional products likely to contain the soybean DP-305423-1. FSANZ report that the Applicant withdrew these lines from market (p. 7 FSANZ, 2009a). Why? *These lines produced as much or more oleic acid and the same or even less linoleic acid than soybean DP-305423-1. What made them marketing failures even though they had superior performance in the intended traits, and what in contrast will make the relatively inferior DP-305423-1 a marketing success?* In other words, what gives FSANZ confidence that DP-305423-1 will be commercialised and thus produce any of the net benefits asserted under Option 2 when there is a history of market failure with this product? We do not believe the present analysis considered the known history of these particular GM-based traits and included them in a proper cost/benefit analysis.

Table 1: GM high oleic acid soybean lines historic and present.

soybean	oleic acid (g/100g)	linoleic acid (C18:2)* (g/100g)
G94-1	72-85	2
G94-19	72-85	
G168	≥80	
control	23	55
305423	77	4
control	15	62
*Note that this number includes an isomer (called 9,15 of the C18:2 fatty acid) unique to the transgenic plants and not detected in conventional plants.		

FSANZ should be able to indicate the value of additional benefit from introducing what appears to be another product with the same primary trait as those approved in 2000, and which have a history of being a commercialisation failure. FSANZ should include the cost of the application evaluation procedure and submitters' time in considering this application as part of the ongoing public costs in their cost/benefit analysis.

In the absence of any information to the contrary, we think that it is inappropriate to include a hypothetical reduction in product diversity as a cost of rejection or a hypothetical increase in diversity (which history indicates is unlikely) a benefit of approval of the application.

FSANZ suggested that as a cost of rejection, there might be an "increase in price of imported soybean foods due to [a] requirement for segregation of soybean line DP-305423-1". It is a normal practice to segregate crops for particular marketing purposes. In Austria, for example, GM food/feed products are reportedly quite rare even if they are not banned, suggesting that supply chain segregation is both effective and available.

> "[T]he use of certain imported GMOs, like GM-Soybeans, is permitted in line with their EU-wide authorisation. These GMOs and products derived from them are used primarily for animal feed for farm livestock. GM-Foods which are labelled according to the applying regulations are scarcely found. In recent surveys only special food products, like few imported asia foods, were encountered in consumer retail markets" (Umweltbundesamt).

Can FSANZ please quantify what, if any, additional costs would be incurred due to Australia/New Zealand rejecting this application? How much would that translate into an increase in food prices for Australia and New Zealand?

We could find no research on this topic that would allow us to assign any increase in costs from rejection due to segregation beyond normal practice. Likewise, we could find no objective basis for speculating that approval would have any beneficial effects on prices. In the absence of any information to the contrary, we think that it is inappropriate to include this hypothetical cost as a cost of rejection or a benefit of approval of the application.

Importantly, FSANZ have suggested that there are no significant costs to consumers who choose to avoid high oleic acid soybeans in their food because food would be labelled. Our analysis is not consistent with this claim.

1. Consumers would not find it easy to avoid animals raised on this GM soybean.

At least in New Zealand, consumers draw a distinction between animals raised on GM and GM-free feed. This point was clearly made by the New Zealand Royal Commission on Genetic Modification:

> "Products from animals or birds fed on genetically modified pasture or stock feed do not require assessment under Division 1 of Standard A18 because they are not considered to be genetically modified, nor will they require labelling under the labelling provisions to be implemented later this year. *It is important that consumers are able to choose to avoid consuming the products of animals and birds fed on genetically modified feed.* Where a claim that animals and birds have not been fed genetically modified food can be sustained, labelling that identifies the product as being free of genetic modification will be appropriate. We discuss genetic modification-free labelling later in this chapter. Without such a label, consumers must assume that a genetically modified food may have been used" (paragraph 126, emphasis added).

The above and the Royal Commission's recommendation 8.2:

> "that Government facilitate the development of a voluntary label indicating a food has not been genetically modified, contains no genetically modified ingredients and has not been manufactured using a process involving genetic modifification [sic]"

in our opinion indicate that the Royal Commission saw that it was important to clearly differentiate between that which was GM or raised on GM feed, from those things that were not GM or exposed to GM feed. Hence, even the use of high oleic acid soybeans only in animal feed has implications for food and should be formally considered in a cost/benefit analysis. Unless appropriate labelling is in place, the cost of tracking the use of high oleic acid soybeans will fall to consumers wishing to avoid it in food or in animals used as food. To our knowledge, this would not be possible for consumers in Australia/New Zealand unless they sought more expensive organic certified sources of animal products.

At least in New Zealand we are unaware of any provision requiring those who supply animals raised in part on soya products to disclose the use of particular GM products. Hence, how would a meat-eating consumer wishing to avoid high oleic acid soybean exercise this right if DP-305423-1 soybeans were approved?

In Austria, labelling is required for food sold in restaurants.

> "GM-Foods which are labelled according to the applying regulations are scarcely found. In recent surveys only special food products, like few imported asia foods, were encountered in consumer retail markets. *These products as well as food produced from GM-products, which are served in restaurants need to be unambigously labelled according to the EU rules to ensure freedom of choice for consumers*" (emphasis added to Umweltbundesamt).

In New Zealand, however, restaurants do not have to disclose the use of GM ingredients (NZFSA). Could FSANZ please provide the costs to consumers and restaurateurs who would have to source organic certified poultry, meat, oil for frying and farmed fish in order to avoid potential exposure to high oleic acid soybeans?

2. Even "appropriate" labelling would not be sufficient for consumers to avoid exposure. Appropriate labelling has not prevented exposure to other illegal GM products from the human food supply, notably Starlink corn, BT10 corn, and GM rice from various sources including China, Bayer and Monsanto (Heinemann, 2007b, Heinemann, 2009, Vermij, 2006). Even food labelled as GM-free can have up to 1% GM content if this contamination was deemed unintentional (NZFSA). Thus, approval of this product by Australia/New Zealand is likely to increase the costs to consumers who wish to avoid all exposure, because they will have to source organically certified sources to ensure themselves of that. New Zealand consumers who wish to avoid this product, and not just experimentally detectable amounts or amounts up to 1%, cannot do so using the labelling provisions. Thus, their product choices will be reduced in order to reliably avoid exposure. FSANZ should incorporate this practical reality into the cost/benefit analysis. We believe that it is more likely that the costs to the minority of consumers who would resort to other sources of soybean and soy-derived foods outweighs the cost to the majority of consumers who might or might not experience any difference in food choice because DP-305423-1 was rejected.

3. FSANZ has not quantified the costs to consumers who read labels and take other measures to avoid GM foods, and thus has underestimated the costs of acceptance.

A recent US-based survey found that 61% of households read food labels (Hale, 2009). Those with higher incomes and who shop in stores associated with GM-free foods are more likely to read labels. The cost to consumers of reading labels or taking other time-consuming steps to avoid GM foods is high. For example, 34% of households with earnings of $100,000+ agreed completely to the statement that they "usually" read labels. Based on an eight hour day and 330 day working year, the value of this time to the economy is $38/hour/person.

In 2007, the average Australian wage was reportedly $55,600 (news.com.au). Applying the US figures to Australia, we estimate that between 25-35% of shoppers usually read labels. The additional costs to the Australian economy for the time used to read more labels to avoid this particular GM ingredient in food would be approximately an average of $21/hour for up to a third of the population. In contrast, Option 1 would incur no objective cost to consumers.

It is reasonable to assume that those attempting to avoid GM foods will be motivated to spend time doing it. In FSANZ's 2007 survey of consumer attitudes, they found that among Australians listing GM as a food concern (25% of survey respondents), the level of concern was extremely high (FSANZ, 2008). In Table 9 of that report, Australians listed their level of concern as 6 on a scale of 7 ("extremely concerned"). Likewise, New Zealanders concerned about GM food (29% of respondents) listed their mean level of concern as 6 on a scale of 7 (Table 10 of the same report). These numbers also agree with the proportion of survey respondents who consult labels for GM content. Twenty-seven and 28% of Australians and New Zealanders, respectively, read labels specifically for GM content the first time they purchase a product.

Conservatively assuming that a quarter of Australian shoppers are reading labels to avoid GM foods, and that this exercise adds as little as 30 minutes/week to the time used shopping, the total time used to read labels for identifying foods with GM content would be ~900 hours/week among the estimated 7,000 Australian households (Australian Government) alone. The total cost amounts to ~$1 million per year. This cost far exceeds any verified costs of Option 1 or benefits of Option 2 and still fails to take into account how consumers might avoid high oleic acid soybeans in the food chain and from restaurants.

While these are rough cost estimates, what is certain is that using labelling to avoid some or all GM products amounts to some cost as it takes time to exercise this option. The estimated cost of Option 2 (accept) is far more certain than the unspecified costs of Option 1 (reject) and benefits of Option 2. Moreover, the costs of Option 2 are borne across the Australian and New Zealand economies while any hypothetical benefit of high oleic acid soybeans is largely concentrated into a few private pockets.

FSANZ should provide quantitative estimates of the hidden costs to the public to exercise their legitimate option to source GM-free food using labelling. Without these, then the benefits of Option 1 appear to outweigh the hypothetical costs of Option 1 and benefits of Option 2.

The only remaining hypothetical cost for Option 1 (reject) would be a cost of WTO action taken by the USA or other country against Australia for this reason. FSANZ should provide both an estimate of this cost and the likelihood of the action for rejection of just this application. We are not aware of a similar WTO action against any other country for rejecting a single application, so at present this hypothetical cost appears unrealistic. Moreover, this hypothetical cost is borne only if Australia were unjustified in rejecting this application. Since significant uncertainties still exist in the evaluation of this product (see below), it is premature to suggest that Australia would be found by the WTO to be acting outside of its responsibilities to the WTO. We recommend that FSANZ rigorously pursue its right to request experimental data from the Applicant to answer the questions outlined in the INBI submissions, before concluding that a rejection would not be justified on the basis of safety.

Part 3: Additional scientific information needed

The FSANZ preference for Option 2 (accept the application) is based on FSANZ being satisfied that there are no safety concerns. However, we could not find information that we consider necessary for arriving at the conclusion that soybean line DP-305423-1 was as safe as conventional soybean.

1. High oleic acid soybeans are being proposed for use as human food and in particular for use in high temperature applications. However, we could find no safety studies on the chemical composition of the oil after heating, feeding studies using products fried in the oil, or solid soy food products derived from DP-305423-1. Given that high oleic acid soybean oil is chemically different from oils derived from conventional soybeans, oilseed rape, sunflower, safflower and olives, how has FSANZ determined that there are no hazards from this novel food?

   FSANZ in fact do have evidence of negative effects of cooking high oleic acid soybeans which it reported in its previous evaluation of the similar products from the same Applicant (FSANZ, 2000). FSANZ summarised two separate feeding studies, one involving pigs and the other chickens, where the Applicant reported that processing the soybean at cooking temperatures ranging from 80-105ºC reduced its nutritive value (see Tables 13 and 14 of A387). However, we cannot tell from these data whether the effects were nutritive or toxic. Nevertheless, those studies provided an "indication of how much food (in pounds) it takes to put on 1 lb of body weight in the animal" (p. 37 FSANZ, 2000) and revealed that animals fed on heated high oleic acid soybeans often were less able to convert food energy into body mass. When pigs or chickens were fed the GM high oleic acid soybeans, the efficiency of feed conversion fell in comparison to control diets.

   FSANZ offered no explanation for the effect on pigs. At the time FSANZ attributed the effect on chickens to lower amino acid levels in the test diets. The tested varieties of high oleic acid soybeans were also modified to produce higher levels of lysine [through a modification similar to a recent application from Monsanto to increase lysine levels in corn (LY038)]. We have already pointed out to FSANZ that at temperatures used to cook soybeans and corn, the lysine will react with sugars to both reduce the amount of

available lysine and also create potentially toxic compounds (Cretenet et al., 2006). During our previous exchange, FSANZ denied the need to require the Applicant to conduct both chemical composition studies and feeding studies with material derived from high lysine plants after it had been subjected to high temperature processing or cooking. This is now even more surprising given that FSANZ had acknowledged nine years ago that "[t]his result is most likely attributable to the lower amino acid content of the test diets, although may also be due to differences in processing" (p. 38 FSANZ, 2000), i.e., at higher temperatures normal to how humans would eat this material. The key point here is that the cause of the processing effect on high oleic acid soybeans was never determined. It could have been an effect of lysine at high temperature; in which case FSANZ should review its approval of LY038. It may have been caused by other intended or unintended effects of silencing the *fad2-1* gene, high oleic acid or high linoleic acid isomer 9,15 alone or in combination with lysine. We find no evidence of a processing experiment on soybean DP-305423-1 to prove that it would not cause the same potential adverse effects as the previous generation of GM soybeans that have high oleic acid and linoleic acid isomer 9,15.

We recommend that FSANZ exercise their option under Codex Alimentarius to request a full chemical compositional description of whole foods prepared under a range of normal cooking and processing conditions using oil derived from DP-305423-1 and compared to oil from the proper conventional comparator line[3]. This should be followed by animal feeding studies using whole foods produced using this GM soybean DP-305423-1 and its closely related conventional parent.

2. Oleic acid has antibacterial and anti-viral properties (Thormar et al., 1987, Zheng et al., 2005). These properties may result in a change in flora that use soybeans as a habitat, and may increase quantities of oleic acid in human food as this source of oil becomes adopted for food preparation. New combinations of food may be exposed to a soybean source of high oleic acid which might also then quantitatively increase pressure on food-borne microorganisms to acquire resistance to oleic acid. The resistance to oleic acid should be evaluated for the possibility that it may confer cross-resistance to clinical antibiotics or antiseptics. There is no indication from the Assessment Report that FSANZ considered the antibacterial/viral properties of oleic acid, or the impact on microbial flora inhabiting soybeans or humans.

We recommend that FSANZ request information from the Applicant on the effects of oleic acid on environmental flora that may flow through to human food and the dietary effects on human flora, particularly the ability of increased exposure to select for resistance and cross-resistance to clinical antibiotics and antiseptics.

3. The modification of DP-305423-1 is based on dsRNA silencing, which has not benefited from human food safety studies to our knowledge. To emphasise the uncertainty such methods bring to hazard identification and thus risk assessment we quote FSANZ where they say: "The Applicant speculates that suppression of expression of the endogenous

[3] Please refer to INBI submission by Kurenbach et al. for discussion of proper comparator.

> *gm-fad2-1* gene is mediated via co-suppression in which the introduced fragment leads to an overabundant production of sense mRNA which in turn leads to production of dsRNA *via a pathway that is still not understood*" (emphasis added to p. 12 FSANZ, 2009b). Under such circumstances where the biochemistry of the modification itself is considered to be *speculation and is not understood*, it is difficult to understand how FSANZ has achieved confidence that the Applicant could report all unintended effects of the modification.
>
> Research by the Monsanto Corporation has shown that novel dsRNA molecules at unique concentrations in transgenic plants can transfer through food to animals wherein these molecules or derivatives of these molecules cause adverse effects (Baum et al., 2007). Researchers demonstrated that dsRNA can be infectiously transferred through food to gut cells in insects, and subsequently spread within the animals (Gordon and Waterhouse, 2007). The dsRNA created in the transgenic dsRNA-insecticide plants were in fact derivative or "secondary" RNA species, and notably Baum et al. (2007) are sure that they were the cause of more derivative RNA molecules after processing by the RNAi activity in the target insects. How has FSANZ been assured that secondary processing in human cells of novel dsRNA molecules created by high oleic acid soybeans would not generate a biologically active dsRNA in human cells?

We believe that FSANZ has a responsibility to demonstrate how it found unintended or unanticipated dsRNAs—which may still await description—produced in the DP-305423-1 soybean or secondarily in human cells had no adverse effects.

> A history of consuming small RNA molecules in plants is not the same as extrapolating the safety of all small RNA molecules, any more than a history of consuming proteins attests to the safety of every protein. When a small RNA molecule will or might not act as a gene regulator is not always known in advance. Therefore, it cannot be assumed that novel small RNAs that might be created in high oleic acid soybeans will likewise be safe. Certainly, the dsRNA used as an insecticide is not safe from the perspective of pest insects targeted in other work described above (Auer and Frederick, , Baum et al., 2007) and by extrapolation some small RNAs may not be safe for humans. Indeed, the plants that humans traditionally consume may be precisely those that produce small RNAs that have not been toxic to us.
>
> It is now clear that dsRNA can have significant biological impact. Recent research (Baum et al., 2007, Gordon and Waterhouse, 2007, Mao et al., 2007) establishes beyond doubt that novel RNAs of recombinant or synthetic origin cannot be "generally regarded as safe" but must be tested and demonstrated to be safe. The insecticide findings provide powerful argument for those companies and regulators who have previously dismissed the need for proper profiling of the transcriptome and proteome in human health and environment safety assessments of GM crops to now accept the importance of such enquiry (Heinemann, 2007a).
>
> In addition, FSANZ report that a second non-target gene, *fad2-2*, may be partially suppressed by the use of dsRNA against the target, *fad2-1*. This could be expected based

on known sequence similarities between the two *fad2* genes, and FSANZ have made the assumption that this is the explanation. However, there are other possible explanations for the reduced level of *fad2-2* transcription, including biochemical feedbacks that would have nothing to do with silencing. Such feedbacks may have other complex physiological implications for the high oleic acid soybeans. So while the co-silencing effect is plausible, we found insufficient evidence to regard that as the explanation for lower transcript levels of *fad2-2*.

We recommend that the cause of reduced *fad2-2* be determined rather than be left to assumption.

Moreover, dsRNA molecules generate many off-target effects that may significantly alter the range and concentration of normal metabolites. FSANZ is already aware of two unintended and unanticipated changes in the levels of heptadecanoic (C17:0) and heptadecenoic (C17:1) fatty acids. The explanation for these two changes was described as a hypothesis rather than a scientific determination. Could these changes also be indicating additional off-target effects of dsRNA, or biochemical pathways that are unknown to FSANZ and the Applicant? Unless the Applicant has provided FSANZ with a complete profile of the transcriptome, additional off-target effects could be missed.

The genes silenced by dsRNAs are specific to the dsRNA, rather than dsRNAs are specific to target genes (Jackson et al., 2003). Sometimes hundreds of off-target transcripts are reduced or silenced (Jackson et al., 2003, Jackson et al., 2006, Ma et al., 2006). For example, Semizarow et al. found that a set of 5 different dsRNA molecules that silence the same gene (AKT1) collectively silenced 840 genes (Semizarov et al., 2003). Species-specific differences in RNA editing further contribute to unanticipated dsRNA species and off-target effects (O'Connell and Keegan, 2006). Therefore, the transcriptome of the GM crop should be evaluated for all novel dsRNAs. Second, off-target effects sometimes only change protein levels and not transcript levels (Jackson and Linsley, 2004, Scacheri et al., 2004), making it even more complicated to track effects. Therefore, both the transcriptome and proteome of the GM crop should be profiled.

"[F]urther research into off-target effects should be encouraged because the current lack of information creates uncertainties about this particular hazard" (p. 6 of 8 Auer and Frederick).

FSANZ already know of at least two putative unintended off-target transcriptional effects, those on *fad2-2* and *kti3* (p. 18 FSANZ, 2009b). The off target effects are likely caused by two different parts of the transgene, the coding sequence with similarity to *fad2-2* and the non-coding region with sequence similarity to *kti3* cis-acting elements. Based on the work discussed above, each of these regions may induce the silencing of several hundred other unintended and undisclosed genes. These other effects simply would not be detected using northern blots because that type of profiling technique requires sequence knowledge of target genes. Since in this case the concern is effects on unintended and unanticipated genes, only microarray or preferably high throughput sequencing techniques would be suitable.

> *High-throughput sequencing proved to be a powerful and quantitative method to sample transcriptomes deeply at maximal resolution. In contrast to hybridization, sequencing showed little, if any, background noise and was sensitive enough to detect widespread transcription in >90% of the genome, including traces of RNAs that were not robustly transcribed or [were] rapidly degraded* (p. 1239 Wilhelm et al., 2008).

Additionally, researchers have applied this technique to organisms at different stages of their life cycles and under different environmental conditions, demonstrating that this technique can be effectively used to describe the transcriptome of different tissues, stages of development and at different times (Wilhelm et al., 2008). It can be used on any kind of GMO (Lu et al., 2007).

Not only has full transcriptome profiling become possible, it is also seen as "necessary to sample the full complexity of small RNAs in plants and likely other organisms as well. Application of this method to several key mutants affecting small RNA biogenesis pathways can quickly lead to the identification of candidate miRNAs, trans-acting siRNAs and other interesting classes of small RNAs" (p. 116 Lu et al., 2007). The sequencing technique is less prone than global microarrays to ambiguities due to background detections (Kristensen et al., 2005, Wilhelm et al., 2008).

Codex Alimentarius allows FSANZ to ask for information on RNA molecules without concern of action from the WTO.

> "Information should be provided on any expressed substances in the recombinant-DNA plant [or microorganism]; this should include: A) the gene product(s) (e.g. a protein or an untranslated RNA)…E) where possible, the amount of the target gene product(s) if the function of the expressed sequence(s)/gene(s) is to alter the accumulation of a specific endogenous mRNA or protein" (p. 14 and 39 Codex,, 2003).

We recommend that FSANZ request information from the Applicant on all RNA molecules unique to DP-305423-1, or at unique concentrations in DP-305423-1, all off-target changes to gene expression in DP-305423-1, and the potential for the novel molecules (or molecules at novel concentrations), and possible derivatives that may be made in human cells, to cause effects on human cells. Moreover, that information should be informed by appropriate high throughput sequencing methodologies.

Finally, there is evidence that "[m]utation rates in genes for small RNAs can be high relative to protein-coding genes" (p. 5 of 8 Auer and Frederick). Thus, approval of GMOs that rely on small RNA molecules for their effects may not be suitable for a single approval regulatory system because changes in these sequences over time can lead to further and unanticipated off-target effects.

FSANZ should indicate how they or the Developer will monitor ongoing nucleotide-level changes in the transgene and subsequent changes to the off-target effects of the dsRNA. In the absence of such monitoring, approval should be conditional and limited to a period of no more than three years.

4. There are too many statistically significant differences between DP-305423-1 and conventional soybeans for FSANZ to assume equivalence. The list of significant differences and unanticipated changes includes: higher levels of heptadecanoic and heptadecenoic acids; lower levels of myristic, palmitic and stearic acids; and higher levels of palmitoleic, arachidic, eicosenoic and lignoceric acids (p. 34 FSANZ, 2009b). FSANZ attempts to dismiss most of these differences by invoking averages from historical measures and uncontrolled comparisons, e.g.: "All of these levels except for eicosenoic acid were within the statistical tolerance range for the 4 commercial cultivars although the eicosenoic level was within the published range for this analyte" (p. 34 FSANZ, 2009b). We continue to counsel that the use of genotypically uncontrolled comparisons, and comparisons made across environments, undermines the usefulness of the comparator and the scientific process.

   Moreover, FSANZ have not demonstrated that any other soybean in history has had this particular pattern of extreme values in this particular combination of metabolites. Failure to do so sets a standard lower than "as safe as". It is a methodological mistake to consider each significant difference in isolation because people do not eat the individual components of soybean, they eat the whole food or the whole oil.

We recommend that FSANZ restrict their evaluation of compositional differences to those of significance between the proper, isogenic and conventional comparator grown under identical conditions and at the same time as DP-305423-1, in multiple environments and over several years, and not "water down" their significance by including uncontrolled comparisons. FSANZ should consider the risks of the whole food rather than each significant difference in isolation.

5. FSANZ report satisfaction with an allergenicity test in which the sera from "soy-sensitive subjects" was incubated with proteins from DP-305423-1 and the 'Jack' variety as a comparator. Based on similarity of reaction profiles, FSANZ have concluded that the allergenic potential of DP-305423-1 is unchanged from conventional soybean.

   As we understand it, the study used sera from people sensitised to conventional soybean, not high oleic acid soybean. These individuals would not have mounted an immune reaction to an unknown allergen unique to high oleic acid soybean DP-305423-1. Therefore the study only provides baseline data about the generic allergenicity of soybeans, it is not capable of distinguishing the allergenic potential of DP-305423-1 from conventional soybean for people never exposed to DP-305423-1. We fail to understand the relevance of this study for demonstrating the safety of DP-305423-1.

   Moreover, the study was limited to 5 soy-sensitive individuals with unknown histories of sensitisation. People could be exposed to DP-305423-1 in the diet and through inhalation of flour. Therefore, the study should include an assessment of the allergenic potential of DP-305423-1 through both dietary and inhalation sensitisation.

We recommend that FSANZ require data from proper immunostimulation and allergenicity testing of DP-305423-1 including tests from diet and inhalation exposures.

6. There are many potential health benefits from substituting oleic acid for other fatty acids

that may form trans fats particularly after being hydrogenated. However, there is at present no substantial scientific claim that in all foods and for all people oleic acid is preferential. By increasing the range of basic food sources that are homogenised for being high oleic acid sources, we simultaneously remove food options from those who may wish to avoid high oleic acid foods, or increase the costs and challenge to consumers wishing to avoid these foods. For example, high oleic acid levels are associated with potential health hazards among those with certain respiratory conditions.

"[O]lives (and thus oleic acid) are important ingredients of the healthy Mediterranean diet. On the other hand, patients with acute respiratory distress syndrome have elevated serum levels of oleic acid, and infusion of oleic acid in animals results in an acute lung injury–type syndrome" (p. 424 Matalon and Ji, 2005).

Oleic acid is used to induce acute respiratory distress syndrome in animal models, usually through blood infusion. Humans may more likely have direct, non-dietary exposure to oleic acid through high oleic acid soybeans than other sources of oleic acid. This is because soybean flour is a very common product and thus inhalation of soy flour is more likely than inhalation of meal produced from olives. Edible soybean flour production was estimated at 2 million tons by 1992, up from only 60,000 tons in 1960 (Berk, 1992). It is used in baking, cereals and pasta. It has important uses in replacing wheat flours especially for those with coeliac disease (Berk, 1992).

Inhalation provides direct lung cell exposure to oleic acid, and may more closely mimic infusion. Moreover, inhalation sensitisation to allergens can be more important than dietary sensitisation.

"[I]it has to be considered that transgenic plants may be used in industrial processing; hence other exposure routes and sensitization scenarios might become important. For example, manufacturing large amounts of transgenic soy containing a food allergen may induce respiratory sensitization due to the generation of allergen-containing dust" (Spok et al., 2005).

The apparent oversight in the risk evaluation by FSANZ in not evaluating inhalation effects is even more concerning in this case, since an unintended and unanticipated effect of the modification was elevation in levels of heptadecanoic acid. According to the Material Safety Data Sheet for Oxford University (UK), the concern about heptadecanoic acid is that it is "irritating to eyes, irritating to the respiratory system, irritating to skin" (MSDS). In short, it is reasonable to expect that high oleic acid soybeans produce more of two compounds that may provoke reactions through inhalation of soy flour. The assessment in this case should evaluate any combinatorial or synergistic effects of this soybean to provoke a toxic or allergenic effect, especially on people prone to respiratory distress.

We recommend that FSANZ request information from the Applicant on the effects of DP-305423-1 inhalation in animals that are used as models of acute respiratory syndrome, compared with inhalation of the proper conventional comparator. This should include an analysis of allergenicity and toxicity.

Respectfully submitted on behalf of the Centre,

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