Application AI041 – Additional Information

1. A discussion and comparison of the levels of <u>total</u> trans fatty acids in RBD oil from MON 87769 soybean and conventional soybean is required. In addition, data are required on the nature and levels of *trans* fatty acids in processed fish/marine oil products used in the food industry and, if relevant, commonly consumed vegetable oils, other than soybean. The requirement for this information is based on the understanding that SDA soybean oil would largely substitute for fish oil as a source of omega-3 fatty acids, and therefore fish oils appear to be the closest comparator in terms of the diet.

Response :

Commercial grade SDA soybean oil produced from MON 87769 was analyzed for fatty acid composition and total trans-fat content as part of the U.S. GRAS affirmation process[1,2]. The total tans-fat levels in five lots of commercial grade SDA soybean oil analyzed for the GRAS affirmation ranged from 0.5% to 0.8% (% of total fatty acids). The total amount of trans-fat present in SDA soybean oil from MON 87769 is comparable or less than the total amount of trans fat found in other fat sources (e.g., vegetable oils, beef and dairy, fish). SDA soybean oil is intended to be formulated into processed foods, and as such, will largely substitute for commonly consumed vegetables oils currently used in those foods. SDA soybean oil is not intended to replace consumption of fish or fish oils (e.g. as supplements), however, these products still provide important context for trans fatty acid intakes.

Limited attention has been paid in recent years to the trans-fat content of commercially available refined, bleached and deodorized (RBD) oils and, as a result, levels are often assumed to be nil. This misconception is perpetuated in a number of world areas by current labeling, which considers such oils to be "zero-trans-fat" based upon de-minimus standards. However, trans-isomerization has been known to occur as a result of oil processing since at least 1974, with the work of Ackman and Hooper (1974) in Canola oil.

Kellen and de Greyt (2000) summarized trans-fat content of typical oils (Table 1) and note that trans-fats, formed as a result of deodorization, are usually required by commercial expectations to be below 1%.

[1] http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn000283.pdf
[2] http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm185688.htm

Table 1. Trans fat content in commercial oils[1]

Oil Type	Trans-Fat Content (% of total fatty acids)
Soybean	0.9 - 3.5
Sunflower	0.3 – 1.3
Rapeseed	0.9 – 1.5
Corn	0.6 – 4.1
Peanut	0.1- 0.3

[1]Kellen and deGreyt, 2000.

Trans-fat levels in processed foods vary widely depending upon choice of oils used and, especially, hydrogenation, and have shifted over time, making meaningful comparison difficult on a global basis.

Fish oils are widely recognized for their cardiovascular benefits due to their high content of polyunsaturated fatty acids (e.g., EPA, DHA). However, given the chain-length and degree of unsaturation of EPA and DHA, and the fact that fish oils are also refined and deodorized, some trans-fat formation would seem to be inevitable. Fornier et al (2007) reported an analytical method for trans-fat in fish oils and reported values for trans isomers of EPA and DHA in commercially available fully and partially refined fish oils (Table 2, below, or Table 5 in Fornier et al., 2007; samples D-G). Reported as percent of total fatty acids, with total EPA levels of 6.34-16.49%, trans -EPA levels ranged from 0.12-0.31%, and with DHA levels of 10.66-22.97%, trans-DHA levels ranged from 0.31-0.62%. For refined algal oils (same table, samples A-C) containing 40.98-43.51% DHA (with negligible EPA), trans-DHA levels ranged from 0.37-0.86%.

Hauff and Vetter (2009) reported a value for mono-unsaturated trans-fat isomers of 0.35% of total fatty acids for cod liver oil. While it is not appropriate to sum these values, it is apparent that total trans-fat in SDA soybean oil is comparable or possibly less than that of fish oils. In addition, the variety of trans fatty acid isomers in fish oil is likely to be more complex than commercial vegetable oils, given the number of different polyunsaturated fatty acids present (i.e. linoleic acid, linolenic acid, SDA, EPA and DHA).

Additionally, it is worth noting that beef and dairy fats typically contain 3% trans-fatty acids (Hunter, 2005), primarily related to ruminal trans-fat formation.

Table 2. Reproduction of Fornier et al, Table 5. Note that samples A-C are algal oils containing mainly DHA while samples D-G are commercially available fish oils.

Level of *trans* isomers of EPA and DHA found in commercially available marine oils (results expressed as g/100 g of fatty acids)

Sample	Eicosapentaenoic acid (EPA)					Docosahexaenoic acid (DHA)				
	All *cis*		*trans* isomers		ID%	All *cis*		*trans* isomers		ID%
	MV[a]	SD[b]	MV	SD	MV	MV	SD	MV	SD	MV
A	–	–	–	–	–	40.98	0.19	0.86	0.02	2.10
B	0.34	0.01	–	–	–	41.61	0.37	0.37	0.03	0.90
C	0.38	0.00	–	–	–	43.51	0.21	0.62	0.03	1.40
D	16.37	0.14	0.31	0.03	1.90	10.66	0.07	0.31	0.00	2.90
E	16.49	0.05	0.34	0.03	2.00	11.30	0.07	0.35	0.04	3.00
F	6.60	0.03	0.13	0.02	1.90	22.97	0.17	0.57	0.00	2.40
G	6.34	0.10	0.12	0.04	1.90	22.10	0.04	0.62	0.04	2.70

The isomerization degree (ID%) indicates the relative level of degradation of EPA and DHA.

[a] MV: mean value.

[b] SD: standard deviation.

Chardigny et al (1996) summarized previously reported data (Ackman and Hooper, 1974; Wolfe, 1992; Wolfe, 1993) on the occurrence of trans-fatty acids in commercial vegetable oils. The data summarized below (Tables 3 and 4) illustrate the nature and range of trans fatty acids present in soybean and canola (oil blends and walnut oil also reported in original publication).

Table 3. 18:2 and 18:3 Isomers in Refined Vegetable Oils (weight% of total fatty acids)
(see Chardigny et al., 2006 for original references)

Fatty Acid	Soybean n=3	Soybean n=8	Soybean n=6	Canola n=7	Canola n=4
18:2 cc	**--**	**51.82-55.05**	**53.30-54.81**	**17.59-22.58**	**19.24-21.73**
18:2 ct	--	0.05-0.51	0.16-0.40	0.06-0.42	0.07-0.32
18:2 tc	--	≤ 0.40	0.17-0.41	0.1-0.35	0.05-0.27
18:3 ccc	**--**	**5.26-7.13**	**6.10-6.82**	**5.74-9.46**	**7.45-9.03**
18:3 tct	--	≤ 0.27	0.04-0.09	0.01-0.34	0.03-0.27
18:3 cct	--	0.04-0.77	0.21-0.89	0.34-1.46	0.46-1.21
18:3 tcc	--	0.04-0.67	0.15-0.82	0.27-1.31	0.37-1.04
18:3 ctc	--	≤ 0.11	0.02-0.10	0.04-0.28	0.05-0.22
Total 18:3 trans	0.46-0.57	--	--	--	--

Table 4. Percentage of Trans Isomers of Linoleic and Linolenic Acids Present in Commercial Oils

(note- expressed as percentage of total 18:2 or 18:3, not % of total fatty acids)

Oil type	18:2	18:3
Soybean	0.2-1.7%	2.3-27.7%
Canola	0.3-3.3%	7.0-37%
Rapeseed	0.7-2.6%	10.5-53.8%
Walnut	0.3-0.8%	4.9-10.4%
Blended veg.	0.3-0.8%	8.0-10.9%

It is expected that highly unsaturated fatty acids will isomerize more readily. Thus, it is not surprising that in the commercial oils (excluding walnut and rapeseed, not generally used for cooking in Australia) 0.2-3.3% of linoleic acid and 2.3-37% of linolenic acid are isomerized.

Thus, the total amount of trans-fat present in SDA soybean oil from MON 87769 (0.5% to 0.8% of total fatty acids) is comparable or less than the total amount of trans fat found in other fat sources (e.g., vegetable oils, beef and dairy, fish oils).

2. Analysis of the physiology and biochemical fate (absorption, transport and metabolic pathways) of *trans*-ALA and *trans*-SDA is required. The response should include information on whether these isomers are converted to long chain polyunsaturated fatty acids, incorporated into tissues and/or converted into energy.

Response :

The fatty acids present in SDA soybean oil, or indeed any oil, are metabolized primarily via mitochondrial beta-oxidation (Mayes and Botham 2004). For example, similar to any 18-carbon fatty acid, SDA can undergo beta-oxidation to yield 9 units of acetyl-CoA. No other means for the shortening of fatty acid chain length is known in mammalian or plant biological systems. SDA that does not undergo beta-oxidation can also undergo elongation to form long-chain omega-3 fatty acids such as EPA and DHA. Compared to elongation, the beta-oxidation for energy is the predominant pathway in the metabolism of polyunsaturated fatty acids and therefore only a fraction of the SDA that is consumed is expected to undergo elongation to LCPUFA (McCloy et al, 2004). In regards to beta-oxidation, it would appear that unsaturated trans-isomers undergo catabolism at least as effectively as the cis-isomers (Bretillon et al., 2001; Chen et al., 2001). This is not surprising in that the initial step in the beta oxidation process is the creation of a double bond, which subsequently undergoes oxidation. This double bond is actually in the trans-configuration (Mayes and Botham, 2004). It is possible that a very small amount of the trans-ALA and trans-SDA could undergo elongation to form the trans LCPUFA. But, according to Hussein et al (2005), the cis isomer will compete with the trans isomer for elongation and thus the trans isomers are poorly elongated to LCPUFA (Hussein et al., 2005; McCloy et al., 2004). Additionally, trans-ALA (0.44% of total fatty acids) and trans-SDA (0.18% of total fatty acids) levels in SDA soybean oil is so small that the amount of elongation product formed from these trans isomers will be negligible compared to elongation product formed from ALA and SDA.

3. Discussion of any adverse effects or potential risks arising from the consumption of *trans*-ALA and *trans*-SDA, in particular any known effects on lipid levels, including LDL and HDL-cholesterol levels, or heart disease.

Response :

The trans-fats relevant to vegetable oils are not differentiated as to their impact on cardiovascular health at this time. Limited evidence suggests that naturally occurring 16:1 trans-fatty acids may have less impact than 18 carbon trans-fatty acids on inflammation and oxidative stress (Gebauer et al., 2007), but 16 carbon fatty acids are not a major component of vegetable oils. Limited studies indicate that naturally occurring trans-fat from ruminant sources (e.g. conjugated cis(9)-trans linoleic(11) acid) may have no association or perhaps beneficial association with coronary heart disease risk. However, these fats are associated with saturated fats and it is not possible to plan diets that emphasize the ruminant trans-fats at a level that would be expected to provide health benefits (Gebauer et al., 2007). The effects of 18 and higher carbon trans fats relevant to vegetable oils have not been differentiated, and thus total trans-fat appears to be an appropriate metric for comparison of vegetable oils and has been incorporated into food labeling in many countries (Gebauer et al., 2007). The total trans-fat content of SDA soybean oil is consistent with the total trans-fat content of commercially available conventional soybean and canola oils, and does not present an identified differential risk.

A review of the trans-fat literature by Hunter (2005) looks at the impact of trans-fat content in the diet on LDL and HDL cholesterol parameters, which are believed to be markers of cardiovascular risk. It is notable that statistically significant changes in lipid parameters were not observed at trans-fat intakes below 4% of total energy. It is our understanding that a review conducted by FSANZ in 2009 found that the average intake of total trans fat in Australia and New Zealand was 0.5% and 0.6% of total energy, respectively (http://www.foodstandards.gov.au/consumerinformation/transfattyacids.cfm), levels also well below that recommended by WHO.

Finally, we would note that SDA soybean oil has been the subject of a 90 day toxicology study in rats (Hammond et al., 2008) and has also been the subject of two human clinical trials (Harris et al., 2008, Lemke et al., 2010), with results as tabulated below (Table 4). In the rodent study, declines were seen (high dose group) in total cholesterol and triglycerides, with statistically significant declines in cholesterol in males and triglycerides in females. While rodents are not an ideal model for predicting efficacy of lipid lowering in humans or for predicting impacts on human cholesterol metabolism, these data provide some assurance of safety at doses that exceed expected human consumption levels. We would note that in the rodent study, declines were seen (high dose group) in total cholesterol and triglycerides, with statistically significant declines in cholesterol in males and triglycerides in females. Of greater importance are the human data. In the first human study (Harris et al., 2008; n=11 per protocol subjects in each group), no differences were observed in lipid profiles (triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol), and no "trends" of concern are apparent. In the second trial (Lemke et al., 2010), no effects on total cholesterol, LDL-cholesterol, or HDL-cholesterol were observed. In this second clinical study a trend was observed for a decline in triglycerides, but the observation was not statistically significant based on pre/post values across the entire group. Based upon this observed trend, however, a post-hoc statistical analysis was conducted with the high-triglyceride subset (intended for a post-prandial trigyceride study, see paper), and a statistically significant decline in triglyceride values was noted (Krul et al., 2010. As this is a post-hoc analysis and numbers are limited, this observation should not be over-interpreted and will require validation in future studies before a definitive conclusion can be drawn. However, we would note that reduced plasma triglycerides after consuming SDA, an omega-3 fatty acid, is consistent with observations seen in other clinical studies following consumption of foods rich in long-chain omega-3 fatty acids (Harris, 1997).

Overall, significant quantities of trans-ALA exist in commercial oils, as indicated in the response to question 1. However, existing SDA content in foods is low and, given limitations in analytical sensitivity, it is not surprising that trans-SDA has not been reported in oils or foods unless specifically chosen for SDA content (i.e., echium oil). It should be noted, however, that trans-SDA was present in the oils utilized for safety assessment studies in rodents, and safety margins are therefore established by these studies as they are for SDA itself. Most critically, SDA soybean oil has been the subject of two human clinical trials to date in which plasma lipid profiles were assessed. These studies did not demonstrate an adverse effect of SDA soybean oil intake on lipid profile parameters, and suggest (based on post-hoc subgroup analysis) that beneficial effects on triglycerides (consistent with expectation based on studies with fish oil) may be present.

Based on the above discussion, there should not be any risk or adverse effect from the consumption of the very low levels of trans-ALA and trans-SDA present in SDA soybean oil.

Table 4. Results from the Rat Toxicology and Human Clinical trials

90 day rat (Hammond 2008)		Control SBO 4g/kg/d	Menhaden 4g/kg/d	SDA SBO 1.5 g/kg/d	SDA SBO 3 g/kg/d	Notes
Triglycerides		112 ±43	77 ±23*	97 ±24	75 ±15*	Males (n=10)
Cholesterol		87 ±27	39 ±9*	91 ±23	67 ±6	Males
Triglycerides		44 ±8	63 ±47	40 ±7	51±30	Females (n=10)
Cholesterol		73 ±21	36±12*	60 ±22	48 ±15*	Females
Human Clinical (Harris 2008)		**Control SBO**	**EPA 1 g/d**	**SDA SBO 4 g/day**	**Notes**	
TGY*	Initial	149.8±68.5	122.7 ±83.7	90 ±40	n = 11 per protocol, all groups and all tests presented here.	
	Final	142±94	116 ±76	84 ±33		
T-Chol**	Initial	204 ±46	202 ±35	190 ±27		
	Final	205 ±41	207 ±27	192 ±24		
LDL	Initial	126.7±40.3	120.5±34.8	117 ±29		
	Final	127 ±36	123 ±27	120 ±30		
HDL	Initial	47.5 ±10.0	56.9 ±17.4	55.6 ±20.8		
	Final	50.1 ±16.5	60.4 ±17.1	55.1 ±14.8		
Human Clinical (Lemke 2010)		**Control SBO**	**EPA 1 g/d**	**SDA SBO 4 g/day**	**Notes**	
TGY*	Initial	112.4±65.0	125.4±66.4	126.2±75.4	n = 65/62/53 respectively	
	Final	124.0±77.7	123.6±59.9	112.5±61.6		
T-Chol**	Initial	201.9±37.8	194.3 ±33.1	198.6±37.5	n = 65/62/53 respectively	
	Final	205,0±34.0	201.7±34.0	195.7±32.3		
LDL	Initial	123.9±31.4	120.3±26.9	120.5±31.6	n = 62/61/53 respectively	
	Final	123.8±30.8	127.5±27.8	121.2±28.2		
HDL	Initial	56.0 ±15.8	49.1 ±10.6	52.7 ±14.3	n = 65/62/53 respectively	
	Final	56.3 ±17.1	50.0 ±11.3	52.0 ±13.9		

*triglycerides; **total cholesterol

4. More detailed information on possible food uses of SDA soybean oil is required. For example, it is not clear from the Application whether SDA soybean oil is suitable for cooking or is limited for use in manufactured foods currently fortified with omega-3 fatty acids. Is it likely that RBD oil from MON 87769 soybean will be directly available to consumers as a vegetable oil? Does SDA soybean oil have any physicochemical or technological properties that would favour its use in particular foods, for example, bread or cereal products?

Response:

As a replacement for omega-3 oils or omega-3 fatty acid containing products in food, the use of SDA soybean oil from MON 8769 would be limited by (1) functional suitability for incorporation into food, (2) providing acceptable sensory properties (no off-flavors or bad taste) to food, and (3) imparting the appropriate stability profile and shelf life during food production and storage. As expected, SDA soybean oil from MON 87769 contains high levels of SDA (approximately 20-30 wt% of total fatty acids), a polyunsaturated fatty acid. Vegetable oils containing high levels of polyunsaturated fatty acids are known to undergo rapid oxidation during frying applications that will impart undesirable taste and odor to the fried foods. Therefore, similarly SDA soybean oil will not be suitable for all food applications and may not be suitable as a substitute for saturated fats in food recipes. However, SDA soybean oil can partially replace regular soybean oil or other oils in many food categories (e.g., salad dressings, yogurts, bars, etc.). The current anticipated food applications for SDA soybean oil are in a variety of packaged foods such as baked goods and baking mixes, breakfast cereals, grain products and pastas, gravies and sauces, milk products, soups and soup mixes[3]. Given the likely use of bottled vegetable oil for frying in home cooking, it is unlikely that RBD oil from MON 87769 will be directly available to consumers as a bottled vegetable oil for home cooking.

As is the case with fish oils, hydrogenation of SDA-containing oil would be without purpose, as hydrogenation would convert SDA to saturated fatty acids. Thus, hydrogenation is not applicable to MON 87769 oil.

5. Based on the proposed food uses outlined in the GRAS notice (US FDA), dietary modelling with SDA soybean oil indicates a slight reduction in the intake of dietary TFA in the context of the U.S. diet. In order to gain an understanding of any possible relevance for diets in Australia/New Zealand, FSANZ requires further details of the modelling that was conducted with SDA soybean for the purposes of the GRAS notification.

Response:

The consumption of SDA soybean oil from all proposed food uses was estimated by Exponent using the proposed food uses and use levels in conjunction with food consumption data included in the U.S. National Health and Nutrition Examination Surveys (NHANES 1999-2002) (CDC, 2007).

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[3] U.S. FDA Food classifications 21 CFR §170.3(n).

The current intake of fat, trans-fat, and fatty acids in the diet, as well as intake following the addition of 20 or 30% SDA soybean oil to the proposed food uses, was calculated. SDA soybean oil was either added to foods or replaced an unhydrogenated oil (including soybean oil, oil 'not further specified', corn oil, cottonseed oil, peanut oil, sunflower oil, coconut oil, olive oil, canola oil, or palm oil). In order to achieve 375 mg SDA per serving of food, every target food needs to have 1.8 g of 20% SDA soybean oil or 1.3 g of 30% SDA soybean oil per serving of food. Exponent used their proprietary recipes to determine the amount and type of oil in each food, and either added in or replaced soybean oil or non-soybean liquid oil with SDA soybean oil to ensure this measured oil quantity. When the main oil variety for a food was a hydrogenated oil, it was assumed, based on knowledge of the food industry, that this hydrogenated oil contained a blend of 60% solid fat and 40% liquid oil. Only the liquid 40% portion of the hydrogenated oil blend was then made available for substitution of SDA soybean oil in order to maintain functionality of solid fat..

Following the introduction of 20% SDA soybean oil to the proposed foods, the per capita mean and 90th percentile intakes of SDA soybean oil are estimated to be 10.1 and 19.6 g/day, respectively. Fat intake increased from 78.8 and 136.5 g/day at the mean and 90th percentile, respectively, to 84.0 and 143.6 g/day, respectively. This increase is attributable to the addition of SDA soybean oil to foods that do not contain fat. Intake of SDA from all dietary sources increased from 0.004 g/day at the mean and 90th percentile to 2.1 g at the mean, and to 4.0 g/day at the 90th percentile. Trans fat intake was estimated to decrease from 5.9 g/day to 4.9 g/day at the mean and 11.6 g/day to 9.8 g/day at the 90th percentile.

In regard to the estimated decrease in trans fat, it should be noted that recipes do not contain specificity in regard to the exact proportions of hydrogenated and liquid oil in foods. Monsanto and Exponent developed the baseline fatty acid profiles for a number of foods that historically contained partially hydrogenated oils using the USDA Trans Fatty Acid Database and food industry knowledge. In addition, Monsanto and Exponent utilized an assumption based on food industry knowledge to estimate the proportion of hydrogenated oil that could be functionally replaced by SDA soybean oil (i.e., 40% of hydrogenated oil in a given recipe). As a result of these assumptions, a decrease in trans fat was estimated in the modeling. In practice, the actual amount of replaceable hydrogenated oil will depend on the specific food application and recipe. It is expected that use of SDA soybean oil would predominantly be in substitution for liquid oils. As such, a small decrease or "no appreciable change" in trans fat intake is anticipated on a total population diet level as a result of using SDA soybean oil.

Please refer to pages 1 – 17 of MSL 002190 (submitted along with the petition) for detailed methods of the U.S. nutritional assessment of SDA soybean oil.

6. In addition to the information requirements outlined above, which are considered necessary to complete the safety assessment of food derived from MON 87769 soybean, FSANZ considers that additional information on the biology of this line would enhance the assessment of the trait itself. The compositional analyses show that the levels of SDA in MON 87769 soybean seeds vary approximately between 16% and 36%, with a mean of around 26% (total fatty acids) (Monsanto Study Report MSL 0020866). Given the broad range of expression of the trait observed in field trials under normal agricultural conditions, FSANZ requires discussion of the possible environmental or other factors that are likely to be contributing to this observed variability in SDA levels.

Response:

The *Pj.D6D* gene in SDA soybean is from the garden plant, *Primula Juliae*. Plants of the genus *Primula* are typically found in cooler climates. These plants contain high levels of SDA in their leaves, presumably to improve the structure and function of chloroplast membranes in their native cooler climates. Therefore MON 87769 is expected to produce more SDA if grown in colder regions and thus it is not surprising that an empirical relationship has been observed between SDA levels and the region where MON 87769 was grown; the colder the region the higher the expression of SDA. It is also known in general that soybeans grown in colder regions have more highly unsaturated fatty acids compared to soybeans grown in warmer regions (Wolf et al., 1982).

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