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Supporting Document 1

RISK ASSESSMENT REPORT

Executive Summary

The FSANZ approach to the safety assessment of this Application is to provide an update of the previous safety assessment for Application A360.

For the assessment of Application A360, FSANZ conducted a thorough risk assessment which established a tolerable daily intake (TDI) of 6 micrograms of THC per kilogram of bodyweight (6 ug THC per kg bw).

For the present Application, additional THC studies, which were identified in a recent review, were considered, in order to establish whether new data indicate a need to change the TDI. The updated safety assessment concludes that the TDI of 6 µg THC per kg bw remains valid and that the maximum limits for THC content of hemp foods are appropriate.

The safety assessment for this Application included an update on the dietary modelling conducted for Application A360. The updated dietary modelling included food consumption data from the recent national children's surveys in Australia and New Zealand, which were not available at the time of the Application A360 assessment. The dietary exposure assessment indicates that potential dietary exposures to THC are below the TDI of 6 µg/kg bw/day for all age groups for the Australian and New Zealand populations.

The nutrition assessment for this Application reinforces the outcome of the Application A360 nutrition assessment, and concludes that low THC hemp in food products may provide a useful alternative dietary source of many nutrients and polyunsaturated fatty acids, particularly omega-3 fatty acids. Only small quantities of whole hempseed or hempseed oil need be consumed to meet the adult Adequate Intake for alpha-linoleic acid (an essential omega-3 fatty acid).

Abbreviations

Time		Weight	
h	Hour	bw	Bodyweight
d	Day	wt	Weight
		ng	Nanogram
		µg	Microgram
		mg	Milligram
		g	Gram
		kg	Kilogram
Dosing			
mg/kg bwt/day	mg/kg bodyweight/day		

Chemistry	
ALA	*Alpha*-Linolenic Acid
DHA	Docosahexanoic Acid
EPA	Eicosapentaenoic Acid
GLA	*Gamma*-Linolenic Acid
LA	Linolenic Acid
SAA	Sulphur containing Amino Acids
SDA	Stearidonic acid
THC	δ–9-delta tetrahydrocannabinol
PUFA's	Poly Unsaturated Fatty Acids
Terminology	
AI	Adequate Intakes
AUS	Australia
C_{max}	Maximum Concentration
CNS	Central Nervous System
DEA	Dietary Exposure Assessment
DIAMOND	Dietary Modelling of Nutritional Data
IEFS	Institute of European Food Studies
ML	Maximum Levels
MS	Multiple Sclerosis
n	Number
NCS	Australian National Nutrition Survey
NNS	Australian National Nutrition Survey
NOAEL	No Observed Adverse Effect Level
NRV	Nutritional Reference Value
NZ	New Zealand
NZCS	New Zealand Children's Nutrition Survey
NZS	New Zealand Adult Nutrition Survey
p	Probability
PDCAAS	Protein digestibility corrected amino acid score
TDI	Tolerable Daily Intake
WHO	World Health Organisation

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1.   Hazard Assessment

1.1.   Background

1.1.1   Previous assessments of THC in foods by FSANZ

FZANZ has previously evaluated the safety of THC in foods in relation to Application A360 – Use of industrial hemp as a novel food, (completed in 2002). This evaluation concluded that on the basis of the data available, there is no evidence of adverse health effects in humans at low levels of THC exposure and a tolerable daily intake of 6 µg/kg bw can be established. If the products from industrial hemp plants are used as food, the level of THC in the final products should be such that the dietary intake of THC is no greater than 6 µg/kg bw.

1.1.2   Scope of the hazard assessment

The scope of this hazard assessment is to evaluate relevant data published after FSANZ's most recent (2002) evaluation.

1.2   Tolerable daily intake of THC

1.2.1   Introduction

For the assessment of Application A360, FSANZ conducted a risk assessment which concluded that, while the bulk of the human data on the toxicity of THC is derived from inhalation of *Cannabis* rather than consumption of THC as a component of food, there were adequate human data to assess the toxicity of THC following oral administration and establish a tolerable daily intake (TDI).

1.2.2   Oral administration studies in humans

It was concluded that following oral administration the most sensitive adverse effects observed in humans appear to be related to skill performance (e.g. hand-eye coordination and reaction time) and cognitive tasks (e.g. performance on arithmetic tasks). The TDI was derived from the results of a human study in which the effect of oral THC on skill performance, cognitive function and mood was examined at dose levels of 0, 5, 10, 15 and 20 mg/person (Chesher et al. 1990). Doses could not be expressed as mg/kg bodyweight (bw) because no information on mean group bodyweights was provided in the published report. THC, dissolved in sesame oil and taken as capsules, was administered orally to groups of university students (n = 16/group with variable ratios of males:females in each group). The subjects consumed a light breakfast prior to ingesting the capsules. The performance measures included standing steadiness, hand-eye coordination, reaction time tests, and an arithmetic test. Degree of intoxication was self-reported on a scale of 0 to 5. The subjects completed the test battery at 1.3, 2.3, 3.3 and 4.3 h after swallowing the capsules. The results indicated an approximately linear dose-response relationship between THC intake and a composite measure of performance decrement at the first three time-points. On the self-reporting intoxication scale, the lowest dose level (5 mg/person) was not distinguishable from placebo, although there was a dose-related effect reported at the other dose levels. The safety assessment concluded that a slight but reversible effect on skill performance may occur at an oral dose of 5 mg/person. By using the highest bodyweight individual in the study (84 kg) the threshold effect dose (5 mg/person) was reduced to be equivalent to 60 µg/kg bw. In order to take account of the possible variability in response in the human population, an uncertainty factor of 10 was applied to derive an overall TDI of 6 µg/kg bw. The use of an acute human study to establish a TDI is considered appropriate because of the known development of tolerance to THC following regular exposure. Thus, it

is plausible that effects on skill performance and cognitive function may be observable after a single low dose of THC but not apparent when the same daily dose is received over an extended period.

In relation to psychotropic effects, the safety assessment for Application A360 concluded that the studies available indicated that the more sensitive individuals require a minimum oral dose of 10 mg THC to experience a psychotropic effect, while the majority of individuals require an oral dose of 15-20 mg to experience a psychotropic effect. Thus, the lowest psychotropic effect level is around 140 µg/kg bw for a 70 kg person (i.e. approximately 20-fold greater than the TDI).

1.2.3   Studies in other species

The risk assessment also considered data on reproductive and developmental toxicity, genotoxicity and carcinogenicity. Reproductive and developmental toxicity studies in animals gave effects only at higher doses of THC and it was concluded that the findings are unlikely to be relevant to low-dose human exposure. In vitro genotoxicity data indicated that THC is not mutagenic while evidence regarding the possible induction of chromosome aberrations was considered to be inconclusive. However, two-year oral gavage studies in mice and rats gave no evidence that THC was carcinogenic. Based on these findings it was considered appropriate to base the TDI on the most sensitive known endpoint, namely skill performance in humans.

1.2.4   New data considered since the 2002 application

The previous risk assessment considered published data up to and including 1998. For the present Application, oral THC studies identified in a recent review were considered (Zuurman et al. 2009), along with any relevant studies published subsequently up to December 2010, in order to establish whether new data indicate a need to change the TDI.

Zuurman et al. (2009) reviewed published studies relevant to biomarkers for the effects of *Cannabis* and THC exposure in healthy volunteers. Oral, intrapulmonary and intravenous routes of exposure were considered. Studies with <10 subjects were not included. The literature search conducted for the review yielded 165 different studies on *Cannabis* and THC that met the specified criteria, published between 1966 and November 2007. There were only 10 cited studies published post-1998 that included data on oral THC administration, however the lowest THC doses tested in these studies were all greater than the low dose of 5 mg/person tested by Chesher et al. (1990). For example, two studies used single dose levels of 10 mg/person (Ploner et al. 2002) or 20 mg/person (Hart et al. 2002) while four studies used oral THC dose levels of 7.5 and 15 mg/person (Kirk and de Wit 1999; Wachtel and de Wit 2000; Curran et al. 2002; McDonald et al. 2003). Because the doses used in these 10 studies were higher than the dose of 5 mg/person from which the TDI was derived, any findings in these studies cannot be used to justify a lower TDI for THC.

The review by Zuurman et al. did not aim to specifically establish a threshold dose for effects observed after oral administration, however one of the major conclusions of the review was that the subjective reporting of feeling 'high' appeared to be the most sensitive CNS biomarker for the effects of THC. This is in contrast to the Chesher study which reported slightly decreased skill performance at 5 mg/person but no self-reported feeling of intoxication at this dose. It is possible that the reported decreased skill performance at 5 mg/person may be an artefact of the statistical analysis used in the Chesher study. This possibility is supported by the analysis of the data collected at the 3rd time-point (3.3 h post-dose) which indicated that skill performance following the 10 mg/person dose was slightly less impaired relative to the 5 mg/person dose. In addition, Chesher et al. reported a statistically significant ($p < 0.05$) trend of performance decrement with increasing THC dose,

however the paper did not state whether the performance decrement reported at the dose of 5 mg/person was statistically significant. Since a dose of 5 mg/person was associated with no subjective feeling of intoxication, and any association with decreased skill performance is questionable, it is considered that this dose level represents a no observed adverse effect level (NOAEL) in this study. This conclusion is consistent with recent studies which measured plasma/serum concentrations of THC following *Cannabis* smoking and oral administration of THC. In a study on smoked *Cannabis* it was concluded that the threshold of impairment of skill performance is associated with a serum THC concentration of 2 ng/mL (Raemakers et al. 2006). This compares to the results of an oral study in which the mean C_{max} for THC after a dose of 14.8 mg/person administered to 6 subjects was 1.2 ng/mL (Goodwin et al. 2006).

Several studies investigating the effects of oral THC in humans have been published subsequent to the literature search conducted by Zuurman et al. (2009), however only one study was located which employed dose levels of 5 mg/person or lower. This was a small double-blind study investigating the tolerability and effects of oral THC in a group of adolescents with marijuana use disorders (Gray et al. 2008). Eight participants (ages 16–21 years), smoking an average of ~5 days/week and 2.5 "joints"/day, completed this four-session study, during which they received one of four oral THC doses (0, 2.5, 5, 10 mg/person) each session. The participants were instructed to abstain from marijuana use 24 hours prior to each oral dose. Physiological (blood pressure, heart rate), psychomotor, and subjective measures (mood, experience of a drug effect) were assessed at baseline and at three time-points after THC administration (+60, +120, and +180 min). Psychomotor performance was evaluated using a computerised task designed to assess visual-spatial processing.

Oral THC had no effect on psychomotor performance, heart rate or blood pressure. Oral doses of 2.5 and 5 mg/person had no statistically significant effect on subjective rating of a drug effect while the 10 mg/person dose significantly increased subjective ratings of "good drug effect" and feeling "high" as compared to placebo ($p < 0.05$), while producing no significant effects on ratings of "bad drug effect." However, two participants reported "good drug effect" and feeling "high" when they received placebo indicating that these subjective measures are not generally reliable at the relatively low oral doses used in this study. In addition, the 5 mg/person dose resulted in statistically significant ratings of decreased irritability and decreased tiredness relative to placebo while the doses of 2.5 and 10 mg/person had no reported effect on these subjective measures. It is concluded that none of the oral THC dose levels tested in this study were associated with adverse effects.

The Zuurman review did not consider publications that reported the results of clinical trials with oral THC. Extensive data on the clinical use of oral THC have been published in the past 10 years, in particular for the treatment of spasticity and other symptoms related to multiple sclerosis (MS). When used as a therapeutic agent, oral THC has shown a favourable safety profile even at relatively high doses. For example, a study in MS patients receiving a maximum oral dose of 25 mg THC daily for up to 12 months reported that minor adverse events were evident in 361 patients: 109 receiving THC, 125 receiving *Cannabis* extract and 127 on placebo (Zajicek et al. 2005). It was stated that most of the 74 serious adverse events reported (24 THC, 27 *Cannabis* extract, 23 placebo) were as expected in the patient population participating in the trial. Thus, oral THC was indistinguishable from placebo with regard to the incidence of adverse events.

Published human data on the potential adverse effects of chronic oral exposure to THC are lacking. However, with regard to chronic exposure to THC from smoking *Cannabis*, a recent review concluded that case-control studies suggest that some adverse health outcomes may be elevated among heavy *Cannabis* users, namely, fatal motor vehicle accidents, and possibly respiratory and brain cancers (Calabria et al. 2010). It was also concluded that there was insufficient evidence to assess whether the all-cause mortality rate is elevated

among *Cannabis* users in the general population. THC per se has not been shown to possess genotoxic or carcinogenic potential and any association with respiratory and brain cancers may be explained by exposure to other chemicals in *Cannabis* smoke.

1.3   Conclusion

In conclusion, consideration of data published subsequent to the assessment of Application A360 indicates that the TDI of 6 µg THC per kg bw remains valid.

2.   Nutrition Assessment

2.1   Key risk assessment questions

For the nutrition assessment of Low THC hempseed & hempseed oil the following questions are posed:

   a)   How does the nutrient content of hempseed/hempseed oil compare with similar foods?
   b)   Could hempseed/hempseed oil potentially contribute to dietary recommendations for omega-3 and omega-6 fatty acids?

2.2   Nutrient composition of low THC Hemp as a Food

Whole, low THC hempseed is a nutritious food containing sizable amounts of protein, polyunsaturated fats and dietary fibre (Callaway 2004) as well as micronutrients such as thiamin, vitamin E, phosphorus, potassium, magnesium, calcium, iron and zinc (Rodriguez-Leyva and Pierce 2010). Hempseed oil contains the second highest amounts of omega-3 fatty acids of all commonly available plant-based oils (Callaway, 2004).

This nutrition assessment describes in more detail the protein content and quality of hempseed as well as the fatty acid profile of whole hempseed and hempseed oil.

2.2.1   Protein content

Table 2.1 provides a comparison of the total protein content of hempseed with egg, soy flour, and other nuts and seeds. Although hempseed (whole and meal) has a higher amount of protein than egg, the traditional animal reference protein, whole hempseed is comparable to other seed and nut protein sources. Both forms of hempseed are second only to soy flour, and higher than whole soy bean.

Table 2.1   *Protein content of hempseed and selected foods (g/100 g edible portion)*

Food name	Protein[1]
Soy flour, low fat	46.5
Hempseed, meal, defatted	**33.5**
Hempseed, whole, raw	**24.8**
Peanut, with skin, raw	24.7
Pumpkin, seed, hulled & dried	24.5
Sunflower, seed	22.7
Sesame, seed, white	22.2
Almond, with skin	19.5
Flaxseed	18.3

Soy bean, dried, soaked, boiled, drained	13.5
Egg, whole, raw	12.7
Tofu (soy bean curd), firm, as purchased	12.0
Egg white, boiled	11.6
Egg white, raw	11.2

1 The data source for all foods was AUSNUT 2007 (FSANZ 2011), except for whole hempseed and hempseed meal (Callaway, 2004).

2.2.2 Protein quality

The protein quality of hempseed, egg white and soy flour is shown in Table 2.2 using the method of the protein digestibility corrected amino acid score (PDCAAS) described in WHO, 2007 (WHO 2007). This method estimates the relative utilisation of food proteins based on a calculation using the digestibility of a protein and its essential amino acid profile. The amino acid score describes the content of essential amino acids in a protein compared with the amino acid requirement pattern (for protein synthesis). The digestibility of a protein source is an estimate of the proportion of a food protein which is absorbed compared with the total consumed (accounting for faecal, urinary and other metabolic nitrogen losses). The purpose of the PDCAAS is to enable the comparison of the relative ability of food protein sources (individually or mixed) to meet the human demand for amino acids and nitrogen, providing a measure of the overall efficiency of the protein utilisation of particular protein sources (WHO, 2007).

Table 2.2 shows that, of the essential amino acids shown, lysine in all three foods makes the lowest relative contribution to adult essential amino acid requirements but only for hempseed is lysine the limiting amino acid (below 1.00) where 100 g provides less than the adult amino acid requirement.

Calculations of PDCAAS were also done for other population age groups: infants, pre-school children, and older children (data not shown). Lysine in hempseed was the most limiting amino acid for these population groups also.

Table 2.2 *Protein Digestibility Corrected Amino Acid Score (PDCAAS) for hempseed, egg white and soy flour relative to adult requirement*

Food	Digestibility	Protein digestibility corrected amino acid score[1]			
		Lysine	SAA[2]	Threonine	Tryptophan
Egg white	0.97	1.23	2.58	1.88	2.49
Soy flour	0.86	1.03	1.31	1.58	1.84
Hempseed	**0.90[3]**	**0.82**	**1.62**	**1.38**	**1.20**

1 The data source for egg and soy is AUSNUT 2007 (FSANZ 2011), except hempseed (Callaway, 2004).
2 SAA is an acronym for the Sulphur-containing Amino Acids, cysteine and methionine.
3 Cotton seed, sunflower seed flour digestibility score used for hempseed (WHO, 2007).

2.2.3 Fatty acid profile

The most nutritionally important aspect of hempseed is its fatty acid profile. Over 80% of fatty acids in hempseed are polyunsaturated comprising mostly linoleic acid (LA; 18:2 *omega*-6) and *alpha*-linolenic acid (ALA; 18:3 omega-3) (Callaway, 2004). Other minor derivatives of LA also present are gamma-linoleic acid (GLA, 18:3 omega-6) and stearidonic acid (SDA, 18:4 omega-3) (Callaway, 2004).

Table 2.3 provides the fatty acid profile of hempseed and other plant-based oils in descending order of ALA content. Hempseed oil is comparable to soybean oil and sunflower oil in LA content however it is higher than most other plant-based oils in ALA content, being

second only to flaxseed oil.

Table 2.3 *Fatty acid composition of hempseed oil and comparable oils (g/100 g)*

Oil[1]	Saturated fatty acids, total	Monounsaturated fatty acids, total	Polyunsaturated fatty acids		
			Total	LA	ALA
Flaxseed, oil	8.5	17.8	68.7	14.2	54.6
Hempseed, oil[2]	**6.7**	**8.6**	**80.3[3]**	**53.5**	**21.0**
Canola, oil	6.9	59.5	28.5	18.5	10.0
Soybean, oil	14.7	18.5	62.3	55.2	7.2
Olive, oil	16.0	69.9	9.5	8.8	0.7
Sunflower seed, oil	10.7	25.1	59.8	59.5	0.3
Peanut, oil	18.1	43.9	33.6	33.3	0.3

1 The data source for all oils is AUSNUT 2007 (FSANZ 2011), except hempseed oil (Callaway, 2004)
2 Derived from Callaway, 2004 by applying 0. 956 lipid conversion factor representing proportion of total fatty acids in total fat
3 Includes 1.9 g/100 g GLA and 3.8 g/100 g SDA

Table 2.4 (presented in descending order of ALA content) shows that, in comparison with whole seeds, nuts and soybean, whole raw hempseed has comparable LA content to pumpkin seed while being lower than walnut and sunflower seed. Whole raw hempseed is much higher in ALA content than most nuts and seeds; it is second only to flaxseed (NHMRC and NZMoH 2006).

Table 2.4 *Fatty acid composition of whole raw hempseed and comparable seeds and nuts, and soybean (g/100 g)*

Food name[1]	Fat, total	Saturated fatty acids, total	Mono-unsaturated fatty acids, total	Polyunsaturated fatty acids		
				Total	LA	ALA
Flaxseed	42.2	3.6	7.5	29.0	6.0	23.0
Hempseed, raw[2]	**35.5**	**2.4**	**3.1**	**28.5[3]**	**19.0**	**7.5**
Walnut, raw	69.2	4.4	12.1	49.6	43.3	6.3
Soy bean dried	20.2	2.9	3.1	12.7	11.1	1.6
Soy bean, dried, soaked, boiled, drained	7.7	1.1	1.2	4.8	4.2	0.6
Pumpkin, seed, hulled & dried	45.9	8.5	14.2	20.9	20.7	0.2
Hazelnut, raw	61.4	2.7	48.8	7.2	7.04	0.1
Sunflower, seed	51.0	4.3	9.8	34.5	34.5	0.0
Peanut, with skin, raw	47.1	7.1	23.1	14.9	14.9	0.0

1 The data source for all foods is AUSNUT 2007 (FSANZ 2011), except hempseed (Callaway, 2004).

2 Fatty acid composition derived from hempseed oil (Callaway, 2004)
3 Includes 0.7 g/100 g GLA and 1.3 g/100 g SDA

2.2.4   Role of LA and ALA in health

LA is also a structural component of cell membranes and important in cell signaling as well as being a precursor for the long chain fatty acid arachidonic acid (20:4, *omega*-6), and eicosanoid production. ALA is less common in the diet than LA and is the precursor for eicosapentaenoic acid (EPA, 20:5, omega-3) which is in turn metabolised to docosahexanoic acid (DHA, 22:6, omega 3) (NHMRC and NZMoH, 2006).

2.2.5 Nutrient reference values for omega-3 and omega-6 PUFAs

The most recent revision of Nutrient Reference Values[1] for Australia and New Zealand include Adequate Intakes (AIs) for the essential fatty acids: LA (men 13 g/day; women 8 g/day) and ALA (men 1.3 g/day; women 0.8 g/day.)

Table 2.5 shows the contribution of 20 g whole hempseed or hempseed oil to essential fatty acid AIs for men and women. Twenty grams of whole hempseed or hempseed oil could contribute as much as 5 times the AI for women. In other words, the AI for ALA could be achieved by consuming about 11–17 g raw hempseed or 4–7 g hempseed oil.

Used in the diet as an alternative or addition to other seed or nut oils or as a whole food in place of soy bean or commonly available nuts and seeds, hempseed could provide a useful dietary source of the essential fatty acids LA and particularly ALA.

Table 2.5 *Potential contribution of 20 g hempseed to LA and ALA Adequate Intakes*

	LA			ALA		
	(g/20 g)	% AI men	% AI women	(g/20 g)	% AI men	% AI women
Hempseed, whole, raw	3.8	29	47	1.5	115	187
Hempseed, oil	10.7	82	133	4.2	323	525

2.3   Conclusion

Hempseed contains protein and many vitamins and minerals like many nuts and seeds but is much higher in omega-3 polyunsaturated fatty acids except for flaxseed. The protein quality of hempseed is slightly lower than the quality proteins of egg and soybean. Removing the prohibition on the use of low THC hemp in food products may provide a useful alternative dietary source of many nutrients and polyunsaturated fatty acids, particularly omega-3 fatty acids. Only small quantities of whole hempseed or hempseed oil need be consumed to meet the adult Adequate Intake for alpha-linoleic acid.

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[1] Nutrient reference values (NRVs) indicate the daily amount of essential nutrients required for good health, as well as a safe intake of nutrients.

3.   Dietary Exposure Assessment

3.1   Background

A Dietary Exposure Assessment (DEA) was undertaken for Application, A360. For the purposes of assessing the current Application, this earlier DEA was updated to incorporate dietary exposure estimates based on the dietary survey data for both the Australian and New Zealand populations that has since become available.

A DEA was undertaken for Application A360 to ensure that the proposed maximum permitted levels of δ–9-delta tetrahydrocannabinol (THC) within foods containing industrial hemp would not lead to dietary exposures greater than 6 μg/kg bw, the tolerable daily intake (TDI) for the human population (see Section 2 – Hazard Assessment).

Dietary modelling integrates food consumption data with food chemical concentration data to estimate dietary exposure:

Dietary exposure = food chemical concentration x food consumption

A brief explanation of how dietary exposure assessments are conducted at FSANZ is provided in Appendix 1.

3.2   Food consumption data

The food consumption data used for the dietary modelling were derived from the four most recent national nutrition surveys (NNSs) conducted in Australia and New Zealand:

- 1995 National Nutrition Survey of Australia (1995 NNS), surveying 13858 people aged 2 years and over. This survey used one 24-hour recall for all respondents and a second 24-hour recall for approximately 10% of respondents.
- 1997 New Zealand NNS (1997 NZS), surveying 4636 people aged 15 years and over. The survey used one 24-hour recall for all respondents and a second 24-hr recall for approximately 15% of respondents.
- 2002 New Zealand Children's Nutrition Survey (2002 NZCS), surveying 3275 people aged 5-14 years. The survey used one 24-hour recall for all respondents and a second 24-hr recall for approximately 15% of respondents.
- 2007 Australian National Children's Nutrition and Physical Activity Survey (2007 NCS), surveying 4487 people aged 2-16 years. The survey used two 24-hr recalls for all respondents.

DIAMOND, FSANZ's custom built dietary modelling program, provides access to the individual dietary records from each NNSs, which included records of individual body weights. The use of DIAMOND to access individual dietary records gives more information about the distribution of the individual dietary exposure estimates than is possible using point estimates of population food consumption.

Further information on the national nutrition surveys and some of the limitations associated with using consumption data derived from these surveys is set out in Appendix 1.

3.3 Food chemical concentration data

As little information is available on actual concentrations of THC in foods, and in order to minimise the risk to public health and safety, maximum levels (MLs) of THC in certain commodities were calculated. These MLs were then used in the dietary modelling.

3.3.1 Calculation of MLs

Proposed MLs for various commodities likely to contain industrial hemp were derived by estimating a maximum concentration of THC in each commodity that would not result in consumers exceeding the TDI for THC, assuming consumption at the 95th percentile[2] level. The highest 95th percentile consumption figure from the 1995 NNS in each commodity group was taken; for example, the 95th percentile consumption of olive oil was the highest of all potential salad oils considered. The maximum concentration of THC for each commodity group that would not result in exposure above the TDI was estimated. These calculations assume that the entire commodity contains THC and that it is the only product consumed. An exception was made for wheat flour, where it was considered unrealistic to assume that 100% of the commodity contained industrial hemp; therefore 10% of the 95th percentile consumption of wheat flour was used. The equation used for these calculations is as follows:

$$\text{Maximum concentration (mg/kg)} = \frac{\text{TDI (mg/d)}}{\text{Consumption (kg)}}$$

The consumption figures used in the calculations and the results are shown in Table 3.1.

Table 3.1 Calculations for derivation of proposed MLs for THC in various food groups

Commodity	Source of consumption figures (1995 NNS)	Age (years)	95th Percentile Food Consumption (kg)	Resulting maximum THC concentration (mg/kg)
Hemp oils	Olive oil	2 – 12	0.016	10.22
		20 and above	0.028	16.07
Hemp seed	Mustard seed	2 – 12	0.007	24.56
		20 and above	0.013	33.58
Hemp tea, brewed	Black tea, brewed	2 – 12	0.615	0.27
		20 and above	1.776	0.25
Hemp-based beverage	Mammalian milk	2 – 12	1.461	0.12
		20 and above	1.558	0.29
Hemp flour	10% Wheat flour	2 – 12	0.021	8.1
		20 and above	0.024	18.5

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[2] FSANZ previously routinely used 95th percentile food consumption amounts or dietary exposure estimates to represent the high consumer. Following international peer review of its dietary modelling procedures FSANZ has since adopted a policy that a high consumer's chronic dietary exposure is best represented by the 90th percentile of exposure. For further information on the use of the 90th percentile for dietary exposure assessments, refer to the FSANZ information paper: Protecting 'high consumers' at:
http://www.foodstandards.gov.au/scienceandeducation/scienceinfsanz/dietaryexposureassessmentsatfsanz/protectinghighconsum4441.cfm
The MLs have not been revised for the purposes of assessing A1039. The use of 95th percentile food consumption is more conservative than the 90th percentile from a dietary risk perspective.

Note: The TDI in mg/d for adults aged 20 years and above is 0.45 mg/d (based on a mean body weight of 75 kg and TDI of 6 μg/kg bw/day), and for children aged 2-12 years is 0.168 mg/d (mean body weight of 28 kg).

Proposed MLs have been derived from the worst case scenario presented in Table 3.1, usually from the maximum concentration for children aged 2-12 years old, by use of the convention of rounding down to the nearest 1, 2, 5 or 10 mg/kg figure.

From the above table, the proposed ML for hemp oil is 10 mg/kg; the proposed ML for hemp seed alone would be 20 mg/kg and the proposed ML for hemp flour is 8 mg/kg.

As hemp flour is a product of hemp seed and is the major food derived from hemp, the data from hemp flour was used and proposed ML rounded down to 5 mg/kg, and applied to both hemp seed and hemp flour.

For hemp-based beverages, although the maximum concentration would be 0.1 mg/kg, it was concluded that 0.2 mg/kg would be appropriate because it is very unlikely that hemp-based beverages would replace all mammalian milk consumption. In other countries, hemp-based beverages are sold in 125 ml containers and it is therefore unlikely that it would be consumed in the large quantities that have been reported in the 1995 NNS for milk (1.4-1.6L).

Proposed MLs were derived using Australian food consumption data only. It was assumed that the consumption of the food groups in New Zealand were similar.

In summary, the proposed MLs are as follows:

- Hemp seed and hemp flour   5 mg/kg
- Hemp oil   10 mg/kg
- Hemp-based non-dairy beverages 0.2 mg/kg
- Other foods   0.2 mg/kg

3.4   THC dietary exposure estimate

To assess if exposure to a diet containing THC at the proposed MLs posed a public health and safety risk, a dietary exposure estimate was undertaken using those proposed MLs. Foods likely to contain industrial hemp that were considered for inclusion in the modelling are as follows:

Hemp seeds can be used to make muesli bars and baked goods, as well as being eaten by themselves. Hemp seeds were not a part of the Australian or New Zealand diet when the NNSs were conducted, and therefore consumption data from the 1995, 1997, 2002 and 2007 NNSs for seeds that could be used similarly to hemp seeds were included in the modelling (poppy seeds, sesame seeds, sunflower seeds and mustard seeds). A THC level of 5 mg/kg in hemp seeds was used.

Hemp oil is a product that would be mainly used as a salad oil. An approach similar to that used for hemp seeds was used for hemp oil, where oils with similar uses were included in the modelling. The oils modelled were rapeseed oil, soybean oil, cotton seed oil, safflower oil, sesame seed oil, sunflower seed oil and olive oil. A THC level of 10 mg/kg in hemp oil was used.

Hemp flour can be made in one of two ways. Whole hemp seeds can be ground into flour, whereby the flour would have a similar THC concentration as the hemp seed (assuming no

destruction of the THC due to processing). Alternatively, the husk can be removed from the seed, and the hulled seed can be ground into flour. The THC concentration would be lower using this process. In the model, a THC level of 5 mg/kg in flour, which is the same as the proposed ML for seed, was used.

Hemp based non-dairy milk is made from soaking hemp seeds in liquid. A THC level of 0.2 mg/kg was used for this beverage.

Other hemp containing food groups were identified, as they were either available overseas as a hemp product, or likely to be produced containing hemp (Grotenhermen, Jarus & Lohmeyer, 1998). For example, hemp tofu is another product made from industrial hemp. Also, hemp tea is made from soaking hemp leaves in liquid. Although the above calculation suggests an ML of 0.2 mg/kg is suitable for hemp-based tea as consumed, no information was available to propose an ML for dried hemp leaves used for preparation of hemp-based tea. As these foods are minor uses for hemp, their contribution to the total diet would be minimal. Their inclusion in the modelling would have very little impact on estimated dietary exposures to THC.

Another product that may contain industrial hemp is beer. This product was not included in the dietary modelling for THC because the process that is involved in the brewing of beer is believed to destroy the THC.

Table 3.2 contains the THC concentrations for the various commodities used in the modelling.

Table 3.2 *THC Concentrations used in dietary modelling for various food groups*

Food	Proposed ML (mg/kg)
Flour	5
Hemp-based non-dairy milk	0.2
Seeds	5
Oils	10

It was not considered realistic to assume 100% of commodities in the model are hemp products exclusively, for the following reasons:

- hemp flour needs to be mixed with other flour for baking. Consumers would not bake all products containing flour with hemp flour (i.e. cakes, bread, pasta etc.);

- it would be difficult to consume hemp seeds exclusively as part of a bar for example. Muesli bars can contain around 3-10 % of hemp seeds; and

- hemp-based non-dairy milk is a very sweet product, a property that could make it difficult to consume in the same quantity as cow's milk.

Ten percent of the food products (except hemp-based non-dairy milk, see below) have been identified as potentially containing hemp (Grotenhermen, Jarus & Lohmeyer, 1998). Therefore, an adjustment factor of 10% was used in the model to represent the amount of the mainstream commodity (oils, seed, and flour) that would be likely to be replaced by hemp containing products. From the 1995 NNS it was estimated that approximately 3% of milk consumers drink soy beverages. In estimating the dietary exposure to THC it was assumed that consumption of hemp-based beverages would be similar to that of soy beverages. There is little information on soy beverage consumption for the 1995 Australian and 1997 New Zealand NNSs so mammalian milk consumption was used with a 3%

adjustment factor for these surveys. Soy and rice beverages were used to estimate THC exposure from hemp-based beverages for the 2002 and 2007 New Zealand and Australian Children's surveys with a 10% adjustment factor.

Modelling to estimate THC exposure was conducted for specific age groups using data derived from the most recent Australian and New Zealand NNSs:

- 1995 NNS – Used to estimate THC exposure for Australians aged 2 years and above and 17 years and above.
- 1997 NZS – Used to estimate THC exposure for New Zealanders aged 15 years and above and 15-19 years.
- 2002 NZCS – Used to estimate THC exposure for New Zealanders aged 5-14 years.
- 2007 NCS - Used to estimate THC exposure for Australians aged 2-12 years and 13-16 years.

The Australian and New Zealand populations were broken down into age groups to better characterise the risk associated with THC consumption in younger people including children and adolescents. Children are more vulnerable to exceeding a TDI due to their large food consumption compared to their small body weight. Adolescents can also eat large quantities of foods per kilogram of body weight. A breakdown of population sample details can be found in Table 3.3.

Table 3.3 *Population sample details for THC dietary modelling for Australia and New Zealand*

Population	Group Description	Number of Respondents	Number of Consumers	Consumers as a % all Respondents	Mean body Weight (kg)
Australia	2 years & above*	13858	13818	99.7	67
	2 – 12 years°	3268	3268	100	29
	13 – 16 years°	1219	1219	100	61
	17+ years*	11129	11090	99.6	74
New Zealand	15 years & above^	4636	4620	99.7	71
	5 - 14 years¤	3275	3269	99.8	40
	15 - 19 years^	297	296	99.7	65
	20+ years^	4339	4324	99.7	71

* 1995 NNS, ° 2007NCS, ^ 1997 NZS, ¤ 2002NZCS

3.4.1 Results

Dietary exposure estimates for mean and 90th percentile THC consumers are displayed below in Table 3.4 as µg THC/kg bw/d and as a percentage of the TDI.

Table 3.4 *Estimated dietary exposures to THC for potential consumers of foods containing hemp and various age groups for Australia and New Zealand*

Population	Group Description	Mean exposure µg/kg bw/d (% TDI)	90th %tile exposure µg/kg bw/d (% TDI)
Australia	2 years and above*	1.0 (16.3)	2.0 (33.2)
	2 - 12 years°	1.9 (32.0)	3.4 (55.9)
	13-16 years°	1.2 (19.5)	2.1 (34.4)
	17 years and above*	0.8 (12.6)	1.4 (23.7)
New Zealand	15 years and above^	0.8 (14.0)	1.6 (26.2)
	5-14 years¤	1.9 (31.8)	3.5 (58.8)
	15-19 years^	1.2 (19.5)	2.3 (37.6)
	20+ years^	0.8 (13.6)	1.5 (25.3)

* 1995 NNS, ° 2007NCS, ^ 1997 NZS, ¤ 2002NZCS

3.4.2 Discussion

The results, shown in Table 3.4, illustrate that it is likely that no consumers in Australia or New Zealand, for the total population, or in sub population groups, for both mean consumers, and consumers of THC at the 90th percentile, are at risk of exceeding the TDI for THC, using the proposed MLs. The major contributors to THC exposures for Australian consumers 2 years and above were hemp flour (89%) and hemp-based non-dairy beverage (7%). For New Zealand consumers (15 years and over) the major contributors were hemp flour (89%) and hemp-based non-dairy beverage (7%).

It should be noted that dietary exposures are likely to be overestimated, due to a number of reasons:

- there is the conservative assumption that 10% (3% for milk for the 1995 and 2007 NNS) of all foods consumed from the food groups will contain hemp;

- the models assume that all of the 10% (3% for hemp-based beverages modelled using 1995 Australian and 1997 New Zealand NNSs) contains the THC at the proposed maximum levels. The actual THC levels resulting in the food should be lower than the ML; and

- 24-hour recall food consumption data tends to overestimate habitual consumption of a given commodity, leading to higher estimates of potential dietary exposure than would be the case over a long period of time.

3.5   Conclusion

Proposed MLs for various commodities containing industrial hemp were derived by estimating a maximum concentration of THC in the commodity that would not result in consumers exceeding the TDI for THC, assuming consumption at the 95th percentile level. The proposed MLs were then used for the dietary exposure assessment to ensure that they would not lead to a total dietary exposure greater than the TDI.

The dietary exposure assessment indicates that potential dietary exposures to THC are below the TDI of 6 μg/kg bw/day for all age groups for the Australian and New Zealand populations. The exposures obtained are likely to be an overestimate because THC levels were assumed to be at the proposed ML and it is unlikely that the proportion of foods containing hemp would be as high as that assumed (10% for all foods groups considered except mammalian milk at 3%).

4.   Conclusions

The conclusions from this updated risk assessment are consistent with those for the A360 application.

The TDI of 6 µg THC per kg bw remains valid and the proposed maximum limits for THC content of hemp foods are appropriate.

The potential dietary exposures to THC are below the TDI of 6 μg/kg bw/day for all age groups for the Australian and New Zealand populations.

Low THC hemp in food products may provide a useful alternative dietary source of many nutrients and polyunsaturated fatty acids, particularly omega-3 fatty acids.

5. References

Calabria B, Degenhardt L, Hall W, Lynskey M (2010) Does *Cannabis* use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of *Cannabis* use. Drug Alcohol Rev 29(3):318-330.

Callaway J (2004) Hempseed as a nutritional resource: An overview. Eupytica 140:65–72

Chesher GB, Bird KD, Jackson DM, Perrignon A, Starmer GA (1990) The effects of orally administered delta 9-tetrahydrocannabinol in man on mood and performance measures: a dose-response study. Pharmacol Biochem Behav 35(4):861-864.

Curran HV, Brignell C, Fletcher S,Middleton P, Henry J (2002) Cognitive and subjective dose-response effects of acute oral delta 9-tetrahydrocannabinol (THC) in infrequent *Cannabis* users. Psychopharmacology 164:61-70.

FSANZ (2011) AUSNUT 2007 Database. FSANZ http://www.foodstandards.gov.au/consumerinformation/ausnut2007/ausnut2007microsofte4060.cfm. Accessed 24 December 2010.

Goodwin RS, Gustafson RA, Barnes A, Nebro W, Moolchan ET, Huestis MA (2006) Delta(9)-tetrahydrocannabinol, 11-hydroxy-delta(9)-tetrahydrocannabinol and 11-nor-9-carboxy-delta(9)-tetrahydrocannabinol in human plasma after controlled oral administration of cannabinoids. Ther Drug Monit 28(4):545-551.

Gray KM, Hart CL, Christie DK, Upadhyaya HP (2008) Tolerability and effects of oral delta9-tetrahydrocannabinol in older adolescents with marijuana use disorders. Pharmacol Biochem Behav 91(1):67-70.

Grotenhermen F, Jarus M & Lohmeyer, 1998, *THC Limits for Foods – A Scientific Study*, Nova Institute, Germany.

Hart CL,Ward AS, Haney M, Comer SD, Foltin RW, Fischman MW (2002) Comparison of smoked marijuana and oral delta(9)-tetrahydrocannabinol in humans. Psychopharmacology 164:407-415.

Institute of European Food Studies (IEFS), 1998, *The effect of survey duration on the estimation of food chemical intakes, Report Number 3*, IEFS, Ireland.

Kirk JM, de Wit H (1999) Responses to oral delta9-tetrahydrocannabinol in frequent and infrequent marijuana users. Pharmacol Biochem Behav 63:137-142.

Koethe D, Gerth CW, Neatby MA, Haensel A, Thies M, Schneider U, Emrich HM, Klosterkotter J, Schultze-Lutter F, Leweke FM (2006) Disturbances of visual information processing in early states of psychosis and experimental delta-9-tetrahydrocannabinol altered states of consciousness. Schizophr Res 88:142-150.

McDonald J, Schleifer L, Richards JB, de Wit H (2003) Effects of THC on behavioral measures of impulsivity in humans. Neuropsychopharmacology 28:1356-1365.

NHMRC and NZMoH (2006) Nutrient Reference Values for Australia and New Zealand. National Health and Medical Research Council and New Zealand Ministry of Health,

Canberra

Ploner CJ, Tschirch A, Ostendorf F, Dick S, Gaymard BM, Rivaud-Pechoux S, Sporkert F, Pragst F, Stadelmann AM (2002) Oculomotor effects of delta-9-tetrahydrocannabinol in humans: implications for the functional neuroanatomy of the brain cannabinoid system. Cereb Cortex 12:1016-1023.

Ramaekers JG, Moeller MR, van Ruitenbeek P, Theunissen EL, Schneider E, Kauert G (2006) Cognition and motor control as a function of delta9-THC concentration in serum and oral fluid: limits of impairment. Drug Alcohol Depend 85(2):114-122.

Rodriguez-Leyva D, Pierce GN (2010) The cardiac and haemostatic effects of dietary hempseed. http://www.nutritionandmetabolism.com/content/7/1/32. Accessed 1 December 2010

Wachtel SR, de Wit H (2000) Naltrexone does not block the subjective effects of oral delta(9)-tetrahydrocannabinol in humans. Drug Alcohol Depend 59:251-260.

Wachtel SR, ElSohly MA, Ross SA, Ambre J, de Wit H (2002) Comparison of the subjective effects of delta(9)-tetrahydrocannabinol and marijuana in humans. Psychopharmacology 161:331-339.

WHO (2007) WHO Technical Report Series. Protein and amino acid requirements in human nutrition : report of a joint FAO/WHO/UNU expert consultation. 935. WHO Press, Geneva Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, Nunn AJ, Teare LJ, Fox PJ, Thompson AJ (2005) Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 76(12):1664-1669.

Zuurman L, Ippel AE, Moin E, van Gerven JM (2009) Biomarkers for the effects of *Cannabis* and THC in healthy volunteers. Br J Clin Pharm 67(1):5-21.

Dietary exposure assessments at FSANZ

A dietary exposure assessment is the process of estimating how much of a food chemical a population, or population sub group, consumes. Dietary exposure to (or intake of) food chemicals is estimated by combining food consumption data with food chemical concentration data. The process of doing this is called 'dietary modelling'.

Dietary exposure = food chemical concentration x food consumption

FSANZ's approach to dietary modelling is based on internationally accepted procedures for estimating dietary exposure to food chemicals. Different dietary modelling approaches may be used depending on the assessment, the type of food chemical, the data available and the risk assessment questions to be answered. In the majority of assessments FSANZ uses the food consumption data from each person in the national nutrition surveys to estimate their individual dietary exposure. Population summary statistics such as the mean exposure or a high percentile exposure are derived from each individual person's exposure.

An overview of how dietary exposure assessments are conducted and their place in the FSANZ Risk Analysis Process is provided on the FSANZ website at:
http://www.foodstandards.gov.au/scienceandeducation/scienceinfsanz/dietaryexposureassessmentsatfsanz/dietaryexposureandin4438.cfm

FSANZ has developed a custom built computer program 'DIAMOND' to calculate dietary exposures. More information on DIAMOND is available on the FSANZ website at:
http://www.foodstandards.gov.au/scienceandeducation/scienceinfsanz/dietaryexposureassessmentsatfsanz/fsanzdietaryexposure4439.cfm

Further detailed information on the principles and practices of conducting dietary exposure assessments at FSANZ is provided in *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ, 2009), available at:
http://www.foodstandards.gov.au/_srcfiles/Principles%20&%20practices%20exposure%20assessment%202009.pdf

1   Food consumption data used

The most recent food consumption data available were used to estimate exposures to THC for the Australian and New Zealand populations. The national nutrition survey (NNS) data used for these assessments were:

- The 2007 Australian National Children's Nutrition and Physical Activity Survey (also known as '*Kids Eat Kids Play*') (2007 AusNNS)

- The 1995 Australian National Nutrition Survey (1995 AusNNS)

- The 1997 New Zealand National Nutrition Survey (1997 NZNNS)

- The 2002 New Zealand National Nutrition Survey (2002 NZNNS)

The design of each of these surveys varies somewhat and key attributes of each are set out below.

1.1   2007 Australian Children's Nutrition & Physical Activity Survey (2007 AusNNS)

The 2007 AusNNS collected data on nutrition and physical activity for 4,487 children aged 2-16 years across Australia. The survey was conducted over a seven month time period, from February to August 2007.

In contrast to other national nutrition surveys used to date by FSANZ (the 1995 Australian and 1997 New Zealand surveys), in the 2007 AusNNS each respondent completed two 24-hour recalls on non-consecutive days. The availability of two days of food consumption data provides a more realistic estimate of long term consumption of infrequently consumed foods, because it takes account of those who may eat a food on one day of the survey but not on the other. Using one 24-hour recall may capture an unusual eating occasion for an individual that does not describe how they normally eat.

In this assessment, exposure to THC was estimated from each consumer's average exposures from foods containing THC across Day 1 and Day 2. The results of the 2007 AusNNS were weighted to represent the overall population of Australian children because stratified sampling with non-proportional samples was used.

1.2   1995 Australian National Nutrition Survey (1995 AusNNS)

The 1995 AusNNS provides comprehensive information on dietary patterns of a sample of 13,858 Australians aged from 2 years and above (McLennan & Podger 1998). It is the most recent NNS for Australians aged 17 years and above. The survey used a 24-hour recall method for all respondents, with 10% of respondents also completing a second 24-hour recall on a second, non-consecutive day. The data were collected over a 13 month period. Food frequency data are available for a subset of the national sample (respondents aged 12 years and above) as are responses to a series of short dietary questions about food habits. These data are used unweighted in DIAMOND.

1.3   1997 New Zealand National Nutrition Survey (1997 NZNNS)

The 1997 NZNNS provides comprehensive information on the dietary patterns of a sample of 4,636 respondents aged from 15 years and above. The survey was conducted on a stratified sample over a 12 month period. The survey used a 24-hour recall methodology with 15% of respondents also completing a second 24-hour recall with an additional food frequency questionnaire and questions on food consumption patterns. These data are used unweighted in DIAMOND.

1.4   2002 New Zealand National Nutrition Survey (2002 NZNNS)

The 2002 New Zealand Children's National Nutrition Survey provides comprehensive information on the dietary patterns of a nationally representative sample of 3,275 New Zealand children aged 5-14 years, including sufficient numbers of children in the Mäori and Pacific groups to enable ethnic-specific analyses. The survey was conducted using a 24-hour recall methodology and collected data on dietary supplements as well as foods and beverages. A repeat 24-hour diet recall was obtained from a subsample, which enabled the statistical adjustment of the data to present the 'usual' intake distribution for nutrients by subgroup.

Further information on how the Australian National Nutrition Surveys are used to conduct dietary exposure assessments is available on the FSANZ website at: http://www.foodstandards.gov.au/scienceandeducation/scienceinfsanz/dietaryexposureassessmentsatfsanz/foodconsumptiondatau4440.cfm

Further information on the New Zealand National Nutrition Surveys is available from the New Zealand Ministry of Health website at: http://www.moh.govt.nz/moh.nsf/indexmh/dataandstatistics-subjects-nutrition

2   Limitations of dietary exposure assessments

Dietary exposure assessments based on the most recently available food consumption data provide the best estimate of actual consumption of a food and the resulting estimated dietary exposure for the Australian New Zealand populations. However, it should be noted that NNS data do have limitations. Further details of the limitations relating to dietary exposure assessments undertaken by FSANZ are set out in the FSANZ document, *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2009a).

In particular, it should be noted that the range of food consumption figures reported in 24-hour and two day recall surveys will tend to be far greater than that reported in 7-day surveys which report on dietary patterns averaged over a greater period of time. For staple foods that are frequently consumed, there may be little difference between the range of consumption reported over 24 hours and that averaged over a longer time period. However, for occasionally consumed foods the amount of food reported as consumed from single or two day 24-hour recall data will be much greater than that from surveys that reported over a longer period of time. A collaborative study undertaken by the Institute of European Food Studies (IEFS 1998) to assess the influence of survey duration on reported food consumption shows very clearly that as the duration of the surveys increases, the number of consumers of each food item increases but mean consumption for consumers only (eaters) decreases when averaged over the number of days in the survey. However, for staple foods, such as bread, the change is much less marked than that for occasionally consumed foods, such as pizza. The amount of food consumed by all respondents does not change over time.