FDA ATTY

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November 2, 2018

Via E-Mail
Patrick Cournoyer, Ph.D.
Consumer Safety Officer
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration

Re: FDA Additional Questions Regarding GRN 765, 771, and 778

Dr. Cournoyer,

Thank you again for your time by telephone on October 26, 2018, and subsequent e-mail on October 29, 2018. In the pages that follow are the detailed replies to your questions.

Kind Regards,

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Marc C. Sanchez, Esq.
Regulatory Counsel
Fresh Hemp Foods Ltd.

FDA Questions Received October 26, 2018

1. In question 1, we noted that NOAEL or LOAEL values from animal studies can be useful to calculate a margin of exposure. In typical food safety assessments, a NOAEL/LOAEL value from one study is identified as pivotal and used, along with the exposure estimate, to calculate a margin of exposure. Amongst the large number of relevant studies, the pivotal study would be the most informative for safety, possibly because it is well-designed, the most sensitive, or the most relevant to the key safety concern at hand.

In your response, you stated, "… these low total THC exposures are 100 to 1000 fold lower than the total THC exposures described above in the animal toxicology data." Please identify a specific study (or studies) you consider to be pivotal, explain why you consider it (or them) to be pivotal, and calculate a more specific safety margin based on the NOAEL/LOAEL from the study (or studies). You may wish to consult EFSA (2015) as an example of this approach.

Response:

The EFSA (2015) selected the BMDL10 of 0.73 mg/kg bw per day from the pivotal study evaluating the increased length in oestrus cycle observed in the subchronic rat study. If we select the highest individual exposure from our table, there are three values to consider, the Total THC Exposure at maximum specification levels in µg/kg body weight (90% Percentile Cumulative Consumption), the Total THC Exposure based on the Monte Carlo predicted daily exposure in µg/kg Body Weight with 99.99% certainty and 90% percental cumulative consumption, and finally basing the exposure based on previous historical data from concentrations of THC within Fresh Hemp Foods products.

Refer to Table below. The greatest THC exposure scenario for females 2 years and older was 2.5 µg/kg/bw. This value is 0.73/0.0025 or 292 fold lower than the THC exposure based on the EFSA preclinical rat study. Furthermore, in our evaluation of children from newborn to 11 years, the greatest THC exposure was in 11-23 month old males, who had THC exposure from eating the maximum amount of three Hemp Food Products of 12.7 µg/kg/bw or 0.0127 mg/kg/bw. All other infants and adults would have lower concentrations of exposure. Furthermore, if you utilize the data projected from the Monte Carlo modeling the worst case scenario is 6.4 µg/kg/bw or 0.0064 mg/kg/bw, and if you include the historical data of THC content in Fresh Hemp Food products, the exposure would be 3.5 µg/kg/bw or 0.0035 mg/kg/bw. Therefore, the greatest exposure in children less than 12 years is between 0.73/0.0035 or 0.73/0.0127 or 57-208 fold lower THC exposure based on the EFSA preclinical rat study of 0.73 mg/kg/bw. Therefore, we established that the THC exposure from consuming the maximum amount of three different Fresh Hemp Food products is well below that set by the most conservative EFSA standard of 730 µg/kg/day and does not pose a safety issue.

2. Like your response to question 1, your response to question 9 lacked a comparison of your exposure estimate in infants/toddlers to a specific, appropriate NOAEL/LOAEL to derive a specific margin of exposure. Please perform this comparison and derive a margin of exposure for infants/toddlers and discuss how this supports your safety argument for this subpopulation.

Response:

Toddlers (12 to 24 months old) receive a larger amount of food than infants; however, no normative data were available on the amounts, so a conservative approach was to use the data for 2-5 year olds. Assuming addition of hemp food products at every meal and snack, and the maximal THC concentrations allowable in Fresh Hemp Foods Ltd. products the total THC exposure would be 12.7 µg/kg bw for male and 11.5 µg/kg bw for female toddlers. This may be an overestimation based on using food intake amounts for 2 to 5 year olds. Using the historical THC data, total exposure in the toddlers would be 3.5 and 3.3 µg/kg bw and according to the Monte Carlo predictions 6.2 and 5.8 µg/kg bw. Compared to the EFSA Scientific Opinion $BMDL_{10}$, the actual THC exposures are much lower, see columns C, E and G for

fold lower estimates based on the TOTAL THC EXPOSURE AT MAXIMUM SPECIFICATION LEVELS (column B, from 57-332 fold lower exposure), the TOTAL THC EXPOSURE USING MEAN VALUES CACULATED FROM HISTORICAL DATA (Column E, 207-1285 fold lower exposure) and TOTAL THC EXPOSURE BASED USING MONTE CARLO PREDICTED DAILY EXPOSURE (Column G, 114-585 fold lower exposure). These data assume that toddlers receive maximal hemp food supplementation at every meal and snack during the day. Despite these overestimations, total THC exposure based on maximum specification, historical data and monte carlo predicted exposures are 57 to 1285 fold lower than the most conservative EFSA $BMDL_{10.}$

3. On pg. 12 of addendum, you state, "In human studies, for example, 800mg CBD oral administration has produced no adverse effects." Please cite the source for this information.

Response:

Several studies assessed CBD oral administration at high doses including 800 mg. Zuardi et al, 1993 reported decreased cortisol following an oral 300-400 mg CBD dose. Consroe et al., 1991a; Zuardi et al., 1993, 2006, 2009; and Borgwardt et al., 2008 administered 600 to 1280 mg CBD to humans without toxicity or serious adverse events. Manini et. al., 2015 dosed individuals with 400 and 800 mg CBD followed by intravenous fentanyl because preliminary studies in rodents indicated that there was a significant effect of CBD on heroin reinstatement.

Borgwardt SJ, Allen P, Bhattacharyya S, et al. Neural basis of delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. Biol Psychiatry 2008;64:966–973.

Consroe P, Kennedy K, Schram K. Assay of plasma cannabidiol by capillary gas chromatography/ion trap mass spectroscopy following high-dose repeated daily oral administration in humans. Pharmacol Biochem Behav 1991a;40:517–522.

Manini AF, Yiannoulos G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, Winkel G, Sinha R, Jutras-Aswad D, Huestis MA, Hurd YL. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. Journal Addiction Medicine. 2015 May-Jun;9(3):204-210.

Zuardi AW, Guimar˜aes FS, Moreira AC. Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. Braz J Med Biol Res 1993;26:213–217.

Zuardi AW, Hallak JE, Dursun SM, et al. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol 2006;20:683–686.

Zuardi AW, Crippa JA, Hallak JE, et al. Cannabidiol for the treatment of psychosis in Parkinson's disease. J Psychopharmacol 2009;23: 979–983.

4. On pg. 13 of addendum, you use the unit "µg/g per day" for estimated exposure of chemicals in hempseed products other than THC/THCA. We presume you meant to express the units in terms of "µg/person/day". Please confirm.

Response:

Yes, the units should have been expressed as µg/person/day on page 13 of the addendum.

5. On pg. 13 of addendum, you cited several sources not included in the list of references on pages 25-28 (e.g. de Meijer et al. 1992, Bergamaschi et al. 2011, and Karniol et al. 1975). For completeness, please provide the references for all cited studies.

Response:

Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA.) Safety and side effects of cannabidiol, a Cannabis sativa constituent. 2011; Curr Drug Saf. Sep 1;6(4):237-49.

de Meijer EPM, van der kamp, HJ, van Eeuwik FA. Characterisation of Cannabis accessions with regard to cannabinoid content in relation to other plant characters. Euphytica 1992, 62:187–200.

Karniol IG, Shirakawa I, Takahashi RN, Knobel E, Musty RE. Effects of delta9-tetrahydrocannabinol and cannabinol in man. Pharmacology. 1975;13(6):502-12.

6. On pg. 13 of addendum, you mention that "Karniol et al. (1975) evaluated an oral 50 mg/day CBD dose…," while the following sentence discusses CBN. We assume that Karniol et al. studied the effects of CBN, not CBD. Please confirm.

Response:

Yes, Karniol et al. (1975) evaluated an oral 50 mg/day CBN dose.

7. On pg. 15 of addendum, you state:

"Health Canada therefore advises in their review that clinicians should be aware of other medications that the patient is taking and carefully monitor patients using other drugs along with cannabis or cannabinoids."

Given your estimation of cumulative exposure (i.e. CBDA, CBD, CBG, CBC, CBN) from the intended uses, we presume that, from the available literature, you conclude that the exposure of non-THC cannabinoids is not expected to be a safety issue from your intended use. Please confirm whether this is your conclusion and elaborate.

Response:

Yes, we conclude that the exposure to non-THC cannabinoids resulting from the upper bound estimated cumulative consumption of the hemp materials detailed in GRN765, 771, 778 is not a safety issue.

The Health Canada 2013 Review was created to assist clinicians who treat patients using cannabis and cannabinoids for various illnesses, many of which are severe and require concomitant use of prescription medications. Some of these medications may be metabolized by the Cytochrome P450 enzyme system.

The cannabinoid preparations referenced in the 2013 Review refer to prescription products which are highly purified and are therefore not directly comparable to the naturally occurring cannabinoid concentrations that occur in industrial hemp. The Review also references cannabis (marijuana) products which have high THC, variable content of non-THC cannabinoids and could have as much as 0.5% CBD.

The 2013 Review reports that THC and CBD are metabolized by the Cytochrome P450 enzyme system and that results from in vitro experiments suggest that THC inhibits CYP3A4, CYP3A5, CYP2C9, and CYP2C19, while CBD inhibits CYP2C19, CYP3A4, and CYP3A5; however, higher concentrations than those seen clinically appear to be required for inhibition. It is reasonable to assume that the levels of CBD used clinically are much higher than what is found in the hemp materials described in GRN765, 771, 778. Tables 3, 4, 5 of the addendum to

GRN765, 771, 778 report that the hemp materials contain low concentrations of CBDA, CBD, CBG, CBC, CBN. CBDA was found in the highest concentration at 150 µg/g while the other cannabinoids ranged between 10 and 30 µg/g. If CBD, the most well researched cannabinoid after THC is assumed to also be potentially present at 150 µg/g, it would be present at a level of 0.015% which is 33 times lower than the level of CBD that could be present in marijuana which has up to 0.5% CBD. It would also be expected that the CBD level in the hemp materials is substantially lower than the levels evaluated in clinical studies (refer to response to Question 3 for examples).

October 29, 2018 Email Request

We identified a citation in the original GRN765 submission lacking a correspondence reference. In your responses to the latest questions, please include the reference for Gustafson et al., 2014.

Response:

The reference to Gustafson et al., 2014 in GRN 765 is a typographical error. These references on pages 32 and 68 should refer to Gustafson et al., 2004. This reference is listed below.

Gustafson RA, Kim I, Stout PR, Klette KL, George MP, Moolchan ET, Levine B and Huestis MA. Urinary pharmacokinetics of 11-nor-9-carboxy-delta-9-tetrahydrocannabinol after controlled oral delta-9-tetrahydrocannabinol administration. Journal Analytical Toxicology, 2004 Apr; 28(3):160-167.

Comparison of Total THC Exposure from Hemp Materials Versus BMDL10 from Pivotal Animal Study

Age & Body Weight	TOTAL THC EXPOSURE AT MAXIMUM SPECIFICATION LEVELS (µg/kg bw per day)[1] 90% Percentile Cumulative Consumption	EFSA Scientific Opinion, 2015[2] $BMDL_{10}$ 730 µg/kg bw per day	TOTAL THC EXPOSURE USING MEAN VALUES CACULATED FROM HISTORICAL DATA (µg/kg bw per day)[1] 90% Percentile Cumulative Consumption	EFSA Scientific Opinion, 2015[2] $BMDL_{10}$ 730 µg/kg bw per day	TOTAL THC EXPOSURE BASED USING MONTE CARLO PREDICTED DAILY EXPOSURE (µg/kg bw per day)[1] 99.99% Certainty 90% Percentile Cumulative Consumption	EFSA Scientific Opinion, 2015[2] $BMDL_{10}$ 730 µg/kg bw per day
	Exposure	Fold Difference from EFSA Exposure Limits Compared to Total THC Exposure at Maximum Specification	Exposure	Fold Difference from EFSA Exposure Limits Compared to Historical THC Exposure	Exposure	Fold Difference from EFSA Exposure Limits Compared to Monte Carlo Predictions
Newborn - 2 months Males - 5.4 kg	0.0	Not applicable	0.0	Not applicable	0.0	Not applicable
Newborn - 2 months Females - 4.8 kg	0.0	Not applicable	0.0	Not applicable	0.0	Not applicable
2 - 5 months Males - 7.3 kg	0.0	Not applicable	0.0	Not applicable	0.0	Not applicable
2 - 5 months Females - 6.8 kg	0.0	Not applicable	0.0	Not applicable	0.0	Not applicable
6 - 11 months Males - 8.5 to 9.7 kg	6.7	109	0.6	1285	2.5	293
6 - 11 months Females - 8.0 to 9.3 kg	7.1	103	0.6	1210	2.7	275
11 to 23 months Males - 11.4 to 14.2 kg	12.7	57	3.5	207	6.4	114
11 to 23 months Females - 11.2 to 13.3 kg	11.5	63	3.3	220	5.9	124
2 to 5 years Males - 14.2 kg	10.2	72	2.8	258	5.1	143
2 to 5 years Females - 13.3 kg	9.7	75	2.8	261	5.0	146
6 to 11 years Males - 23.9 kg	6.6	111	2.0	366	3.5	209
6 to 11 years Females - 23.8 kg	6.9	106	2.1	345	3.7	197
2 years & older Males - 88.8 kg	2.2	332	0.7	1040	1.3	562
2 years & older Females - 75.48 kg	2.5	292	0.8	884	1.5	487

[1]Refer to Table 1 of the addendum to GRN765, 771, 778. Values were obtained by estimating daily cumulative consumption of all hemp materials.

[2]Scientific Opinion on the Risks for Human Health related to the Presence of Tetrahydrocannabinol (THC) in Milk and Other Foods of Animal Origin. EFSA Journal 2015;13(6):4141. BMDL10 0.73 mg/kg bw per day.