Hemp Protein Powder GRAS Notice

GRN #771

THE SAFETY AND THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF THE PROPOSED USE OF HEMP PROTEIN POWDER IN HUMAN FOOD

Submitted By: Fresh Hemp Foods Ltd.

Prepared By: Marc C. Sanchez, Esq. (Contract In-House Counsel and Consultants, LLC d/b/a FDA Atty).

Table of Contents

Section 1

March 19, 2018

HEMP PROTEIN POWDER GRAS NOTICE

Introduction

Fresh Hemp Foods (the "Notifier") has determined that the intended use of its Hemp Protein Powder and Hemp Protein Concentrate (aka "Hemp Protein Powder") derived from whole hemp seeds and/or portion of hemp seeds is Generally Recognized As Safe (GRAS), based on section 201(s) of the Food Drug and Cosmetic Act and provisions of the related regulations (Subpart E of Part 170).

The Hemp Protein Powder is marketed both as a bulk ingredient and as a branded product. Both are intended for use as an ingredient in conventional foods.

The bulk ingredient and branded are available as organic or conventional product and they are registered as kosher, halal and non-gmo. Gluten free bulk ingredient is also available in both organic and conventional.

The determination of GRAS status is based on scientific procedures, in accordance with 21 C.F.R. § 170.30(b) and conforms to the guidance issued in § 170.36.

Administrative Information

1.1 Claim Regarding GRAS Status

Fresh Hemp Foods Ltd. is hereby submitting a GRAS notice (the "Notice") in accordance with 21 CFR 170.255 Part 1.

This Notice based on scientific procedures, in accordance with 21 C.F.R. § 170.30(b) and conforms to the guidance issued in § 170.36.

1.2 Name and Address of Notifier

Notifier/Manufacturer	Notifier's Agent
Fresh Hemp Foods Ltd. (d/b/a Manitoba Harvest Hemp Foods, Hemp Oil Canada and Just Hemp Foods) 69 Eagle Drive Winnipeg, MB R2R1V4 Canada	Marc C. Sanchez, Esq. Contract In-House Counsel and Consultants LLC (d/b/a FDA Atty) 1717 Pennsylvania Ave. #1025 Washington, D.C. 20006 Ph: 202.765.4491 E-mail: msanchez@fdaatty.com

1.3 Common or Usual Name of GRAS Substance

The name of the notified substance is Hemp Protein Powder and Hemp Protein Concentrate (hereinafter, "Hemp Protein Powder").

Cultivar: The Hemp Protein Powder is generally derived from the hemp seeds of Cannabis sativa L and they may be organic or conventional. All cultivars used comply with Health Canada's Healthy Environments and Consumer Safety Branch Industrial Hemp Regulations (Subsection 39(1) of the *Industrial Hemp Regulations*).

1.4 Intended Use

Food additive in various finished conventional foods in human food products (See Section 5 below). The food products are intended for the general population (age 2 and above). It is not intended to be added to any USDA/FSIS regulated products and is not intended to be added to any infant formulas.

Refer to Table 1 for application levels of organic and conventional Hemp Protein Powder for the General Population.

1.5 Basis for GRAS Determination

The Notifier is submitting notification to the FDA that it has concluded the intended use of Hemp Protein Powder as an ingredient in human food products is Generally Recognized as Safe (GRAS) based on scientific procedures as described in 21 C.F.R. § 170.30(b).

The content of this submission, as described herein, demonstrates that Hemp Protein Powder is GRAS for the intended use as a human food and/or food ingredient based on (1) Estimated exposure under the intended conditions of use; (2) Literature pertaining to the safety of plant based protein; (3) Literature pertaining to the safety of Delta 9-tetrahydrocannabinol ((6aR, 10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo [b,d] pyran-1-ol) commonly known as THC (hereinafter, "THC"); (4) Expert interpretation of published literature pertaining to safety of THC (Appendix 1); and, (4) Established identity of Hemp Protein Powder as a

substance characterized as meeting Fresh Hemp Food Ltd. specifications and produced in accordance with current Good Manufacturing Practices (cGMP) and Health Canada's Healthy Environments and Consumer Safety Branch Industrial Hemp Regulations.

1.6 Exemption from Food Additive Petition

Based on the information contained herein the Notifier asserts the notified substance, Hemp Protein Powder, is not subject to premarket approval requirements under the Food Additive Amendments of 1958 to the Food Drug and Cosmetic Act on the basis the notified substance is GRAS under the conditions of its intended use.

1.7 Availability of Information for FDA Review

The data and information that serve as the basis for the GRAS conclusion herein are available to the FDA and copies may be made during normal business hours at the Firm's address as provided in Section 1.2 above.

The Firm will provide the FDA a complete and accurate copy of any data or information used to conclude the notified substance is GRAS in an electronic format during the Agency's evaluation of this notice.

1.8 Exemption from Disclosure

The data and information of this GRAS notice are NOT exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552.

1.9 Certification

The undersigned certifies that to the best of their knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to the Firm and pertinent to the evaluation of the safety and GRAS status of the use of the Hemp Protein Powder.

1.10 Name and position of Signatory

Signature	Notifier's Agent
(b) (6) Digitally signed by Marc C. Sanchez, Esq. Date: 2018.03.21 09:13:01 -04'00' Adobe Acrobat Reader version: 2018.011.20038	Marc C. Sanchez, Esq. Contract In-House Counsel and Consultants LLC (d/b/a FDA Atty) 1717 Pennsylvania Ave. #1025 Washington, D.C. 20006 Ph: 202.765.4491 E-mail: msanchez@fdaatty.com

Section 2

2. Product Identity and Specifications

2.1 Common or Usual Name of the Notified Substance

The name of the notified substance is Hemp Protein Powder and Hemp Protein Concentrate (hereinafter, "Hemp Protein Powder").

Cultivar: The Hemp Protein Powder is generally derived from the hemp seeds of *Cannabis sativa* L. All cultivars used comply with Health Canada's Healthy Environments and Consumer Safety Branch Industrial Hemp Regulations.

The Hemp Protein Powder is marketed both as a bulk ingredient and as a branded product. Both are intended for use as an ingredient or garnish with conventional foods.
The Hemp Protein Powder ingredient and branded product are available as organic or conventional product and they are registered as kosher, halal and non-gmo. Gluten free bulk ingredient is also available in both organic and conventional.

Fresh Hemp Foods produces Hemp Protein Powder from whole hemp seed through two processes. Hemp Protein Powder is produced through a dry mechanical process and involves cold pressing to separate the oil followed by milling to the desired particle size. There are three grades of Hemp Protein Powder produced through the mechanical dry process. They differ based on protein content and other nutritional variables. Hemp Protein Concentrate is produced through a combination of mechanical and wet processing and involves cold pressing to separate the oil, milling and pH controlled water extraction to concentrate the protein followed by spray drying to remove the water.

2.2 Growing information

Fresh Hemp Foods Ltd. abides by the Industrial Hemp Regulations as set by Health Canada (1998).

Delta 9-tetrahydrocannabinol ((6aR, 10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo [b,d] pyran-1-ol) commonly known as THC ("THC") and its precursor THCA are present in the hemp plant at about a 1 to 9 ratio (EIHA 2017). THC is not found in the interior of hemp seed unless there has been physical cross contamination of the seed hull with cannabinoid-containing resins in bracts and leaves during maturation, harvesting and processing. THC is psychoactive but THCA has no psychotropic effect as long as it is not heated.

The Industrial Hemp Regulations ensure that all hemp acres and producers are licensed, indicating that THC levels in the crop are in accordance with regulated limits. Further, as per the Industrial Hemp Regulations, products derived from hemp seeds shall have a maximum allowable THC limit of 10 µg/g.

Fresh Hemp Foods Ltd. is licensed by Health Canada and contracts only licensed hemp seed acres meeting the Industrial Hemp Regulations (Health Canada 1998). Fresh Hemp Foods Ltd.

tests hemp seed product at third party accredited laboratories to confirm THC levels are compliant with the regulated limits of not more than 10 µg/g.

Fresh Hemp Foods Ltd. prohibits the use of in-crop herbicides and pesticides as a normal practice for the production of hemp seed grown under contract.

2.3 Identity, Composition and Quality Specifications

Specifications

Refer to Table 2 for specifications applied by Fresh Hemp Foods Ltd. to the organic and conventional Hemp Protein Powder.

Nutritional Data

Refer to Table 3 for typical nutritional data for organic and conventional Hemp Protein Powder.

Labeling and Storage Information

Dry Process –Cold Milled Hemp Powder or Organic Cold Milled Hemp Powder.

Wet Process –Hemp Protein Concentrate (Natural Oregano Extract) or Organic Hemp Protein Concentrate (Natural Oregano Extract)

Storage conditions: Should be stored in a cool, dry location and in the original sealed package away from odorous material.

Shelf life: The shelf life is a minimum of 15 months from date of manufacture when stored in the original sealed packaging.

Allergens

Refer to Table 4 for the allergen declaration for organic and conventional Hemp Protein Powder.

Amino Acid Profile

Refer to Table 5 for the amino acid profile for organic and conventional Hemp Protein Powder.

2.4 Manufacturing Process

Narrative on Manufacturing Method

All whole hemp seed processed by Fresh Hemp Foods Ltd. is grown from Health Canada approved cultivars of industrial hemp which has been grown by licensed growers who are producing industrial hemp seed under license from Health Canada.

Throughout the planning and growing seasons, company agronomists provide services and guidance to ensure growers implement best management practices for field selection, growth, harvest and storage of hemp seed to ensure safety and quality of the seed.

After harvest and drying, a field harvest sample is requested from the grower to review safety and quality. Prior to processing, the seed is sent to a seed cleaner for mechanical removal of debris, weed seeds and other crop seeds. The seed is then shipped by an approved trucking company to the GFSI (BRC) certified Fresh Hemp Foods Ltd. facility for processing.

The seed is further mechanically cleaned to remove foreign materials prior to being cold pressed to extract the oil. Cold pressing is a mechanical process. No additives or processing aids are added to the seed during extraction of the oil.

Defatted hemp seed cake is extracted from the presses. The hemp seed cake is milled and sifted to produce powders with varying particle size and grades of protein. No additives or processing aids are added to the Hemp Protein Powders during the milling and sifting processes.

The Hemp Protein Powders are packaged in bulk totes. Representative in-process samples are taken and sent to the laboratory for testing. The materials are tested for safety and quality before being packaged or released for sale or further processing.

The 50%, 43% and 33% protein grade Hemp Protein Powders are either shipped bulk or packaged into smaller packages and shipped to customers.

Hemp Protein Powder may be further processed using aqueous extraction to produce Hemp Protein Concentrate. Potable water is added to the powder, followed by pH adjustment and solids removal. A natural food grade antioxidant (oregano extract) is added to the aqueous extract prior to drying. The dry Hemp Protein Concentrate is prepared by spray drying the extract to remove the water.

The Hemp Protein Concentrate is screened to remove foreign material and is packaged in bulk totes. Representative in-process samples are taken and sent to the laboratory for testing. The Hemp Protein Concentrate is tested for safety and quality and is either shipped bulk or packaged into smaller packages and shipped to customers.

List of Products Added During Manufacturing (Raw Materials)

No products are added during the manufacturing of the 50%, 43% and 33% protein grade Hemp Protein Powders.

Potable water and food grade potassium hydroxide, citric acid and phosphoric acid are used during the aqueous extraction of hemp protein powder to produce Hemp Protein Concentrate. A food grade natural antioxidant is added to the Hemp Protein Concentrate prior to spray drying (oregano extract).

Flow Chart

Refer to Figures 1 and 2 for manufacturing Flow Charts for Dry Process and Wet Process respectively.

Batch/Lot Analysis

Consistency on Final Product Specifications

To demonstrate conformance to listed product specifications in Table 2, Fresh Hemp Foods Ltd. has provided analysis from multiple lots of Hemp Protein Powder prepared using the dry process and wet process to show typical results (refer to Tables 6 and 7). Although lot to lot variation can occur, all results are within specification indicating consistency in the process and compliance to the product specifications set forward.

Refer to Tables 8 to 10 for representative analytical data for Hemp Protein Powder prepared using the dry process and wet process confirming conformance with heavy metals and aflatoxin specifications.

The plant *Cannabis sativa L.* is well known to uptake and remove heavy metals from the soil. The distribution is such that the content of the heavy metals is lowest in the seed in comparison to other parts of the plant (roots>stems>leaves>seed) (Angelova et.al. 2004). Therefore, the risk of heavy metal contamination is lowest in seed, which is the plant part used to manufacture the hemp food products produced by Fresh Hemp Foods Ltd. Since the risk is low, heavy metals are not tested per lot and testing is completed at a frequency based on risk.

Aflatoxins are the main potential mycotoxin that can be found in oilseeds (https://www.gov.mb.ca/agriculture/food-safety/at-the-food-processor/mycotoxins.html). Mycotoxins production is more likely to occur when the oilseeds moisture content is 20-25% (Manitoba Agriculture 2017). A requirement of Fresh Hemp Foods Ltd. is that a sample arrives at a Fresh Hemp Foods Ltd. facility immediately after harvest and drying and moisture content must be verified. This moisture content requirement manages the risk of aflatoxin production. Aflatoxins are thus not tested every lot and rather at a lower frequency based on risk.

Pesticide and herbicide residues are not tested since Fresh Hemp Foods Ltd. prohibits the use of in-crop herbicides and pesticides as a normal practice for the production of hemp seed grown under contract.

No products are added during the manufacturing of the 50%, 43% and 33% protein grade Hemp Protein Powders.

Potable water and food grade potassium hydroxide, citric acid and phosphoric acid are used during the aqueous extraction of hemp protein powder to produce Hemp Protein Concentrate. A food grade natural antioxidant is added to the Hemp Protein Concentrate prior to spray drying.

There are no known anti-nutritional properties.

Section 3

3. Dietary Exposure

3.1. Overview of Consumption

Hemp has been reconsidered as a valuable industrial crop for both food and fiber in Canada and European countries during at least the last decade. As a result, hempseed and hempseed food products have become available to the general public in a variety of foods from Hulled Hemp Seed, Hemp Protein Powder to hemp oil.

Hemp as a food has long been recognized for its nutritional properties and valued as food for humans throughout Asia, India, Russia and Eastern Europe. In China, roasted hempseed is still sold as snacks by street venders. In Russia, 'black' oil has been pressed from hempseed and used as a substitute for more expensive sources of dietary fat, such as butter and hydrogenated margarines. Traditional hempseed foods can be found in Latvia and much of Eastern Europe.

Although this submission does not make a history of use claim for GRAS, there is a long-history and a variety of uses over a widespread geographic area that reinforces the scientific data and recognition by the scientific community of hempseed's safety and utility as a nutritive food.

The Congressional Research Service (CRS) issued a report on March 10, 2017 titled *Hemp as an Agricultural Commodity* (CRS March 2017). CRS cited current industry estimates of nearly $600 million in U.S. hemp sales. Food uses account for over 16% of those sales. The CRS report favorably covers a wide range of hemp food and beverage products currently sold in the US.

3.2. Exposure Estimates

Hemp Protein Powder

Refer to Table 1 for a summary of the anticipated uses and minimum and maximum levels of inclusion of Hemp Protein Powder in food products.

USDA NHANES 2013-2014 survey data were used to estimate mean and 90th percentile consumption of Hemp Protein Powder for foods anticipated to be consumed daily which could reasonably be expected to be manufactured using Hemp Protein Powder as an ingredient. Refer to Tables 11 to 15 for estimated exposure to Hemp Protein Powder.

To thoroughly assess the probability of harm from Hemp Protein Powder, a conservative and upper-bound level of intake was modeled. The exposure estimates are then used in Section 6 to compare to levels found in the literature.

There is currently no information available in USDA NHANES survey data specific to consumption of industrial hemp seed products. Therefore, food categories were selected based on how industrial hemp seed materials could be used in typical food products. The following list is not all inclusive. It gives examples of foods captured within the categories selected from the

NHANES 2013-2014 survey data. The examples represent typical applications where it is anticipated that ingredients derived from hemp seed are likely to be used:

1. Hemp protein powders would be used in a similar manner to flour from all grains (e.g. wheat, barley, rice, corn, rye, oat). However, due to the functional limitations only a portion of the grain flour can be replaced by hemp protein powder
2. Hemp protein powder would be used in a similar way to dairy and soy based protein powders
3. Hemp Protein Powder, Hemp Oil, Hulled Hemp Seed based non-dairy milk would be used in a similar way to legume-based, cereal-based or nut- or seed-based non-dairy milks and spreads.

Assumptions and Chain of Contingencies Used to Develop Conservative Level of Intake

The quantity of Hemp Protein Powder anticipated to be consumed on a daily basis for individuals aged 2 years and older and children aged 2 to 5 years and 6 to 11 years has been estimated at the lowest, middle and maximum levels based on rates of inclusion specified in Table 1. Refer to Tables 11 to 15. For discussion purposes, the highest level of inclusion and highest levels of consumption have been used to estimate exposure to Hemp Protein Powder.

The intended use of Hemp Protein Powder at the maximum inclusion levels listed in Table 1 will result in mean and 90th percentile intake of 6.91 and 13.84 g/person/day of Hemp Protein Powder from all food categories for the general population ages 2 and older (Table 11). It can be conservatively estimated that maximum inclusions levels would result in mean and 90th percentile intake of Hemp Protein Powder of 6.18 and 12.36 g/person/day for boys aged 2 to 5 years, 5.28 and 10.55 g/person/day for girls aged 2 to 5 years, 6.07 and 12.14 g/person/day for boys aged 6 to 11 years and 6.24 and 12.47 g/person/day for girls aged 6 to 11 years (Tables 11 to 15).

The use of Hemp Protein Powder is not expected to exceed 13.84 grams per day for any of the age groups when used at the maximum level in the food categories in Table 1. The usage level is variable depending on application and is self-limiting due to sensory and functional limitations.

Cumulative Hemp Consumption

Multiple GRAS Notices Used in Conservative Exposure Estimates

Unique to hemp seed, GRAS notifications are split between three (3) separate but interrelated submissions. Those are GRN #### (Hulled Hemp Seed), #### (Hemp Oil), and #### (Hemp Protein Powder). All three notified substances are from the same material, hemp seed, but extract or used different components. The exposure estimate below could not look at one without estimating consumption of the others. Therefore, one key assumption in developing an upper-bound exposure estimate is that consumption of one hemp product would likely mean consumption of other hemp products requiring the use and reference of multiple GRAS notifications.

Refer to Tables 16 to 20 for estimated exposure to all Fresh Hemp Foods Ltd. hemp ingredients, including Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil. To thoroughly assess the probability of harm from Hemp Protein Powder and all other hemp products, a conservative and upper-bound level of intake was modeled. The exposure estimates are then used in Section 6 to compare to levels found in the literature.

USDA NHANES 2013-2014 survey data were used to estimate mean and 90th percentile consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil for foods anticipated to be consumed daily which could reasonably be expected to be manufactured using hemp as an ingredient.

Assumptions and Chain of Contingencies Used to Develop Conservative Level of Intake

The quantity of Fresh Hemp Foods Ltd. hemp ingredients anticipated to be consumed on a daily basis for individuals aged 2 years and older and children aged 2 to 5 years and 6 to 11 years has been estimated at the lowest, middle and maximum levels based on rates of inclusion specified in the respective GRAS Notifications. Refer to Tables 16 to 20 for a summary of the total level of each ingredient anticipated to be consumed by each age group. For discussion purposes, the highest level of inclusion and highest levels of consumption have been used to estimate exposure to each hemp ingredient.

The intended use of each hemp ingredient at the maximum inclusion levels will result in a cumulative mean and 90th percentile intake of 18.05 and 36.12 g/person/day from all food categories for the general population ages 2 and older (Table 16). It can be conservatively estimated that maximum inclusions levels would result in cumulative mean and 90th percentile intake of 14.44 and 28.88 g/person/day for boys aged 2 to 5 years, 12.67 and 25.33 g/person/day for girls aged 2 to 5 years, 15.16 and 30.32 g/person/day for boys aged 6 to 11 years and 15.55 and 31.1 g/person/day for girls aged 6 to 11 years (Tables 16 to 20).

Hemp food products are well established in Europe, especially Germany. It has been estimated by the European Industrial Hemp Alliance (EIHA 2017) that German consumers would be exposed to about 443.81 grams of hemp daily through consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil. EIHA identified similar categories comparable to the ones anticipated in this GRN notice but estimated their level assuming that hemp would be used as a 100% replacement for other materials. This level is not realistic and the authors themselves noted that hemp is unlikely to be used as a full replacement for other standard materials.

The exposure to THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil is dependent upon consumption habits and is self-limiting due to sensory and functional limitations of the hemp ingredients, so it is not expected to exceed 0.1938 mg/person/day when foods from all groups and containing maximum inclusion levels are consumed at the 90th percentile by any individual age 2 years and older (refer to Table 21).

The cumulative total of THC consumed by 2 to 5 years old, 6 to 11 year old and individuals aged 2 years and older is anticipated to be spread over various foods consumed over the course of three main meals in a 24 hour period.

3.3. Dietary Exposure to THC

Refer to Sections 4B.i. and 4.B.ii. for discussion on how much Hemp Protein Powder and cumulative hemp ingredient is anticipated to be consumed by children age 2 to 5 years, 6 to 11 years and all individuals age 2 years and older.

THC has been included in the safety discussion of this GRN since oral consumption of Hemp Protein Powder and foods containing Hemp Protein Powder and/or other hemp ingredients will inadvertently result in the ingestion of small amounts of THC, a psychotropic cannabinoid which naturally occurs in low levels in the seeds of *Cannabis sativa* L.

Hemp Protein Powder

The THC levels in Hemp Protein Powder is controlled through internal Fresh Hemp Foods Ltd. measures in combination with strict enforcement of Health Canada's Industrial Hemp Regulations. All *Cannabis sativa* L seed is grown under license from Health Canada using specific cultivars that have been thoroughly vetted as low THC producing varieties. Fresh Hemp Foods Ltd. ensures that the health risk posed by THC exposure is mitigated by employing a combination of seed cleaning, processing and testing to ensure that all Fresh Hemp Foods Ltd. hemp ingredients (see GRNs filed with this Notice) are compliant with maximum THC limits imposed by Health Canada or the tighter limits self-imposed (on specific materials) by Fresh Hemp Foods Ltd.

The Fresh Hemp Foods Ltd specification is not more than 4 μg/g THC for Hemp Protein Powder which is well below the maximum limit of not more than 10 μg/g set forth by the Industrial Hemp Regulations. For discussion purposes, THC exposure at the maximum Fresh Hemp Foods Ltd. specification of NMT 4 μg/g will be used to evaluate THC exposure from Hemp Protein Powder.

Upper-Bound Estimation – THC from Hemp Protein Powder
Refer to Table 21. At the maximum level of 4 μg/g THC, it can be conservatively anticipated that individuals age 2 years and older would consume a mean and 90th percentile intake of 0.0276 mg and 0.0553 mg/person/day of THC from Hemp Protein Powder if they consumed all food groups at the maximum level of use shown in Table 1.

Refer to Tables 22 to 26. It can be conservatively estimated that a maximum level of 4 μg/g THC would result in the consumption of a mean and 90th percentile intake of 0.0247 and 0.094 mg THC/person/day for boys aged 2 to 5 years, 0.0211 and 0.0422 mg THC/person/day for girls aged 2 to 5 years, 0.0243 and 0.0485 mg THC/person/day for boys aged 6 to 11 years and 0.0249 and 0.0499 mg THC/person/day for girls aged 6 to 11 years if they consumed Hemp Protein Powder at the maximum level in all food groups.

Upper-Bound Estimation – THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil Using Monte Carlo Modelling

Monte Carlo modelling was also used to estimate THC exposure at the 90th percentile based on the mean THC level detected by historical third party analytical testing. The exposure to THC was estimated at 0.0164 mg THC/person/day for Hemp Protein Powder for individuals age 2 years and older (Figure 5). The estimated 90th percentile is 0.0147 mg THC/person/day for boys aged 2 to 5 years, 0.0126 mg THC/person/day for girls aged 2 to 5 years, 0.0145 mg THC/person/day for boys aged 6 to 11 years and 0.0149 mg THC/person/day for girls aged 6 to 11 years (refer to Figures 13, 21, 29, 37 respectively).

For all age groups, these daily amounts are estimated to be the cumulative total consumption of Hemp Protein Powder over the course of a full 24-hour period and are expected to encompass three meals consumed roughly 4 hours apart.

In the hemp crop and hemp food, THC and THCA are present, often in a 1 to 9 ratio (EIHA 2017) . THCA has no psychotropic effect as long as it is not heated. Transformation of THCA to THC is time and temperature dependent. To fully convert THCA to THC at 115 °C it takes about 2 hours (reported by EIHA 2017). For example, a cake in the oven has an internal temperature of less than 100 °C (as long as water is present). Using an average baking time of 45 min, this would mean, that only about 1/3 of the available THCA is able to be converted into THC. The majority of foods made from hemp seeds are anticipated to be exposed to low temperatures or short duration of heat since hemp ingredients contain high amounts of polyunsaturated fatty acids and hemp oil has a low smoke point that makes it unsuitable for frying.

Cumulative Hemp Consumption

The THC levels in Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil is controlled through internal Fresh Hemp Foods Ltd. measures in combination with strict enforcement of Health Canada's Industrial Hemp Regulations. All *Cannabis sativa* L seed is grown under license from Health Canada using specific cultivars that have been thoroughly vetted as low THC producing varieties. Fresh Hemp Foods Ltd. ensures that the health risk posed by THC exposure is mitigated by employing a combination of seed cleaning, processing and testing to ensure that all Fresh Hemp Foods Ltd. hemp ingredients (see GRNs filed with this Notice) are compliant with maximum THC limits imposed by Health Canada or the tighter limits self-imposed (on specific materials) by Fresh Hemp Foods Ltd.

The Fresh Hemp Foods Ltd specification is not more than 4 µg/g THC for Hemp Protein Powder and Hulled Hemp Seed which is well below the maximum limit of not more than 10 µg/g set forth by the Industrial Hemp Regulations. The Fresh Hemp Foods Ltd specification is not more than 10 µg/g THC for Hemp Oil. For discussion purposes, THC exposure at the maximum Fresh Hemp Foods Ltd. specifications will be used to evaluate THC exposure from all hemp ingredients.

Upper-Bound Estimation – THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil
Refer to Table 21. At the maximum THC level permitted by the Fresh Hemp Foods Ltd. specifications, it can be conservatively anticipated that individuals age 2 years and older would consume a mean and 90th percentile intake of 0.0968 and 0.1938 mg/person/day of THC if they consumed all hemp ingredients at the maximum level of use as indicated in Tables 16 to 20.

Refer to Tables 27 to 30. It can be conservatively estimated that a maximum level of THC would result in the consumption of a mean and 90th percentile intake of 0.0722 and 0.1444 mg THC/person/day for boys aged 2 to 5 years, 0.0644 and 0.1288 mg THC/person/day for girls aged 2 to 5 years, 0.0788 and 0.1576 mg THC/person/day for boys aged 6 to 11 years and 0.0816 and 0.1633 mg THC/person/day for girls aged 6 to 11 years if they consumed all hemp ingredients at the maximum level of use as indicated in Tables 16 to 20.

For all age groups, these daily amounts are estimated to be the cumulative total consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil over the course of a full 24-hour period and are expected to encompass three meals consumed roughly 4 hours apart.

Upper-Bound Estimation – THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil Using Monte Carlo Modelling
Monte Carlo modelling was used to estimate THC exposure at the 90th percentile based on the mean THC level detected by historical third party analytical testing of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil. The exposure to THC was estimated at 0.1049 mg THC/person/day for individuals age 2 years and older, 0.0698 mg THC/person/day for boys aged 2 to 5 years, 0.0651 mg THC/person/day for girls aged 2 to 5 years, 0.0794 mg THC/person/day for boys aged 6 to 11 years and 0.0834 mg THC/person/day for girls aged 6 to 11 years (refer to Figures 3, 11, 19, 27, 35 respectively).

3.4. Dietary Exposure to Hemp Protein
Proteins are made up of amino acids. Some amino acids cannot be made by the human body, so they must be provided by the diet (i.e., essential amino acids). While animal derived proteins are a major source of essential amino acids in the human diet, the inclusion of cereal and plant based sources should also be acknowledged. Notable plant and cereal sources include soy, peas, oats, rice, lentils, wheat, potato, nuts and beans. The nutritional value and safety of these sources is evident when one considers that FDA has issued "no questions" letters in response to Generally Recognized As Safe (GRAS) Notifications (GRNs) on various plant and cereal grain based sources including canola (GRN 683), oat (GRN 575) and pea protein (GRN 581).

These notifications each contain reviews of the published safety information including in some cases expert panel reports which reviewed and discussed the metabolism, toxicology, and human health and safety data for protein and protein concentrates/isolates. Based on these GRAS notifications, FDA currently permits the use of a variety of plant-based protein materials at the use levels indicated in the notifications. The level of use and anticipated exposure to hemp derived protein resulting from consumption of Hemp Protein Powder and other hemp ingredients is similar to the exposure anticipated from the consumption of the plant based proteins in these notifications.

In accordance with Section 4.B.iii. Multiple GRAS Notices Used in Conservative Exposure Estimates, risk resulting from exposure to hemp derived protein was determined by assessing the cumulative exposure to protein from all Fresh Hemp Foods Ltd. hemp ingredients. Hemp Oil (GRN XXXX) contains negligible protein. Hulled Hemp Seed and Hemp Protein Powder contain significant amounts of protein and are included in this evaluation.

Refer to Tables 31 to 35 for the upper bound exposure to hemp protein resulting from the conservative cumulative consumption of protein from Hulled Hemp Seed and Hemp Protein Powders. Protein consumption from Hemp Protein Powder ranges from the highest value of 8.72 g for individuals age 2 years and older (Table 31) to the lowest value of 6.65 g for females age 2 years to 5 years (Table 33) which is significantly lower than the level of exposure when cumulative exposure from both protein rich sources are considered. Cumulative protein exposure is 13.5 g/day for individuals age 2 and older, 11.77 g/day for males 2 to 5 years, 10.11 g/day for females 2 to 5 years, 13.22 g/day for males 6-11 years and 11.77 g/day for females 6 to 11 years.

The level of exposure to hemp protein resulting from consumption of Hulled Hemp Seed and Hemp Protein Powders does not exceed the FDA Daily Reference Value (DRV) for protein of 50 g per day for adults and children four or more years of age. Nor does the cumulative protein consumption exceed the Institute of Medicine (I0M, 2005) Recommended Dietary Allowance (RDA) of 56 g per day for adult males, 46 g per day for adult females, 13 g for children age 1 to 3 years, 19 g for children age 4 to 8 years and 34 g for children age 9 to 13 years.

Protein digestibility-corrected amino acid score (PDCAAS) measurements, using rat bioassay for protein digestibility and the FAO/WHO amino acid requirement for children 2 to 5 years of age as reference have been conducted on Fresh Hemp Food's Hulled Hemp Seed and Hemp Protein Powders (House et. al. 2010). The study authors found the protein to be a complete protein source since it contains all amino acids needed by humans.

Refer to Table 36 for a comparison of the amino acids in Hulled Hemp Seed and Hemp Protein Powders to other recognized plant proteins. The amino acid profile of the protein in Hulled Hemp Seed and Hemp Protein Powders is similar to soy isolate, soy concentrate and other GRAS sources of protein. Hemp protein has a PDCAAS that is comparable to lentils and pinto beans and superior to whole wheat (House et. al. 2010).

The safety and efficacy of hemp seed protein has been evaluated and is recognized by Health Canada's Non-Prescription and Natural Health Products Directorate (NNHPD) which has assessed the totality of evidence and has determined that hemp protein concentrate, and hemp protein isolate are safe and efficacious sources of protein for use in human natural health products (NNHPD Workout Supplements Monograph 2016).

Hemp protein isolate, and concentrate are concentrated forms of the protein naturally present in whole hemp seed and are defined as extracts by NNHPD since they have the primary molecular structure of which is identical to that which it had prior to its extraction or isolation. It is

reasonable to anticipate that the protein in the whole seed is the same protein that is present in the Hulled Hemp Seed and Hemp Protein Powder

The NNHPD Workout Supplements Monograph is used by industry to develop and license natural health products for sale in Canada. The Monograph enables licensed products to contain between 2.6 g and 90 g of protein from hemp protein concentrate and isolate. NNHPD has assessed the safety of hemp protein isolate and concentrate and has determined that there are no limitations on the duration of its use, nor are there any contraindications or known adverse reactions associated with the use of hemp protein. The only protein specific warning required by NNHPD for the inclusion of hemp is a statement to the effect that a healthcare practitioner should be consulted if the user has liver or kidney disease. This caution is not specific to hemp protein. It is a typical warning relevant to the consumption of any natural health product containing 30 g or more of protein per day (Workout Supplements Monograph 2016).

NNHPD has assessed the efficacy of hemp protein isolate and concentrate as a source of protein and amino acids for humans and has determined that the totality of evidence supports its inclusion in natural health products. The Workout Supplements 2016 Monograph enables licensed natural health products to make the following claims:

- Source of protein for the maintenance of good health
- Source of protein which helps build and repair body tissues
- Source of amino acids involved in muscle protein synthesis
- Assists in the building of lean muscle [tissue/mass] when combined with regular [weight/resistance] training and a healthy balanced diet

The claims as approved by NNHPD have been included to illustrate that Health Canada, a recognized authority, has assessed hemp protein and deems it to be a safe and nutritious source of protein for human consumption.

4. Self-Limiting Levels of Use

For discussion purposes, the highest level of inclusion and highest levels of consumption have been used to estimate exposure to Hemp Protein Powder. Hemp Protein Powder sold as a branded product at a serving size of 30g is intended as a directly consumed consumer packaged product where consumers mix, sprinkle or garnish within soups, salads, baking, breakfast foods, pasta, smoothies/ blended beverages, non-dairy beverages, meat analogues, crackers, bars and desserts prepared at home.
Hemp Protein Powder is also intended as a food ingredient in conventional foods such as baked goods and baking mixes; beverages and beverage bases; breakfast cereals; dairy product analogs; grain products and pastas; plant protein products at levels ranging from 1 to 100%. When used as an ingredient, the level of use of Hemp Protein Powder is variable but is self-limiting due to sensory and technical limitations so it is not expected to exceed 13.84 grams per serving (Table 11) when used at the maximum level in any of the food categories (refer to Table 1).

The exposure to THC from Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil is dependent upon consumption habits and is self-limiting due to sensory and functional limitations of the hemp ingredients, so it is not expected to exceed 0.1938 mg/person/day when foods from all groups and containing maximum inclusion levels are consumed at the 90th percentile by any individual age 2 years and older (refer to Table 21).

5. Basis for Conclusion of GRAS Status (Narrative)

5.1. Introduction to GRAS Conclusion

Hemp Protein Powder is intended for nutritional fortifications of foods. It has high levels of iron, manganese, zinc and magnesium and is rich in protein, fiber, monounsaturated fat and polyunsaturated fat which make it a desirable addition to human foods.

There is a long history of research and studying into the benefits of hemp seed. Including a report on children during the 1930s and 1940s in Czechoslovakia that emphasized the importance of hempseed protein, the basis of this conclusion of GRAS status is based on scientific procedures, which has led to the relatively recent recognition of safety for human food by Health Canada, Food Standards Australia New Zealand/Australian New Zealand Food Authority, and the European Food Safety Authority. All have looked at the scientific data and found hemp seed safe for human consumption.

Fresh Hemp Foods Ltd. has performed a critical assessment of the publicly available literature on *Cannabis sativa* low THC (industrial hemp) and high THC (marijuana) varieties. Data from both human and animal studies confirm that Hemp Protein Powder produced from Health Canada approved cultivars of low THC industrial hemp which has been produced in accordance with Fresh Hemp Foods Ltd. procedures and specifications is unlikely to result in positive urine THC drug test results and is safe for children, adults and breastfeeding women and their infants when consumed at anticipated levels based on Table 1 and NHANES 2013-2014 food survey data (Tables 1 to 26).

Refer to Table 37 for drug testing programs and recognized limits (Table duplicated below). Fresh Hemp Foods Ltd. has assessed the potential of Hemp Protein Powder to produce positive urine drug test results using the US Department of Defense and Federal Workplace Drug Testing limits of 15 ng/ml.

Table 37 Detection of Cannabinoids in Urine

Drug Testing Program	**Cut Off Limit**
US Department of Defense	15 ng/ml
US Federal Workplace Drug Testing	15 ng/ml
World Anti-Doping Agency	150 ng/ml

Fresh Hemp Foods Ltd. manufacturers multiple ingredients from whole hemp seed. Each ingredient is highly nutritious and is suitable for formulation into human food (refer to GRNs filed with this Notice). Accordingly, an assessment of the safety of the cumulative exposure to these ingredients and the THC resulting from their combined ingestion has been performed. Data from human and animal studies confirms that cumulative exposure to Fresh Hemp Foods Ltd. hemp ingredients (Hulled Hemp Seed, Hemp Oil and Hemp Protein Powders) which have been produced in accordance with Fresh Hemp Foods Ltd. procedures and specifications is unlikely to result in positive urine THC drug test results and is safe for children, adults and breastfeeding women and their infants when consumed at anticipated levels and NHANES 2013-

2014 food survey data (Table 1 and Tables 11 to 30). Fresh Hemp Foods Ltd. has assessed the potential of cumulative hemp consumption to produce positive urine drug test results using the US Department of Defense and Federal Workplace Drug Testing limits of 15 ng/ml.

5.2. Safety Overview

Hemp is different to other varieties of *Cannabis sativa* which are commonly referred to as marijuana as it contains very low levels of THC (delta 9-tetrahydrocannabinol), the cannabinoid associated with the psychoactive properties of marijuana. Hemp has recognition of safety for human food by Health Canada, Food Standards Australia New Zealand/Australian New Zealand Food Authority, and the European Food Safety Authority. All have looked at the scientific data and found hemp seed safe for human consumption.

Hemp seed derived foods including Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil are safe for human food as they contain minimal amounts of THC because THC may have behavioral and physiological effects. Fresh Hemp Foods Ltd. ensures the safety of its hemp derived ingredients by ensuring that all seed processed is a Health Canada approved low THC variety which has been grown and processed in accordance with the Industrial Hemp regulations. Safety is further ensured by testing at third party accredited laboratories to confirm THC levels are in compliance with the mandatory regulated limits and Fresh Hemp Foods Ltd. corporate limits.

Historical trending of Fresh Hemp Food's third party accredited laboratory testing of THC content for Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil reveals that actual THC levels are consistently below the Fresh Hemp Food specifications. Refer to Figures 3 to 45 for Monte Carlo modelled exposure of THC and to Table 38 (duplicated below) for a summary of daily exposure of THC from all hemp ingredients at maximum THC limits based on specifications versus daily exposure of THC based on Monte Carlo probabilistic model.

Table 38. Daily THC Exposure at Maximum Specification Levels and Monte Carlo Modelling of Daily THC Exposure

	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014)					THC EXPOSURE FROM HEMP MATERIAL CONSUMED AT MAXIMUM FRESH HEMP FOODS LTD. SPECIFICATION LIMITS (mg/Day) *Hulled Hemp Seed = NMT 4 µg/g THC *Hemp Protein Powder = NMT 4 µg/g THC *Hemp Oil = NMT 10 µg/g THC					THC EXPOSURE FROM HEMP MATERIAL CONSUMED USING MONTE CARLO MODEL AND HISTORICAL TEST DATA (mg/Day) *Hulled Hemp Seed = Mean of 0.29 µg/g THC *Hemp Protein Powder = Mean of 0.31 µg/g THC *Hemp Oil = Mean of 4.95 µg/g THC				
	2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years	
	Males & Females	Males	Females	Males	Females	Males & Females	Males	Females	Males	Females	Males & Females	Males	Females	Males	Females
HULLED HEMP SEED GRN XXX	14.07 (Table 16)	11.71 (Table 17)	10.2 (Table 18)	12.12 (Table 19)	12.14 (Table 20)	0.0563 (Table 21)	0.0468 (Table 27)	0.0408 (Table 28)	0.0485 (Table 29)	0.0486 (Table 30)	0.0213 (Figure 7)	0.0178 (Figure 15)	0.0155 (Figure 23)	0.0184 (Figure 31)	0.0184 (Figure 40)
HEMP PROTEIN POWDER GRN XXX	13.84 (Table 16)	12.36 (Table 17)	10.55 (Table 18)	12.14 (Table 19)	12.47 (Table 20)	0.0553 (Table 21)	0.0494 (Table 27)	0.0422 (Table 28)	0.0485 (Table 29)	0.0499 (Table 30)	0.0164 (Figure 5)	0.0147 (Figure 13)	0.0126 (Figure 21)	0.0145 (Figure 29)	0.0149 (Figure 37)
HEMP OIL GRN XXX	8.22 (Table 16)	4.81 (Table 17)	4.58 (Table 18)	6.06 (Table 19)	6.48 (Table 20)	0.0822 (Table 21)	0.0481 (Table 27)	0.0458 (Table 28)	0.0606 (Table 29)	0.0648 (Table 30)	0.0772 (Figure 9)	0.0451 (Figure 17)	0.0431 (Figure 25)	0.0566 (Figure 33)	0.0605 (Figure 44)
CUMMULATIVE	**36.12 (Table 16)**	**28.88 (Table 17)**	**25.33 (Table 18)**	**30.32 (Table 19)**	**31.1 (Table 20)**	**0.1938 (Table 21)**	**0.1444 (Table 27)**	**0.1288 (Table 28)**	**0.1576 (Table 29)**	**0.1633 (Table 30)**	**0.1049 (Figure 3)**	**0.0698 (Figure 11)**	**0.0651 (Figure 19)**	**0.0794 (Figure 27)**	**0.0834 (Figure 35)**

The low levels of THC that would be ingested through oral consumption of Hemp Protein Powder and other hemp ingredients will result in metabolites in the urine. Measurement of the

presence of THCCOOH equal to or greater than the threshold value in urine is a standard test used by workplace, military, criminal justice and drug treatment programs to identify use/abuse of Cannabis. Accordingly, an assessment of the potential for Hemp Protein Powder and other hemp ingredients (see other GRNs filed with this Notice) to result in positive urine drug test results has been performed. Fresh Hemp Foods elected to use the tightest current cutoff level of 15 ng/ml as currently used by the US Department of Defense and US Federal Workplace Drug Testing to perform this assessment. The presence of urine metabolites at drug testing cut off levels indicates that THC has been consumed. The THC level consumed may be too low to result in psychological effects, but they are still a significant concern since a failing drug test result has the potential to damage the career and reputation of the individual.

The literature review found no instances of safety discussions outside of THC (delta 9-tetrahydrocannabinol). The overwhelming consensus in the literature and the scientific community is that hemp is a valuable food.

5.3. Safety of THC Exposure – General Population – Hemp Protein Powder and Cumulative Hemp Ingredient Consumption

The exposure to THC from low THC varieties of hemp has recently been evaluated by Food Standards Australia New Zealand/Australian New Zealand Food Authority. Food Standards set their lowest-observable-effect level (LOEL) based on a clinical study assessing impact of oral consumption of THC on the skill performance (standing steadiness, hand to eye coordination, reaction time, numbers test) of young adults (ANZFA Final Assessment Report Inquiry – S.17 Application A360). The participants showed slight but reversible effects on skill performance and no psychotropic effects after consuming 5 mg THC, the lowest level studied. The 2.5 and 5 mg doses evaluated by EIHA and Food Standards are much higher than the 0.0563 mg THC/person/day level anticipated for individuals 2 years and older consuming Hulled Hemp Seed at the 90th percentile and maximum level of inclusion. It is also much higher than the 0.041 to 0.047 and 0.049 levels conservatively anticipated for female and male children aged 2 to 5 years and 6 to 11 years respectively, thereby confirming that the estimated THC exposure resulting from cumulative consumption of hemp ingredients detailed in this GRN is unlikely to result in psychoactive effects and is therefore not a safety concern for the general population.

Law et al 1984 administered 5.0-5.2 mg THC in a meat sandwich to 5 subjects. None of the subjects reported any psychological effects or any reaction associated with cannabis administration. One of 5 subjects had poor pallor and felt faint. It is highly unlikely that individuals would receive the same level of exposure to THC from Hemp Protein Powder since a quantity of about 1.2 kg is needed to provide a comparable amount of THC at the maximum permitted levels resulting from the Fresh Hemp Foods Ltd. Specifications (Table 2).

Brenneisen et al 1996 administered 10 mg Marinol (synthetic THC) to Patient A and 15 mg THC to Patient B for four consecutive days. There were improvements in mobility, walking ability and rigidity in both patients, one patient showed no change in concentration and mood, while the other patient showed mixed changes at the higher 15 mg oral dose. It is not anticipated that individuals would experience any changes in concentration and mood or improvements in

mobility, walking ability and rigidity at the levels of THC exposure anticipated from the consumption of Hemp Protein Powder or cumulative consumption of hemp ingredients (Table 21).

Since 2013, Nabiximols, an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD in each 100 µL spray was approved in Italy for the treatment of Multiple Sclerosis. Low blood concentrations were produced by Nabiximols administration, more than 10 times lower than the blood concentrations known to produce psychotropic effects (Indorato et al 2016). Blood THC Cmax concentrations after a single 2.7 mg THC oromucosal spray were 0.52 ± 0.30 µg/L. Blood samples from 20 patients treated with Nabiximols for short (28 days) or long-term treatment (60 or 90 days) were analyzed. The quantity of THC expected to be consumed from Hemp Protein Powder and cumulative consumption of all hemp ingredients is 0.0553 mg and 0.1938 mg respectively which is far less than the 2.7 mg dose of Nabiximols studied indicating that consumers would not have psychotropic effects following the consumption of the 90th percentile of THC at the highest recommended level of inclusion (Table 21).

Stott et al, 2013 administered single Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses as 2 (5.4 mg THC), 4 (10.8 mg THC), 8 (21.6 mg THC) sprays, or multiple sprays (2, 4 or 8 sprays) for 9 consecutive days. The results demonstrated that low daily THC doses do not appear to accumulate in the blood. There was evidence of dose-proportionality in the single but not the multiple dosing data. The 5 mg THC dose, an amount far exceeding the 0.0553 mg level anticipated from consumption of Hemp Protein Powder, was the lowest level studied. It was found to produce Cmax values (<12 µg/L) well below those reported in patients who smoked/inhaled cannabis, which is associated with significant psychotropic effect. In terms of safety, the authors found that THC/CBD spray was well tolerated in all phases of the study, with no serious adverse events (AEs) or withdrawals due to AEs. All but three AEs were of mild severity, with three of moderate severity. All AEs resolved without sequelae, but most were considered to be related to the study treatment. The most common AEs were dizziness and somnolence. As expected, there was a direct relationship between increasing doses of THC/CBD spray and the frequency of AEs, with all subjects receiving eight sprays of THC/CBD spray experiencing at least one AE.

These data illustrate that the number of adverse events are low and of minor or moderate severity at much higher THC doses than would be expected from the 0.1938 mg THC consumption from all hemp ingredients at the 90% percentile at maximum inclusion levels for all age groups (Table 21).

Perez Reyes et al, 1973 administered 35 mg oral THC (containing 50 µc tritium THC) in five different vehicles (ethanol, sesame oil, 5.5% sodium glycholate, 5.5% sodium glycholate and ethanol, and Tween-80) to 40 individuals after fasting showing that the speed and bioavailability of absorption was highly dependent upon the vehicle utilized. Plasma, urine and feces were analyzed over 72 h. Total radioactivity of thin layer chromatography bands were used to quantify results. The vehicles providing the highest concentrations in plasma were from highest to lowest bioavailability were 5.5% sodium glycholate, sesame oil, Tween-80, ethanol and combined glycholate and ethanol, with peak concentrations between 1-2 h. In addition, with the same vehicle

and dose, a large 4.8 inter-individual variability in peak plasma THC concentrations was observed. Factors determining individual response to oral administration of cannabis include the dose of total THC and THC precursor acid, the degree of conversion of THC precursor acid to THC prior to ingestion, the rate of absorption of THC from the gastrointestinal system that is influenced by the vehicle used, and degree of first-pass THC metabolism. Perez-Reyes et al. 1973 reported that the speed and degree of absorption of THC are greatly influenced by the vehicle used for administration and based on cumulative urinary excretion data over 72 h, the rate of absorption of THC was affected by the nature of the vehicle and not the degree of absorption.

Ohlsson et al 1980, 1981, Wall and Perez 1981, Hollister et al, 1981 and Ohlsson et al 1985 administered 20 mg oral THC in a chocolate cookie, 10 mg smoked THC, and 5 mg intravenous (IV) THC in 95% ethanol over 2 min to 11 males. Plasma was analyzed from 3 to 240 min (4 h) for smoked and IV doses and from 30 to 360 min (6 h) after oral dosing. THC was analyzed by GC-MS. Maximum plasma THC concentrations (Cmax) after the 20 mg oral dose were 4.4-11 µg/L with time of peak concentration (Tmax) between 60 and 300 min. Compared to the IV dose, bioavailability of the oral dose was 6 ± 3% (4-12%), with slow and irregular absorption. The results indicate that an oral dose of 20 mg THC would produce a measurable effect although the likelihood of such an occurrence happening because of consumption of Hemp Protein Powder or other hemp ingredients is highly unlikely since the individual would need to consume about 5 kilograms of Hulled Hemp Seed to be exposed to 20 mg THC.

Wall et al 1983 compared oral and intravenous bioavailability of THC. A mean of 2.2 mg THC was intravenously administered over 15 to 25 min to six women and 4.0 mg to 6 men laced with tritium-labeled THC. Women received 15 mg and men 20 mg oral THC in sesame oil in capsules. Cumulative urinary excretion for cannabinoids was 15.9±3.6 and 13.4±2% of the dose in women and men, respectively. After oral dosing, total cannabinoid excretion in feces was 48±6 and 53±19% of the dose. After the oral route of administration, approximately 13-16% of the dose was excreted in urine by 72 h, while about 50% of the dose was found in the feces. There were no differences between women and men. The bioavailability of THC in the oral dose compared to an IV dose was 10.9% for women and 19% for men. Overall, there were no significant differences between sexes in THC metabolism, disposition and kinetics.

Sadler et al 1984 evaluated oral bioavailability of THC by simultaneously administering 0.141 mg/123 µCi ^{3}H THC intravenous tracer and 20 mg oral THC in sesame oil to 6 males. After 72 h, 21±1% of the tracer was in the urine and 40±2% was in the feces. A low bioavailability of 13% was found which was attributed to an extensive first pass effect in the liver.

Goodwin et al 2005 evaluated the pharmacokinetics and pharmacodynamics of oral THC through a controlled cannabinoid administration study of THC-containing hemp oils and dronabinol. Up to 14.8 mg THC was ingested by six volunteers each day in three divided doses with meals for five consecutive days. There was a 10-day washout phase between each of the five dosing sessions. THC was quantified in plasma by GC/MS. THC and 11-OH-THC were not detected in plasma following the two lowest doses of 0.39 and 0.47 mg/day THC, while peak plasma concentrations of < 6.5 µg/L THC, < 5.6 µg/L 11-OH-THC, and < 43.0 µg/L THCCOOH were achieved after the two highest THC doses of 7.5 and 14.8 mg/day. The findings of Goodwin et

at. 2005 indicate that THC and 11-OH-THC would not be expected to be detected in plasma following consumption of 0.0553 mg or 0.1938 mg THC, the estimated THC exposure from Hemp Protein Powder and cumulative consumption of all hemp ingredients at the 90th percentile and maximum inclusion level (Table 21).

5.4. Safety of THC Exposure – Children – Hemp Protein Powder and Cumulative Hemp Ingredient Consumption

THC's receptor-mediated mode of action appears to provide an additional margin of safety from undesirable health effects. This is particularly true for children. The severity of a toxic effect for most harmful chemicals is a function of exposure concentration and duration (Gaylor 2000). Thus, the no observed adverse effect level (NOAEL) correspondingly decreases with the duration of exposure. This is not the case with THC since the effect of a given exposure level decreases with time, likely due to the development of tolerance to THC by its receptors.

Children are considered particularly sensitive to many harmful chemicals resulting in higher safety factors being chosen to provide adequate protection. However, there are clinical studies that indicate that children are less sensitive to the effects of THC (Abrahamov et al. 1995, Dalzell et al. 1986), although this point is considered controversial.

The body surface of children would suggest a greater impact of THC on children. Clinical studies have shown that children tolerate higher doses of THC than adults before psychotropic side effects become significant (Abrahamov et al. 1995, Dalzell et al. 1986). Eight children age 3 to 10 who were undergoing chemotherapy were given 18 mg delta-8-THC per square meter of body surface, four times daily. Each child received an average of 60 doses. Two of the six children experienced mild psychotropic side effects. Extrapolating this same dosing to adults with an assumed body surface of 1.8 square meters, corresponds to single doses of 30 mg and a daily dose of about 120 mg THC. Delta-8-THC is assumed to be approximately 75% as psychotropic as delta-9-THC so a 30 mg dose is equivalent to about 23 mg of delta-8-THC, an amount which usually produces significant psychotropic effects in adults. Children between the ages of 2 and 11 years can be conservatively estimated to be exposed to between 0.1288 mg (Table 28) to 0.1633 mg (Table 30) of THC depending on their age and gender if they consume all hemp ingredients at the maximum level of inclusion at the 90th percentile level of consumption. These levels are over 100 times less than the 23 mg quantity shown to produce mild psychotropic effects in 2 of the 6 children studied.

5.5. Safety of THC Exposure – Breastfeeding Population – Hemp Protein Powder and Cumulative Hemp Ingredient Consumption

A thorough literature search for data related to transfer of THC from the mother to the infant during breastfeeding was performed. There is a surprising lack of information related to this question in the published literature, and most focused on THC transfer during the perinatal period that included transfer during gestation and breastfeeding.

The lack of controlled THC administration studies is obvious due to ethical and medical concerns with unnecessarily exposing the fetus and neonate to an exogenous compound. After extensive searching, data relating to the ingestion of a known amount of THC by the mother and resultant breast milk THC concentrations was identified. Neither are there controlled studies of THC administration to the infant and resultant infant plasma or urine THC concentrations. There are data estimating the volume of daily breast milk ingested by neonates and infants, effects on

the fetus following in utero THC exposure and on the neonate following THC breast milk exposure. In addition, there are many reports advising for or against breastfeeding if the mother uses cannabis.

Maximum cumulative THC exposure estimates for individuals over the age of two were based on the individual using the maximum amount of all products in a single day (Refer to Table 39). These data were used as mean and maximum exposures for the lactating woman to assess the safety of cumulative THC exposure from Fresh Hemp Foods, Ltd hemp products including Hulled Hemp Seed, Hemp Protein Powders (including protein concentrate) and Hemp Oil in the breastfeeding population (see GRNs filed with this notice). The THC calculations are based on the Fresh Hemp Foods, Ltd specifications for maximum THC content (refer to Table 21). These values were used in determining daily THC intake if the recommended dose of all products were consumed each day.

Preclinical data

Reisner et al 1983 reported that only 0.2% of a labeled THC dose to squirrel monkeys appeared in their breast milk as hydrophilic & lipophilic metabolites within 24 hours; 0.01% of the dose appeared in the squirrel monkeys' offspring's urine. In lactating ewes, milk contained less radiolabel than their feces or urine, with radiolabel being detected 4 and 96 hours after THC injection (Mourh and Rowe 2017). Endocrine and behavioral changes were noted in suckling rodents after THC exposure in breast milk. THC acted as an in vivo weak competitor of the estrogen receptor, producing a primary estrogen effect in male & female rats (Warner et al 2014). In addition, THC was shown to reduce trophoblast cell proliferation and inhibit placenta development. In some studies, THC also produced hormonal changes reducing fertility. In animal models, THC crossed the placenta resulting in fetal plasma concentrations approximately 10% of maternal plasma concentrations after acute exposure; however, significantly higher fetal concentrations were observed after repetitive exposures (American College of Obstetricians & Gynecologists' Committee on Obstetric Practice 2015). Furthermore, these clinicians noted that although animal models may be poor surrogates for the human condition, endocannabinoids played key roles in normal fetal brain development, including neurotransmitter systems, and neuronal proliferation, migration, differentiation, and survival.

Battista et al 2014 noted that the endocannabinoid-CB1 receptor system is important for milk suckling, and in growth and development early in life. It was suggested that increased endocannabinoids and/or cannabinoids in milk might have relevant effects on breastfed newborns.

Murphy et al 1998 showed that THC inhibited gonadotropin, prolactin, growth hormone and thyroid-stimulating hormone release and stimulated release of corticotropin, inhibiting the quantity and reducing the quality of breast milk. In a recent review, Mourh and Rowe 2017 demonstrated that animals exposed to THC in milk had decreased prolactin concentrations and motor, neurobehavioral, & developmental effects. Lactating rats and non-pregnant rhesus monkeys displayed lower prolactin concentrations following THC injections, with maximum reductions of 74% (in male monkeys) and 85% (in female monkeys) over the first 30-90 minutes. There was a >70% reduction in prolactin from baseline after 1.25 mg/kg THC and >90%

reduction following a 4 mg/kg dose over 30-60-min. In addition, lactating rats displayed lower blood oxytocin concentrations following THC dosing. THC prevented suckling-induced oxytocin secretion by the posterior pituitary, leading to a longer delay in initial ejection of milk and between successive ejections. Additional effects seen in monkeys & rats included lethargic behavior, reduced maternal care, and anxiety.

In milk samples from buffalos eating cannabis plants, 50% contained cannabinoids (Ahmad and Ahmad 1990). Consumers of the contaminated milk were passively exposed to THC and metabolites were detectable in at least 30% of children up to the age of 3 years. Mouse pups whose mothers consumed food containing hashish during lactation weighed significantly less (by 10– 14%) than control pups from day 11 onward. The endocannabinoids play key roles in normal fetal brain development, including neuronal proliferation, migration, differentiation, & survival (The American College of Obstetricians & Gynecologists' Committee on Obstetric Practice 2015), suggesting that this occurred due to malnutrition (which could be the result of poorer milk production in the mothers or the direct influence of THC on the pups).

The degree to which we can correlate effects of THC exposure in breast milk in animals and humans, especially neurobehavioral changes, is unclear. Also, the animal doses were frequently greater than those in human studies and were usually administered intravenously, making comparison of pharmacokinetics difficult. Exposure to cannabis includes exposure to numerous other cannabinoids, terpenes and polyaromatic hydrocarbons and might have different effects than synthetic IV THC.

Clinical data & recommendations

All drugs may pass into breast milk depending upon the drug's molecular weight and size, protein binding, amount of free drug in the blood, the lipophilicity of the drug, and the drug's pKa. Berlin and Briggs describe the transport of compounds across the mammary alveolar cells as primarily due to transcellular diffusion, in which small molecules (molecular weight 100-200) pass through with the flow of water due to hydrostatic or osmotic pressure differences. Larger molecular weight compounds may enter milk through intercellular diffusion, explaining the presence in breast milk of maternal proteins such as cow milk antigen and antibodies. The 3-dimensional shape of the molecule also may be a determinant in transfer to breast milk. Ionophore diffusion facilitates charged ions transfer and carrier proteins transfer other substances. THC is a highly lipophilic compound and transfers readily into breast milk.

Perez-Reyes and Wall reported that cannabis & metabolites pass into breast milk in concentrations dependent upon the amount of drug ingested by the mother. These authors published the one and only breast milk/plasma THC ratio data (one single paired sample) as the primary source for THC concentrating in breast milk, and many recommendations to not breastfeed if the mother continues to use marijuana. Breast milk from two chronic frequent cannabis users were studied. There were no data on the amount of THC ingested by the women, thus, there are no data on maternal THC intake per event or per day. Woman #1 reported smoking cannabis once per day and woman #2 reported smoking approximately seven times per day. A single matched plasma and breast milk sample was collected from woman #2, as described as under steady state conditions. THC concentrations in the plasma were 7.2 µg/L

THC, 2.5 µg/L 11-OH-THC, and 19 µg/L THCCOOH, and 60.3, 1.1, and 1.6 µg/L THC, 11-OH-THC and THCCOOH concentrations in the breast milk, respectively. These are the sole data supporting a human THC breast milk/plasma ratio of 8.4, indicating that THC is concentrated up to 8-fold in breast milk compared to maternal plasma. At these concentrations, it was estimated that the infant's daily THC exposure was 0.01 to 0.1 mg THC/day. There were no observable side effects in the infant receiving this amount of THC (Hale 2012). Concentrations in woman #1's breast milk were 105 µg/L THC, with no detectable 11-OH-THC and THCCOOH. Marcei et al 2011 reported cannabinoid concentrations in breast milk from one lactating woman of 86 µg/L THC and 5 µg/L 11-OH-THC, but maternal plasma was not tested. Also, the duration of THC in the breast milk after cessation of use is unknown (Wang 2016). The evidence is unclear if breastfeeding benefits (nutrition, immune protective factors, sudden infant death syndrome (SIDS), bonding, etc.) outweigh potential THC breast milk exposure risks.

There are so few data on THC in human breast milk and the effects of this exposure, that most experts refer to the effects of in utero cannabis exposure as a means of evaluating potential adverse developmental outcomes. Furthermore, most women who use cannabis during pregnancy continue use during breastfeeding, making it difficult to assign causation to one source of exposure. There does not appear to be a need to discuss in utero drug exposure. Clearly, use of cannabis during pregnancy is contra-indicated.

Reported cannabis use prevalence rates in pregnancy vary from 3-34% (Metz & Stickrath 2015), with cannabis the most common illicit drug taken during gestation. Sixty percent of women who used cannabis in the year prior to pregnancy continued to use more than 10 joints per week, indicating that many women continue use throughout pregnancy. Identification of cannabis use in the mother at birth does not differentiate the amount of use and designation of occasional or chronic frequent use. The American College of Obstetricians & Gynecologists' Committee on Obstetric Practice (2015) estimate that 48–60% of cannabis users continue use during pregnancy, with many women believing that it is relatively safe to use during pregnancy & less expensive than tobacco. Colorado's largest local Tri-County health department serves >26 % of the population (Wang 2016). Their Women's Infants & Children (WIC) Program survey revealed 7.4% of mothers aged <30 years & 4% of mothers >30 years are current cannabis users. Of all cannabis users (past, ever, current), 35.8% said they used at some point during pregnancy, 41% since the baby was born & 18% while breastfeeding.

Breast milk samples (N=109) from lactating women were analyzed for cannabinoids and questionnaires were completed about their drug use during pregnancy and while breastfeeding (Mourh & Rowe 2017). Of 19 women reporting drug use, 1 had 20 µg/L THC in her breast milk, with no detectable cannabinol or cannabidiol, and her urine was positive for cannabinoids. Another woman not reporting drug use had 31 µg/L THC in her breast milk with no detectable cannabidiol. Infant THC exposure was estimated as 2 and 3.1 µg THC/100 mL breast milk. Using 12% oral THC bioavailability, infant exposure was estimated at 0.24 & 0.37 µg THC. Maternal THC dose and dosing time in relation to breast milk collection were unknown.

Astley & Little 1990 suggested that cannabis use by the breastfeeding mother during the first month of life could impair neurodevelopment. Glial and myelin formation in the infant brain

continues after birth during breastfeeding and might lead to sedation and weakness. Other disadvantages include the possibility that THC in breast milk may decrease the production, volume, composition & ejection of breastmilk, resulting in poor feeding patterns (Liston 1998).

The American Academy Pediatrics Committee on Drugs 2001 noted that there were no reported adverse effects of cannabis in published studies.

In the WHO Breastfeeding 1997 Report, it was estimated that in one feeding the infant will ingest 0.8% of the weight-adjusted maternal intake of 1 joint (Garry et al 1990). The authors suggest that mothers who use cannabis must stop breastfeeding, or ask for medical assistance to stop cannabis use, to provide their babies with all the benefits of human milk. THC in breast milk could sedate the infant and result in growth delays.

Liston 1998 suggested that infants exposed to marijuana via breast milk show signs of sedation, reduced muscular tonus, & poor sucking. Two studies evaluated the effects of cannabis use by the lactating mother on their child's development. The first study found no significant differences in terms of weaning, growth, and mental or motor development with regard to age. The second study found that cannabis exposure via the mother's milk during the first month postpartum appeared to be associated with a decrease in infant motor development at one year of age. Infants exposed to cannabis for more than half of the days during the 1st trimester of gestation or 1st month of lactation had significantly lower mean Psychomotor Development. Other factors come into play like cannabis exposure during pregnancy, passive exposure to cannabis smoke in ambient air, or the quality of the mother-child relationship. There are no studies relating to the long-term effects of marijuana exposure through breast milk. There are almost no studies of lactation exposure only; the infant was usually prenatally exposed and almost all of their mothers continued use after birth (Reece-Stremtan et. al 2015).

Despite preclinical studies suggesting that THC exposure during breastfeeding can reduce the quality and quantity of breast milk, these effects have not been confirmed in humans (Sharma et al 2012). According to Warner et al 2014, the identification of side effects in the lactation-exposed infant are inconsistent and there are no long-term outcome studies. Hotham and Hotham 2015 stated that the most commonly used drugs are relatively safe for breastfed babies. Drugs contraindicated during breastfeeding include anticancer drugs, lithium, oral retinoids, iodine, amiodarone & gold salts. Estimated breastmilk intake by an exclusively breastfed baby is 150 mL/kg/d.

Hale 2012 placed cannabis in highest risk category, L5 or Hazardous, stating that using cannabis during breastfeeding clearly outweighs the benefits of breastfeeding; however, many lactation experts disagree with this conclusion. Jansson et al 2015 noted the importance of active, passive (from maternal side stream smoke) and cumulative exposures to breastfed infants must be considered. THC delivered via lactation to the infant may affect the ontogeny of various neurotransmitter systems, leading to changes in neurobiological functioning. The recent new recommendation by the Academy of Breastfeeding Medicine was described as erroneous & disappointing. It is unclear why a recommendation would err on the side of breastfeeding with

potentially toxic exposures and other risk factors that could portend short- & long-term infant harm.

Most adverse effects of drugs in breast milk occurred in newborns under 2 months and rarely in those older than 6 months (Jansson et al 2015). A follow-up study of 1-year-old breastfed infants of mothers who used cannabis found some impairment in motor development, although researchers found it difficult to determine whether in utero exposure or breastfeeding was the greater influence. Women should be encouraged to stop using cannabis & avoid exposure of the baby to second-hand smoke.

In a survey of mothers by lactation experts, 15% of women reported using cannabis during breastfeeding (Bergeria and Heil 2015). Forty-four percent of the lactation experts reported that their recommendations were based on marijuana use factors like the severity of maternal use. Another 41% reported recommending continued breastfeeding because benefits outweigh harms, and the remaining 15% recommended that a woman should stop breastfeeding if she cannot stop using marijuana. Infants whose mothers used marijuana during lactation (n = 27) had similar growth outcomes, mental & motor development, & weaning ages compared with infants of non-using mothers (n=35). In contrast in a larger study, significant deficits in motor development was found at 1 year of age among exposed infants (n = 68) versus matched controls (n = 68), however, marijuana exposure occurred during the first trimester of pregnancy & the first month of lactation, making it difficult to determine which period of exposure had a stronger influence on infant motor development.

The American College of Obstetricians & Gynecologists Committee on Obstetric Practice released new recommendations on breastfeeding and marijuana use in 2015. Obstetricians and gynecologists should be discouraged from prescribing or suggesting marijuana use for medicinal purposes during preconception, pregnancy, & lactation. There are insufficient data to evaluate effects of marijuana use on infants during lactation & breastfeeding; thus, marijuana use is discouraged. In animal models, THC crossed the placenta, producing fetal plasma levels that were approximately 10% of maternal levels after acute exposure. Significantly higher fetal concentrations were observed after repetitive exposures. Animal models demonstrate that endocannabinoids play key roles in normal fetal brain development, including in neurotransmitter systems, & neuronal proliferation, migration, differentiation, & survival. Breastfeeding women should be informed that the potential risks of exposure to marijuana metabolites are unknown & should be encouraged to discontinue marijuana use.

The strongest determinant of breast milk medication concentration is the non-protein bound maternal plasma drug concentration (Newton & Hale 2015). THC is a highly bound drug that should result in lower breast milk concentration; however, THC has a large volume of distribution (Vd) in maternal compartments, with especially rapid tissue sequestration that will reduce maternal free drug concentrations. THC is a highly lipid soluble drug that passes through the alveolar cells more easily and is sequestered in milk. Marijuana is an example of a highly lipid soluble drug with higher concentrations in breastmilk based on a single paired maternal plasma and breast milk sample. THC's pKa is 10.2, leading to ion trapping in milk due to the higher ionization at lower pH. The relative infant dose (RID) is amount of the drug dose to the

breastfeeding infant. The infant dose (mg/kg/d) is divided by the mother's dose (mg/kg/d). An RID <10% is considered acceptable in a healthy postnatal infant. The bioavailability of the drug in the infant must be known. THC's oral bioavailability is low- estimated to be about 6% in adults. Premature, term or ill neonates may have higher absorption rate than adults. The ultimate measure of drug in breast milk is the infant's plasma blood concentrations but none have been published. Mothers are advised to choose drugs with a low M/P ratio and to avoid drugs with a long half-life (12-24 h).

The Academy of Breastfeeding Medicine "A recommendation of abstaining from any marijuana use is warranted. At this time, although the data are not strong enough to recommend not breastfeeding with any marijuana use, we urge caution (Foeller & Lyell 2017).

We included the data for marijuana use during breastfeeding because no data are available for oral THC dose and breastfeeding; however, maternal blood THC concentrations following maternal cannabis smoking or vaporization can be as high as 200-300 ng/mL, while blood THC concentrations after oral THC from ingestion of Fresh Hemp foods is expected to be very low.

Based on the studies administering known quantities of THC and blood/plasma/serum concentrations, we can estimate the blood concentrations that would result from a mean intake of 0.0968 mg to a 90th percentile intake of 0.1938 mg oral THC (refer to Table 21). Stott et al 2013 administered two Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses (total 5.4 mg THC) to adults. There are no infant THC administration data. The mean plasma Cmax was <1.2 µg/L THC and <2 µg/L 11-OH-THC. The mean daily amount (0.0968 mg) and 90th percentile (0.1938 mgk) of THC exposure from ingesting all Fresh Hemp Foods, Ltd. Products is 55- and 27-fold lower than this exposure, respectively (Table 33). These data would estimate the plasma Cmax in the breastfeeding mother assuming a 0.0968 mg daily dose as <0.02 µg/L THC and <0.035 µg/L 11-OH-THC, and if the highly conservative 0.1938 mg THC dose is assumed, plasma Cmax in the mother of <0.04 µg/L THC and <0.07 µg/L 11-OH-THC. Refer to Table 39 for a summary of estimated infant THC exposure.

Furthermore, based on the Monte Carlo simulation, the maximum daily THC exposure at the 90th percentile was estimated at 0.1049 mg 99.9% of the time based on cumulative ingestion of all hemp ingredients (refer to Figure 3). This amount is 51 times lower than the 5.4 mg THC Stott et al dose, estimating a maximum THC concentration of <0.02 µg/L and <0.04 µg/L.

In a single maternal plasma and breast milk pair, the THC plasma to breast milk ratio was 8.4 (Hale 2012). Based on this ratio and the mean-90% maternal plasma THC concentrations the maximum THC concentration in the breast milk would be between 0.17-0.34 µg/L. There are no data on breast milk/plasma ratios, but if one assumed a similar distribution for 11-OH-THC into breast milk, maximum 11-OH-THC concentrations in breast milk would be 0.34-0.59 µg/L.

The estimate of daily breast milk intake is 150 mL/kg/day. Our estimates of maximum THC concentration in breast milk and daily intake would suggest THC intake of 0.05 – 0.09 µg/kg/day THC. As 11-OH-THC is equipotent to THC, assuming the breast milk to plasma ratio is also 8.4, the total active cannabinoids exposure for the infant is estimated to be <0.08-0.14 µg/kg/day.

Gustafson et al 2014 administered 0.39 and 0.47 mg THC per day for 5 days, resulting in non-detectable THC concentrations in human plasma. These doses are 2-4 times the dose a breastfeeding mother would consume with all hemp products. This low-level exposure is not expected to produce adverse developmental outcomes in the infant whose mother consumes the maximum amount of all hemp ingredients at the maximum inclusion level per day.

Furthermore, Stott et al 2013 also administered the 5.4 mg THC/day dose for 9 consecutive days and showed that THC and 11-OH-THC concentrations did not accumulate over time. This also demonstrates that daily use of the 3 Fresh Hemp Foods, Ltd hemp ingredients that provide THC at a much lower level than the 5.4 mg Stott dose should not accumulate. At birth, a 10 lb. (4.55 kg) infant would receive about 0.14-0.23 µg/day THC and 0.23-0.41 µg/day 11-OH-THC. The total active cannabinoid dose would be approximately 0.37-0.64 µg/day. The oral bioavailability of THC and 11-OH-THC is low, estimated to be 6-12% in adults; bioavailability could be different in the infant although first pass metabolism would still reduce active cannabinoid exposure. This low concentration of active cannabinoids should not produce adverse developmental effects.

5.6. Safety of THC Exposure – Urine Analysis and Drug Testing – Hemp Protein Powder and Cumulative Hemp Ingredient Consumption

Fresh Hemp Foods Ltd. evaluated publicly available clinical studies to assess the potential for food products containing Hemp Protein Powder to produce positive urine drug test results (refer to summary in Table 40). The cut off level of not more than 15 ng/ml was applied to the assessment in accordance with US Federal Workplace Drug Testing and US Department of Defense requirements (Table 37).

Hemp Protein Powder

The exposure to THC was estimated at the mean and 90th percentile based on consumption of maximum levels of Hemp Protein Powder containing THC at maximum permitted specification levels of 4 µg/g in all food categories identified. Refer to Tables 22 to 26. The estimated mean and 90th percentile is 0.028 mg and 0.055 mg/person/day for individuals age 2 years and older, 0.025 and 0.049 mg THC/person/day for boys aged 2 to 5 years, 0.021 and 0.042 mg THC/person/day for girls aged 2 to 5 years, 0.024 and 0.049 mg THC/person/day for boys aged 6 to 11 years and 0.025 and 0.05 mg THC/person/day for girls aged 6 to 11 years.

Monte Carlo modelling was also used to estimate THC exposure at the 90th percentile based on the mean THC level detected by historical third party analytical testing. The exposure to THC was estimated at 0.0164 mg THC/person/day for Hemp Protein Powder for individuals age 2 years and older (Figure 5). The estimated 90th percentile is 0.0147 mg THC/person/day for boys aged 2 to 5 years, 0.0126 mg THC/person/day for girls aged 2 to 5 years, 0.0145 mg THC/person/day for boys aged 6 to 11 years and 0.0149 mg THC/person/day for girls aged 6 to 11 years (refer to Figures 13, 21, 29, 37 respectively).

The estimated THC exposure levels resulting from consumption of Hemp Protein Powder at the maximum level of THC permitted by the specifications is not expected to screen positive for THCCOOH in urine at 15 µg/L cutoff concentrations. Furthermore, the Monte Carlo probabilistic modelling of THC exposure from Hemp Protein Powder provides further support that Fresh Hemp Foods Ltd. Hemp Protein Powder is unlikely to produce positive urine test results at the 15 ng/ml testing limit. These conclusions are based on the upper bound estimated quantity of THC anticipated to be consumed in contrast to the findings of the comprehensive literature review of publicly available data (refer to Table 39) as well as specific studies that were found highly relevant to this GRN Notification (Bosy and Cole 2000, Leson et. al. 2001, Gustafson et. al. 2003).

Cumulative Hemp Ingredients

In accordance with the assumptions made in Section 4.B.iii. Multiple GRAS Notices Used in Conservative Exposure Estimates, Fresh Hemp Foods Ltd. evaluated publicly available clinical studies to assess the potential for the THC from combined oral consumption of Hulled Hemp Seed, Hemp Oil and Hemp Protein Powders to produce positive urine drug test results. The cut off level of not more than 15 µg/ml was applied to the assessment in accordance with US Federal Workplace Drug Testing and US Department of Defense requirements.

The exposure to THC was estimated at the mean and 90th percentile based on consumption of maximum levels of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil containing THC at maximum permitted specification levels in all food categories identified. Refer to Tables 21, 27 to 30. The estimated mean and 90th percentile is 0.0968 and 0.1938 mg/person/day for individuals age 2 years and older, 0.0722 and 0.1444 mg THC/person/day for boys aged 2 to 5 years, 0.0644 and 0.1288 mg THC/person/day for girls aged 2 to 5 years, 0.0788 and 0.1576 mg THC/person/day for boys aged 6 to 11 years and 0.0816 and 0.1633 mg THC/person/day for girls aged 6 to 11 years.

Monte Carlo modelling was also used to estimate THC exposure at the 90th percentile based on the mean THC level detected by historical third party analytical testing of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil. The exposure to THC was estimated at 0.1049 mg THC/person/day for individuals age 2 years and older, 0.0698 mg THC/person/day for boys aged 2 to 5 years, 0.0651 mg THC/person/day for girls aged 2 to 5 years, 0.0794 mg THC/person/day for boys aged 6 to 11 years and 0.0834 mg THC/person/day for girls aged 6 to 11 years (refer to Figures 3, 11, 19, 27, 35 respectively).

These estimated THC exposure levels are not expected to result in positive urine test results at the 15 ng/ml limit based on the findings of the comprehensive literature review of publicly available data (refer to Table 40) as well as specific studies that were found highly relevant to this GRN Notification (Bosy and Cole 2000, Leson et. al. 2001, Gustafson et. al. 2003).

It should be noted that it is possible but unlikely that individuals consuming 0.39 mg THC per day from Fresh Hemp Foods, Ltd products over a 5 day period could screen positive for THCCOOH in urine at 15 µg/L cutoff concentrations. This level is twice the amount estimated

above for the cumulative consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil which contains THC at the maximum specification limits.

Literature Review

Refer to Table 40 for a tabular summary of the publicly available clinical data.

Bosy & Cole 2000 had 7 daily administered doses of hemp oils between 0.10 and 1.8 mg/day and tested random urine specimens for up to 7 days after the last dose. Peak THCCOOH concentrations in the participants' urine ranged from 1.8 to 48.7 µg/L. There were no positive urine specimens ≥15 µg/L following the 0.10, 0.17, 0.32, and 0.55 mg THC/d for 7 daily doses. The 0.54 mg and 1.8 mg THC/d doses produced positive urine specimens ≥15 µg/L. Subjects ingesting low doses of THC (0.10 & 0.17) mg THC/d had no positive immunoassay results, while the 1 subject ingesting 0.32 mg THC/d had 11 of 18 results ≥ 50-µg/L immunoassay positive cutoff, but none were positive by GC/MS. Subjects ingesting medium doses of THC in hemp oil (0.54 & 0.55 mg THC/d) produced positive immunoassay screen results on the third and fourth days of ingestion. These two subjects had negative immunoassays within 24 h after ingestion ceased. The subject ingesting a high dose (1.8 mg THC/d) screened positive on the first day and was immunoassay negative within 72 h after last ingestion. No psychotropic effects were experienced by any of the subjects during the course of the experiment.

Leson et al 2001 reported results from 15 adults ingesting 10 daily THC doses of 0.09, 0.19, 0.29, and 0.45 mg THC. Urine specimens were collected prior to the first ingestion of oil, on days 9 and 10 of each of the four 10-day study periods, and 1 and 3 days after the last ingestion. All specimens were confirmed for THCCOOH by GC–MS and analyzed for creatinine to identify dilute specimens. There were no positive screening results and no positive GC-MS results ≥15 µg/L for doses below 0.60 mg THC/d. Only one specimen screened positive at the 50 µg/L cutoff at a daily THC dose of 0.6 mg. The highest THCCOOH concentration was 5.2 µg/L, well below the 15 ng/ml confirmation cutoff of federal drug testing programs.

Gustafson et al 2003 determined urinary THCCOOH excretion by GC/MS analysis in 4381 urine specimens collected before, during, and after 5 oral daily 0.39, 0.47, 7.5, and 14.8 mg THC/day doses to 7 participants. All urine voids were collected over the 10-week study. At the federally mandated immunoassay cutoff (50 µg/L), mean detection rates were <0.2% during ingestion of the two low doses typical of current hemp oil THC concentrations. These low dose data are representative of the daily THC concentrations present in Fresh Hemp Food products and suggest that the possibility of positive urine THCCOOH tests following ingestion of 0.39 mg THC from hemp foods is low but measurable. Only four of 7 participants produced a mean of 3.1 positive urine THCCOOH specimens after the 0.39 mg/day and 2 of 7 had a mean of 2.4 positive samples during and for the 10 days following 5 daily doses, range 0-13 total specimens). Positive cannabinoid urine tests ≥15 µg/L occurred as early as 14.6 h and as late as 110.5 h after the start of 5 daily doses. Mean detection rate for the 0.39 mg THC/d was 2.6% positive tests with a range of 0 to 10.3% positive tests at ≥15 µg/L. Mean detection rate for the 0.47 mg THC/d was 2.3%

positive tests with a range of 0 to 8.7% positive tests at ≥15 µg/L. Maximum metabolite concentrations were 5.4 – 38.2 µg/L for the low THC/day doses.

The results of these three studies are not consistent. Bosy and Cole found no positive urine tests after 7 daily doses of 0.10, 0.17, and 0.32 mg THC and testing urine samples up to 6 h after dosing and daily for 7 days. However, dosing 0.54 and 0.55 mg THC per day produced different results, with some urine samples positive after the 0.54 mg regimen and no samples positive after the 0.55 mg regimen. Only a single individual was administered each dose. Leson et al found no positive GC/MS results ≥15 µg/L following 4 daily up to 0.6 mg THC per day doses, but all urine specimens were not collected and analyzed. Gustafson et al administered 5 daily doses of 0.39 and 0.47 mg THC per day to 7 individuals and all urine specimens were collected and analyzed. Less than 0.2% of urine specimens screened positive at a 50 µg/L cutoff; however, in one subject receiving the 0.39 mg regimen, up to 10.3% of urine specimens were positive for THCCOOH ≥15 µg/L. It is apparent that the vehicle is important for absorption, as a 0.47 mg THC per day hemp oil produced fewer positive urine specimens than the 0.39 mg THC per day dose in Gustafson et al.

5.7. Safety of THC Exposure – THC Exposure Based on Body Weight

Hemp Protein Powder

The upper bound estimate of THC exposure based on body weight has been determined. using anticipated THC exposure based on 90th percentile consumption of all food products containing maximum levels of Hemp Protein Powder at maximum Fresh Hemp Foods Ltd. THC specification limits. Refer to Tables 22 to 26 for THC values and to Table 41 (duplicated below) for summary of exposure based on body weight for all hemp ingredients and age groups. It is estimated that males and females age 2 years and older would be exposed to THC at 0.623 and 0.724 µg/kg body weight respectively. Exposure is estimated to be 3.482 µg/kg body weight for boys age 2 to 5 years, 3.172 µg/kg body weight for girls age 2 to 5 years and 2.031 µg/kg body weight for boys age 6 to 11 years and 2.096 µg/kg body weight for girls aged 6 to 11 years.

Table 41. Upper Bound Estimate of THC Exposure Based on Body Weight

	THC EXPOSURE BASED ON BODY WEIGHT AT MAXIMUM SPECIFICATION LEVELS (µg/kg Body Weight)[1,2] *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014) *Hulled Hemp Seed = NMT 4 µg/g THC *Hemp Protein Powder = NMT 4 µg/g THC *Hemp Oil = NMT 10 µg/g THC						THC EXPOSURE BASED ON BODY WEIGHT USING MONTE CARLO MODELLING FROM FIGURES 2 to 41 (µg/kg Body Weight)[1,2] *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014) *Hulled Hemp Seed = Mean of 0.29 µg/g THC *Hemp Protein Powder = Mean of 0.31 µg/g THC *Hemp Oil = Mean of 4.95 µg/g THC						TOLERABLE DAILY INTAKE RECOGNIZED BY OTHER REGULATORY AUTHORITIES (µg/kg Body Weight)					
	2 Years & Older		2 to 5 Years		6 to 11 Years		2 Years & Older		2 to 5 Years		6 to 11 Years		Germany	Switzerland	Australia	New Zealand	Canada	Austria
	Males (Mean BW = 88.8 kg)	Females (Mean BW = 76.4 kg)	Males (Mean BW = 14.2 kg)	Females (Mean BW = 13.3 kg)	Males (Mean BW = 23.9 kg)	Females (Mean BW = 23.8 kg)	Males (Mean BW = 88.8 kg)	Females (Mean BW = 76.4 kg)	Males (Mean BW = 14.2 kg)	Females (Mean BW = 13.3 kg)	Males (Mean BW = 23.9 kg)	Females (Mean BW = 23.8 kg)						
Hulled Hemp Seed GRN XXX	0.634 (Table 43)	0.737 (Table 43)	3.299 (Table 44)	3.067 (Table 45)	2.029 (Table 46)	2.041 (Table 47)	0.240	0.279	1.254	1.165	0.770	0.773						
Hemp Protein Powder GRN XXX	0.623 (Table 43)	0.724 (Table 43)	3.482 (Table 44)	3.172 (Table 45)	2.031 (Table 46)	2.096 (Table 47)	0.185	0.215	1.035	0.947	0.607	0.626	**5**	**7**	**6**	**6**	**Not Set**	**1-2**
Hemp Oil GRN XXX	0.925 (Table 43)	1.075 (Table 43)	3.387 (Table 44)	3.444 (Table 45)	2.536 (Table 46)	2.723 (Table 47)	0.869	1.010	3.176	3.241	2.368	2.542						
CUMMULATIVE	**2.182 (Table 43)**	**2.536 (Table 43)**	**10.168 (Table 44)**	**9.684 (Table 45)**	**6.596 (Table 46)**	**6.86 (Table 47)**	**1.181**	**1.373**	**4.915**	**4.895**	**3.322**	**3.504**						

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States. 2011-2014. National center for Health Statistics. Vital Health Stats 3(39). 2016

[1]Assumes that children would eat all the same foods as an adult.

A more realistic assessment of THC exposure is achieved by using the daily THC exposure predicted by Monte Carlo modelling using historical third-party THC testing data for Hemp Protein Powder to calculate THC µg/kg body weight. Refer to Tables 38 and 41 for a summary of the THC exposure at the 90th percentile for each hemp ingredient and all age groups and the corresponding exposure based on body weight.

It can be realistically estimated that males and females age 2 years and older would be exposed to 0.185 and 0.215 µg/kg body weight respectively, while exposure for children is estimated to be 1.035 µg/kg body weight for boys age 2 to 5 years, 0.947 µg/kg body weight for girls age 2 to 5 years and 0.607 µg/kg body weight for boys age 6 to 11 years and 0.626 µg/kg body weight for girls aged 6 to 11 years. The Monte Carlo estimates are anticipated to be more realistic but are still considered to be relatively conservative because they predict THC exposure at 90th percentile consumption of all food products containing maximum levels of Hemp Protein Powder.

Cumulative Hemp Consumption

The upper bound estimate of THC exposure based on body weight has been determined. using anticipated THC exposure based on 90th percentile consumption of all food products containing maximum levels of Hulled Hemp Seed, Hemp Protein Powders and Hemp Oil at maximum Fresh Hemp Foods Ltd. THC specification limits. Refer to Tables 21, 27 to 30 for THC values and to Table 41 for summary of exposure based on body weight for all hemp ingredients and age groups. Using anticipated cumulative THC exposure based on 90th percentile consumption of all food products containing maximum levels of all hemp ingredients at maximum Fresh Hemp Foods Ltd. THC specification limits, the upper bound estimate is that males and females age 2 years and older would be exposed to 2.182 and 2.636 µg/kg body weight respectively while children would have a higher per kg exposure based on their lower body weight. Exposure calculated based on body weight is conservatively estimated to be 10.168 for boys age 2 to 5 years, 9.684 µg/kg body weight for girls age 2 to 5 years and 6.596 for boys age 6 to 11 years and 6.86 µg/kg body weight for girls aged 6 to 11 years. These THC exposure levels are highly

conservative since they are calculated using the maximum THC levels based on Fresh Hemp Foods Ltd. specifications.

A more realistic assessment of THC exposure is achieved by using the daily THC exposure predicted by Monte Carlo modelling using historical third-party THC testing data for the three Fresh Hemp Foods Ltd. hemp ingredients to calculate THC µg/kg body weight. Refer to Tables 38 and 41 for a summary of the THC exposure at the 90th percentile for each hemp ingredient and all age groups and the corresponding exposure based on body weight.

It can be realistically estimated that males and females age 2 years and older would be exposed to 1.1812 and 1.373 µg/kg body weight respectively, while exposure for children is estimated to be 4.915 µg/kg body weight for boys age 2 to 5 years, 4.895 µg/kg body weight for girls age 2 to 5 years and 3.322 µg/kg body weight for boys age 6 to 11 years and 3.504 µg/kg body weight for girls aged 6 to 11 years. The Monte Carlo estimates (Table 41) are anticipated to be more realistic but are still considered to be relatively conservative because they predict THC exposure at 90th percentile consumption of all food products containing maximum levels of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil.

Refer to summary Table 41 for a comparison of the THC exposure from Hulled Hemp Seed and cumulative hemp consumption versus the Tolerable Daily Intake (TDI) recognized by other international regulatory authorities. The THC exposure estimated in this GRAS notification is similar to these other standards. For instance, New Zealand and Australia legalized low THC hemp foods for human consumption in 2017. Through their clinical review, the TDI was set at 6 µg/kg body weight (Food Standards 2017). The estimated µg/kg body weight exposure for children using maximum THC levels based on Fresh Hemp Foods ltd. specifications is higher than this TDI, whereas the estimates obtained by using historical data are in line with this and other TDI identified by regulatory bodies which have performed similar assessment of the safety of THC from low hemp foods.

Food Standards 2017 based their TDI on a study assessing impact of oral consumption of THC on the skill performance (standing steadiness, hand to eye coordination, reaction time, numbers test) of young adults (ANZFA Final Assessment Report Inquiry – S.17 Application A360). The participants showed slight but reversible effects on skill performance and no psychotropic effects after consuming 5 mg THC, the lowest level studied. A 5 mg THC dose was equivalent to 60 mcg/kg BW for this study. ANZFA applied an uncertainty factor of 10 to this lowest-observable-effect level (LOEL) in order to derive an overall TDI of 6 mcg/kg BW.

The European Industrial Hemp Association (EIHA 2017) proposed, after an extensive review of the literature on the topic of THC consumption and effects, a Lowest Observed Effect Level (LOEL) of 2.5 mg of THC intake per person twice daily (Sarmento et al. 2015). A total daily intake of 5 mg THC (2 x 2.5 mg) results in a LOEL of 0.07 mg THC/kg body weight (BW) per day assuming a body weight of 70 kg. The conclusions were based on the findings regarding the minimal effective THC doses described in the studies by Chesher (1990), Petro & Ellenberger (1981), Beal (1995, 1997), Strasser (2006), and Zajicek (2003, 2005). According to these scientific studies, a single dose of 2.5 mg of THC may usually be regarded as a placebo dose,

since comparable minimal effects were also seen with the placebo. EIHA therefore also concluded that a single 2.5 mg dose could be considered the NO(A)EL (EIHA 2017).

EIHA used an uncertainty value of 10 and a LOEL (and NOAEL) of 0.07 mg/kg BW to determine the Acute Reference Dose (ARfD) of 7 µg THC/kg BW. This ARfD is similar to the conclusions made by the Australia and New Zealand's Food Standards as well as the assessment of the health risks of THC in foods performed by the Swiss Federal Office of Public Health (1995). The Swiss authority recognized a lowest observable physiological effect level of orally administered THC of 5 mg per adult and applied an uncertainty factor of 10 to determine that the provisional tolerable daily intake is 7 µg /kg BW (reported by EIHA 2017).

This GRN notice calculated the THC exposure based on body weight using the 90th percentile level of consumption of all foods anticipated to contain Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil at the maximum level of inclusion (*See*, accompanying GRNs filed with this Notice). It is reasonable to anticipate that the estimated THC exposure for individuals 2 years and older and especially for children ages 2 to 5 and 6 to 11 is greatly over estimated since this upper bound estimate assumes that all hemp containing foods will be eaten and that the maximum level of hemp will be used in these foods. The likelihood of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil completely replacing all comparable existing non-hemp materials in the foods identified is unlikely. Furthermore, anticipating that THC will be consistently present at the maximum limits allowed by the specifications in Table 2 is highly conservative and greatly over estimates actual THC exposure for all ages. Refer to Table 41 for a summary contrasting Tolerable Daily Intake (TDI) levels recognized by other international regulatory bodies versus the exposure anticipated from 90th percentile of Hulled Hemp Seed and cumulative hemp consumption.

5.8. Allergenicity

The simplest definition of an allergen is a substance that causes an allergic reaction, broadly speaking, a hypersensitivity immune response, but usually refers to a type I– or immunoglobulin E (IgE)–mediated hypersensitivity response (Masilamani et. al. 2012). This definition allows for both principal and proximate causes. Allergens are generally recognized by IgE response from patients. Some allergens are not very potent inducers of primary allergic immune responses, so they are weak allergenic immunogens; but they can trigger an effector response if IgE capable of binding them is present (possibly because of cross-reactivity with a strong immunogen).

Some allergens are considered complete allergens because they can induce sensitization and trigger reactions. Ara h 2 from peanut is an example of a complete allergen. Other allergens are considered incomplete because they trigger reactions by being cross-sensitive to other dominant allergens but are themselves not actually an immunogen. Food allergens, are generally considered to be protein that are recognized by IgE and found in the diet. They may or may not be complete allergens. The clinical manifestations of a cannabis allergy can vary from mild to life-threatening and is often dependent on the route of exposure. Sensitization to cannabis allergens can trigger various secondary cross-allergies, mostly for plant-derived food. This

secondary cross-allergy has been designated as the "cannabis-fruit/vegetable syndrome" and it might also imply cross-reactivity with tobacco, latex and plant-food derived alcoholic beverages (Decuyper et. al. 2015). The cannabis-fruit/vegetable syndrome has mainly been described in Europe and appears to result from cross-reactivity between non-specific lipid transfer proteins or thaumatin-like proteins present in *Cannabis sativa* and their homologues that are ubiquitously distributed throughout plant kingdom (Decuyper et. al. 2015).
About 65% of the plant food allergens belongs to one of the following classes of structurally related protein super families: (1) the prolamin superfamily; (2) the cupin super-family; and (3) the pathogenesis-related proteins (PR-10) family, of which Bet v 1 is the best known (Mills et. al. 2003 and Jenkins et. al. 2007). The prolamin superfamily includes seed storage proteins of cereals, lipid transfer proteins (LTPs), alpha-amylase/protein inhibitors and 2S albumins. A 10-kDa protein (2S albumin) has been isolated from hemp seed and shown to consist of two polypeptide chains (small and
large) with 27 and 61 amino acid residues respectively (Odani and Odani 1998). This 2S hemp protein is thought to be a prolamin.

Structural features, such as stability during thermal processing and digestion, seem to be obvious factors in determining allergenic potency of ingested molecules. PR-10 sensitization, a food-pollen syndrome, is a good example since the structural instability of these proteins correlates with the observation that cooking destroys allergenicity and that ingestion of any form is rarely if ever associated with systemic reactions (Masilamani et. al. 2012). However, digestibility, by itself, produces mixed results when tested as a predictor of food allergenicity (Astwood et. al 1996, Bannon 2004, Fu et. al. 2002, Herman et. al. 2007). There are multiple potential explanations for the weak correlation between digestibility and food allergenicity, including limitations of in vitro systems used to mimic digestion, food matrix effects that are lost when assessing purified proteins, alteration of protein structure during protein preparation, relative abundance of proteins in whole food, and others (Masilamani et. al. 2012). However, whatever the explanation, it is believed that IgE-mediated activation of effector cells requires cross-linking and, therefore, interaction with multivalent ligands that possess a complex structure. Food allergens must therefore either survive or bypass digestion in sufficient amounts to provoke immune responses (Masilamani et. al. 2012). Hemp seed protein including the protein in the Hulled Hemp Seed and Hemp Protein Powders has a lack of trypsin inhibitory activity (Aluko 2017) and has been shown to be highly digestible through use of a rat bioassay (House et. al. 2010).

Various routes of exposure and sensitization can lead to primary cannabis allergy. Exposure through oral ingestion of the seeds and resulting sensitization or allergic response is not well represented in the literature since the published data focusses on marijuana and tends to document exposure via the leaves, stems, flowers and buds (all materials outside the scope of this GRN). There is one published case of a male experiencing anaphylaxis after orally consuming a meal containing hulled hemp seed (Stadmauer et. al. 2003) and there is a published case series of five patients with anaphylaxis to hemp seed ingestion (Bortolin et. al. 2016). In the case study reported by Stadmauer et. al. 2003, the patient was administered epinephrine and antihistamine, which are treatments typically used for an IgE-mediated reaction. The Bortolin et. al. 2016 case series involved four male and one female patient ranging in age from 13-40 years

(mean age 25 years). 80% of patients were atopic and all presented to an emergency room with anaphylaxis shortly after ingestion of hempseed. 60% of patients received isolated antihistamine, 20% received isolated epinephrine, and 20% received both treatments. All were prescribed an epinephrine autoinjector and they all had positive SPTs to fresh hemp seed, with an average wheal size of 10.3mm (3/5 patients). Bortolin et. al. 2016 concluded that allergy to hemp seed appears to manifest later in life as anaphylaxis.

Primary cannabis allergy may occur by people becoming sensitized by inhalation of cannabis allergen through active smoking and/or vaporizing, cutaneous contact and sensitization via chewing, ingestion or intravenous use of marijuana. Sensitization to marijuana pollen is also possible since *Cannabis sativa* is an anemophilous plant and the male plants produce a wind-borne pollen which is capable of being transported over long distances (reported in Decuyper et. al. 2015). Secondary cannabis allergy might result from cross-reactivity with allergenic compounds such as non-specific lipid transfer proteins (ns-LTPs) or thaumatin-like proteins (TLPs) present in other plants from closely or more distantly related origin (Larramendi et al. 2013).

The allergenic composition of *Cannabis sativa* is incompletely characterized. Six different bands with a molecular weight of 10-, 14-, 20-, 35-, 38- and 60-kDa that were recognized by the individual patients' sera have been identified (Larramendi et al. 2013). The 10-kDa band binds IgE and is believed to be Can s 3, a ns-LTP (Gamboa et al. 2007) that belongs to the pathogenesis-related proteins (PR)-14 group (Van Loon 1999). In a European study involving patients with a primary Cannabis allergy, sensitization to the purified cannabis ns-LTP was observed in 124 out of 130 patients (Armentia et. al. 2014). The 38-kDa band corresponds with a thaumatin like protein, which belongs to the PR-5 family previously seen in fruit allergens with cross-reactivity to apple, tomato, gold kiwi and cypress (Larramendi et al. 2013). The 14 kDa band is speculated to be a profilin although no homology was found between it and any known allergen (de Larramendi et al. 2008).

Multiple IgE-binding proteins have been observed, the most prominent of which are 23-kDa and 50-kDa, which appear to have the binding ability even after deglycosylation, suggesting that the IgE-binding epitopes do not reside in the carbohydrate moiety of the glycoprotein allergens (Nayak et al. 2013). The 23-kDa band was identified as "oxygen-evolving enhancer protein 2", an enzyme involved in the photosynthesis and the 50-kDa band corresponds with the heavy chain subunit of ribulose-1,5-biphosphate carboxylase/oxygenase (RuBisCo). Nayak et. al. 2013 observed that ubiquitously distributed cross-reactive carbohydrate determinants might also be the cause of some IgE reactivity. They also identified other possible allergens which are glyceraldehyde-3-phosphate and adenosine triphosphate (ATP) synthase. Most interestingly, Nayak et. al. 2013 observed no IgE-binding sequences of the pan allergen ns-LTP in their American/Canadian proteomics study even though IgE reactivity at approximately 10-kDa was observed in two patients. This contrasts to the European studies since most of the Canadian patients apparently did not suffer from a cannabis-related cross-reactivity syndrome. It is unknown whether this indicates cannabis allergic patients display geographically different sensitization profiles.

Patients with IgE-mediated cannabis allergy can display distinct sensitization profiles such as sensitization to ns-LTP (Can s 3), a pan allergen which is ubiquitously present throughout the plant kingdom including fruits and vegetables (Egger et al. 2010). Sensitization to Can s 3 could be an explanation for the high variety of secondary plant-derived food allergies which have been documented in European patients with a cannabis allergy. This cross-reactivity between cannabis and plant-derived food has been described by Ebo et al. (2013) and was recently designated as the "cannabis-fruit/vegetable syndrome" by Van Gasse et al. (2014). Ebo et. al. 2013 found that 10 out of 12 patients with a documented cannabis allergy were sensitized to different ns-LTPs including Pru p 3, the ns-LTP of peach (*Prunus persica*). The food allergies most commonly implicated in the cannabis-fruit/vegetable syndrome were allergies to peach, banana, apple, cherry, nuts, tomato and occasionally citrus fruits such as orange and grapefruit (Ebo et. al. 2013). In general, the allergic reactions were more severe than the oral allergy syndrome that is generally observed in food allergy related to sensitization to Bet v 1, the major birch pollen allergen (Ebo and Stevens 2001) and may be partially explained by resistance of ns-LTP to gastroduodenal proteolysis and thermal processing. Sensitization to Can s 3 might also explain cross-reactions to *Hevea latex* (Beezhold et al. 2003; Faber et al. 2015b; Quadri and Nasserullah 2001; Rihs et al. 2006), alcoholic beverages such as beer and wine (Asero et al. 2001; Jegou et al. 2000) and tobacco (*Nicotinia tabaccum*) (Carnes et al. 2013; Faber et al. 2015a).

The clinical data relating to primary and secondary cannabis allergy is not extensive. The sensitizing potential of hemp proteins in humans is unknown, and it is unclear if patients that show allergic reactions upon consuming hemp seed have been sensitized by hemp-proteins or that hemp proteins mainly cross-react in patients allergic to other allergens.
It appears that exposure to the plant leaves, stems, flowers, buds and pollen does result in sensitization for some individuals and that there is the potential for individuals to be sensitized to the proteins in the seed, albeit at a very low reported level of incidence. Secondary allergy through cannabis-fruit/vegetable syndrome cross-reactivity between ns-LTP or TLP present in *Cannabis sativa* and their homologues which are widely distributed throughout the plant kingdom is also a possibility.

5.9. Nutritional Benefits of Hemp as Food

Hemp seeds and hemp seed products are considered of particular important nutritional value due to their "almost perfect" balance of the omega-3 and omega-6 essential fatty acids which includes the presence of stearidonic acid (SDA) and gamma linoleic acid (GLA) (Journal of Agriculture and Food; Manku 1990; Ross 1996; Science Daily 2014; Parker et al. 2003; Erasmus 1999; Simopoulos 2002; Ross et al. 2000; Lachenmeier and Walch 2005; Karimi and Hayatghaibi 2006; Gibb et al. 2005; Leizer et al. 2000, Callaway 2004, Callaway and Pate 2009).

Hemp seeds and its milled seed cake flour contain a high quality protein. As mentioned above, it is easily digestible, and contains all essential amino acids needed by humans (Amerio 1998; Gibb et al. 2005; Erickson 2007; Hessle, Erik- son and Turner 2008; Callaway and Pate 2009, House et. al. 2010).

Protein digestibility-corrected amino acid score (PDCAAS) measurements, using a rat bioassay for protein digestibility and the FAO/WHO amino acid requirement for children 2 to 5 years of age as reference have been conducted on Fresh Hemp Food's Hulled Hemp Seed (House et. al. 2010). The study determined that the protein is highly digestible and that the PDCAAS is positioned higher than some grains such as whole wheat and is in the same range as major pule protein sources such as lentils and pinto beans.

The safety and efficacy of hemp seed protein has been evaluated and is recognized by Health Canada's Non-Prescription and Natural Health Products Directorate (NNHPD) which has assessed the totality of evidence and has determined that hemp protein concentrate, and hemp protein isolate are safe and effective sources of protein for use in human natural health products (NNHPD Workout Supplements Monograph 2016).

Hemp protein isolate, and concentrate are concentrated forms of the protein naturally present in whole hemp seed and are defined as extracts by NNHPD since they have the primary molecular structure of which is identical to that which it had prior to its extraction or isolation. It is reasonable to assume that the protein in the whole seed is the same protein that is present in the Hulled Hemp Seed which is prepared by mechanically removing the hull from the whole seed and the Hemp Protein Powder which is prepared by either dry or wet processing as detailed in this Notice.

The NNHPD Workout Supplements Monograph is used by industry to develop and license workout supplements for sale in Canada. The Monograph enables licensed products to contain between 2.6 g and 90 g of protein from hemp protein concentrate and isolate. NNHPD has assessed the safety of hemp protein isolate and concentrate and has determined that there are no limitations on the duration of its use, nor are there any contraindications or known adverse reactions associated with the use of hemp protein. The only protein specific warning required by NNHPD for the inclusion of hemp is a statement to the effect that a healthcare practitioner should be consulted if the user has liver or kidney disease. This caution is not specific to hemp. It is a typical warning relevant to the consumption of any natural health product containing 30 g or more of protein per day (Workout Supplements Monograph 2016).

NNHPD has assessed the efficacy of hemp protein isolate and concentrate as a source of protein and amino acids for humans and has determined that the totality of evidence supports its inclusion in natural health products. The Workout Supplements 2016 Monograph enables licensed natural health products to make the following claims:

- Source of protein for the maintenance of good health
- Source of protein which helps build and repair body tissues
- Source of amino acids involved in muscle protein synthesis
- Assists in the building of lean muscle [tissue/mass] when combined with regular [weight/resistance] training and a healthy balanced diet

The above claims as listed in the Workout Supplements Monograph are included in this Notification to illustrate the nutritional benefit of the protein from Hemp Protein Powder and

Hulled Hemp Seed. They support Fresh Hemp Foods GRAS conclusion that Hemp Protein Powder and Hulled Hemp Seed is a safe and nutritious source of protein.

Commercially available protein flour and powders are high in protein and dietary fiber. Hemp protein flour can be used as a food additive in shakes and smoothies, as well as for baking. Nearly 65% of the proteins in hemp foods are in the form of the globulin edestin (EFSA).

Edestin is considered to be the most easily digestible protein for mammals. The remaining 35% of the protein in hemp seed is albumin. Both albumin and globulin are easily digested by mammals as evidenced by the good digestibility results obtained through rat bioassay analysis of Hulled Hemp Seed and Hemp Protein Powders (House et. al. 2010).

5.10. Toxicology

The literature review found no instances of safety discussions outside of THC (delta 9-tetrahydrocannabinol).

5.11. Pharmacology/Metabolism/Half-Life

THC, the primary psychoactive component of cannabis, is rapidly absorbed into the bloodstream following inhalation and is extensively metabolized in the liver into multiple metabolites. The equipotent metabolite 11-hydroxy-THC (11-OH-THC) of THC is further oxidized to THCCOOH and THCCOOH-glucuronide and sulphate (Huestis et. al. 2011). THC is extensively metabolized to multiple other alcohols and acids, but THCCOOH has been selected as the analyte monitored in urine for virtually all drug-testing programs, including workplace, military, criminal justice and drug treatment programs. After alkaline hydrolysis of urine to free THCCOOH from its conjugates, THCCOOH is the most abundant urinary marker of cannabis use (Huestis et. al. 2011).

When ingested, peak concentrations are much lower and peak later than after smoking. Less euphoria is experienced and exposure to the more toxic ingredients produced from burning cannabis is avoided (Huestis et. al. 2011). After oral exposure, THC is slowly and incompletely absorbed from the gastrointestinal tract (EFSA 2015). The oral ingestion of THC shows distinct differences compared to intraperitoneal, intravenous and inhalation administration with regard to metabolism and time course of plasma level. Compared to inhalation, oral ingestion of the same dose will cause less toxicity because of the lower systemic bioavailability. Ingestion may also result in less toxicity compared to inhalation of a dose producing the same bioavailability, due to a less pronounced THC plasma peak. THC detection after oral ingestion is not reached until approximately 2 hours after ingestion (Holler 2008). In addition, bioavailability of THC through oral ingestion is only 6-18% compared to 18-50% via smoking (Holler 2008). The literature points to the THC degradation in the acidic environment of the stomach and first-pass metabolism in the liver as the reasons for lower bioavailability.

THC is a pharmacologically highly active substance with dose-dependent effects on several organ systems and body functions. The most conspicuous effects are those on the central

nervous and the cardiovascular systems. THC produces an increased heart rate, reddened eyes, and a dry mouth. As for psychotropic effects, a mild euphoria, an enhanced sensory perception, fatigue, and eventually dysphoria together with anxiety have been observed. Brenneisen et al. (1996) administered single oral doses of 10 or 15 mg THC to two patients and measured no change to physiologic parameters (heart rate) and psychological parameters (concentration, mood) as a result of the administration. In contrast, Chesher et. al. (1990) dosed healthy people with 5 mg, 10 mg and 15 mg followed by a light breakfast and found no difference in the subjective level of intoxication at 5 mg, a slight difference at 10 mg and 15 mg and a marked difference at 20 mg relative to placebo controls. At the lowest administered oral dose of 5 mg, a minor decrease in several psychomotoric performance scores, primarily related to standing steadiness, reaction time, and arithmetic performance were observed. Findings by other researchers suggest that even doses of 10 or 15 mg of orally administered THC generally result in minor psychomotoric effects (Brenneisen et al. 1996).

These findings relative to the production of effects by THC indicate that the psychotropic threshold of THC is in the range of 0.2–0.3 mg THC per kg body weight for a single oral dose and corresponds to an administration of 10 to 20 mg THC to an adult. A single dose of 5 mg THC can be regarded as a placebo dose or the NOAEL for psychotropic effects and certain physical effects. It can also be considered as the lowest observed adverse effect level (LOAEL) for the slight reduction in psychomotoric performance.

More than 100 metabolites of THC have been identified. The predominant acid metabolite, 11-nor-9-carboxydelta-9-THC (THC-COOH) is commonly used to identify prior use of marijuana in urine tests. Oral consumption results in higher amounts of THC-COOH being formed more rapidly compared to inhalation or intravenous administration (Wall et al. 1983) which has been attributed to the first-pass effect of orally ingested THC through initial metabolism by the liver. There is large variability in the time course of plasma levels of THC and its metabolites amongst individuals after oral consumption. The composition and timing of meals ingested prior to oral THC consumption is one of the factors that influences the time course of plasma level of THC and subjective response. This is believed to be due to the impact on THC absorption. Oral THC intake via hemp containing food is comparable to the repeated intake of smaller doses over the course of a day since it is likely that hemp containing foods would be eaten throughout the waking hours of the day. This pattern causes broader and lower THC levels in plasma over time, compared to higher single or multiple doses.

5.12. Expression Patterns

THC at high concentrations can cause physiological effects. The most common are those on mood and cognition (euphoria, fear, reduced cognitive functions) as well as on the cardiac circulation system (increase in cardiac frequency, changes in blood pressure) (Nova Institute 2015). None of these physiological effects are serious threat or pose a risk of injury or death.

It is also important to note THC differs from non-specifically acting harmful chemicals in food in that it acts on compound-specific binding sites (cannabinoid receptors) on the surface of body cells. This expression provides additional assurances of safety. This is due to the effect of repeated ingestion of THC which can lead to tolerance by cannabinoid receptors (Nova Institute 2015). Additionally, children have a significantly lower density of cannabinoid receptors sites which means the psychotropic effects occur only at much higher THC doses (Nova Institute 2015).

5.13. Benefits of Consumption

A review of the toxicology of THC would be imbalanced absent a discussion of the beneficial effects of low doses of THC. Studies have observed antiemesis, immune-stimulating and neuroprotective effects from low doses of THC (Sides 2015).

This body of research again points to THC at the low levels in industrial hemp ingredients not being a toxicology risk or safety concern.

5.14. Other Regulatory Bodies

Refer to Table 40 for a summary of standards adopted by other regulatory bodies for cumulative THC exposure from uses of industrial hemp.

Fresh Hemp Foods Ltd. is licensed by Health Canada and contracts only licensed hemp seed acres meeting the Industrial Hemp Regulations. Fresh Hemp Foods Ltd. tests Hulled Hemp Seed at third party accredited laboratories to confirm THC levels do not exceed internal specifications for THC content (not more than 4 μg/g).

Hemp varieties grown in the European Union (EU) have a THC content of less than 0.2% (measured in the upper third of the plant) (Matthäus 2008). In Germany, the Federal Institute for Risk Assessment (BfR) estimated a provisional tolerable THC intake of 1–2 mg/kg/day, and from this estimation a precautionary guidance value for THC in hemp seed oil of 5000 μg/kg was defined in the year 2000 (Nova Institute 2015). In contrast, Switzerland has set their maximum limits at 10,000 μg/kg for hulled hempseed and 20,000 μg/kg for oil and Australia and New Zealand has set 5000 μg/kg for Hulled Hemp Seed, 10,000 μg/kg for oil and 5,000 μg/kg for protein powders.

Australia and New Zealand have set their TDI for THC in low hemp foods at 6 mcg/kg BW. This is similar to the provisional TDI of 7 mcg/kg BW set by the Swiss Federal Office of Public Health (1995). In both cases the TDI was determined using the results of studies that found no psychoactive effect at 2.5 mg THC once to twice daily. This THC level and TDI are greater than the THC exposure anticipated from the consumption of Fresh Hemp Foods Ltd Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil.

5.15. Human Studies

Cannabis is one of the most well studied plants. This interest in research extends to hempseeds and oral consumption of THC. Several clinical studies including large-scale studies have been conducted on oral THC or oral cannabis extracts with high concentrations of THC (see, e.g. Zajicek et al. 2003, 2005; Wade et al. 2004;
Rog et al. 2005; Strasser et al. 2006; Collin et al. 2007; Narang et al. 2008; Novotna et al. 2011). These studies and others in the literature expound on the effects of THC in the body. None have raised any questions of safety.

The primary nutritional benefit of hemp and/or hemp protein are the proteins edestin and albumin which are rich in essential amino acids.

Hemp seeds and hemp seed products are considered of particular important nutritional value due to their "almost perfect" balance of the omega-3 and omega-6 essential fatty acids which includes the presence stearidonic acid (SDA) and gamma linoleic acid (GLA) (Journal of Agriculture and Food; Manku 1990; Ross 1996; Science Daily 2014; Parker et al. 2003; Erasmus 1999; Simopoulos 2002; Ross et al. 2000; Lachenmeier and Walch 2005; Karimi and Hayatghaibi 2006; Gibb et al. 2005; Leizer et al. 2000, Callaway 2004, Callaway and Pate 2009).

Hemp seeds and its milled seed cake flour contain a high quality protein. As mentioned above, it is easily digestible, and contains all essential amino acids needed by humans (House et. al. 2010, Amerio 1998; Gibb et al. 2005; Erickson 2007; Hessle, Erik- son and Turner 2008; Callaway and Pate 2009).

5.16. Animal Studies

There have been numerous experimental animal studies on the effect of THC in hemp foods. Studies have found acute exposure doses up to 3,000 and 9, 000 mg Δ9-THC/kg in dogs and monkeys, respectively, were not lethal (EFSA 2015 and Thompson et. al. 1973).

The EFSA conducted an animal feed analysis. It reported the oral LD50 for rats and mice were 666 mg THC/kg and 482 mg THC/kg, respectively (EFSA 2011).

5.17. Conclusion

The daily THC consumption even by extensive users of hemp foods is expected to remain below the LOAEL for oral THC. It is not expected to cause any acute or chronic adverse health impacts because it is below the psychoactive threshold for THC and it is below the level clinically shown to potentially result in positive urine drug test results. The daily THC intake level for all population groups estimated by this GRN for both Hemp Protein Powder and cumulative intake of hemp ingredients is consistent with the TDI identified by other recognized regulatory bodies which have performed similar assessments regarding the safety of low THC hemp foods.

The consensus in the scientific literature is clear – hemp seeds and hemp ingredients including Hemp Protein Powder is safe for consumption. Overwhelming evidence shows hemp seeds and hemp seed products are considered of important nutritional value due to their nutritional profile which includes a balance of the omega-3 and omega-6 essential fatty acids which includes the presence of alpha linolenic acid (ALA) and gamma linoleic acid (GLA).

Section 6

6. References and List of Tables, Figures and Supporting Data

List of Tables

List of Figures

Table 1 Application Levels for the General Population

(applicable to organic and conventional)

Food Category	Level (%)
Dry blend protein powders (Proteins shakes, instant protein powders)	1 to 100
Dry blend beverages	1 to 100
Ready to drink beverages, soups, nutritional beverages (protein fortified smoothies, fruit juices, high protein drinks, vegetable based soups etc.)	1 to 50
Smoothies	1 to 50
Non-dairy products/Milk alternatives	1 to 50
Dairy imitation products (dairy free cheeses, dairy free spreads, dairy free creamers, dairy free desserts, dairy free dips, dairy free whipped toppings)	1 to 25
Grain Products, snack products, baked goods and baking mixes (e.g., breads, rolls, bars, cakes, pasta, cookies, gluten free baked products)	1 to 12
Cereals/Instant Cereals/Breakfast Cereals	1 to 12
Meat Analogs (imitation meat products)	1 to 20
Meal Replacement/ Nutritional bars	1 to 40
Extruded product (crisps)	1 to 20
Soups & Sauces	1 to 20

Table 2 Specifications for Hemp Protein Powder

(applicable to organic and conventional)

Parameter	***Specifications – Dry Process (3 Protein Grades)***			***Specifications – Wet Process***	***Method of analysis***
Protein Content					
Protein	50%	43%	33%	>64.5% dry basis	NIR/N_2 Combustion (N x 6.25)
	47-53%	40-46%	32-38%		
Sensory Characteristics					
Appearance	Light green fine powder			Light tan to greenish fine powder	Visual
Taste	Nutty			Nutty	Organoleptic
Odor	Nutty			Nutty	Organoleptic
Heavy Metals[1]					
Lead	≤ 3ppm			≤ 3ppm	ICP-MS
Cadmium	≤ 1ppm			≤ 1ppm	ICP-MS
Mercury	≤ 0.1ppm			≤ 0.1ppm	ICP-MS
Arsenic	≤ 1ppm			≤ 1ppm	ICP-MS
THC					
THC	≤ 4 µg/g			≤ 4 µg/g	GC-MS[2]
Microbiological					
Standard plate count	<250,000 cfu/g			<250,000 cfu/g	3 M Petrifilm
Total coliforms	<500 cfu/g			<500 cfu/g	3 M Petrifilm
Yeast and Mold	<1000 cfu/g (each)			<1000 cfu/g (each)	3 M Petrifilm
Salmonella	Negative in 25g			Negative in 25g	3 M Petrifilm
Escherichia coli	Negative (<10 cfu/g)			Negative (<10 cfu/g)	3 M Petrifilm
Gluten					
Gluten	< 20 ppm			< 20 ppm	ELISA
Aflatoxin[1]					
Aflatoxin	< 0.5 ppb			< 0.5 ppb	ELISA

[1]Heavy metals and aflatoxins are not routinely reported on COAs.

[2]Basic Analytical Procedure For The Determination Of Delta-9-tetrahydrocannabinol (thc) In Industrial Hemp, Industrial Hemp Technical Manual - Standard Operating Procedures for Sampling, Testing and Processing Methodology. Accessed February 22, 2018.

Table 3 Nutritional Data for Organic and Conventional Hemp Protein Powder

(Average values for 100 g of commercial product, as-is)

Nutrient	Tolerance	Amount per 100 g – Dry Process (3 Grades)			Amount per 100 g – Wet Process
		50%	43%	33%	
Moisture	Average	8 g	8 g	8 g	5 g
Protein	Average	50 g	43 g	33 g	63g
Total Fat	Average	10.5 g	10.5 g	9 g	15 g
Polyunsaturated Fat	Average	9	7	7	13 g
Monounsaturated Fat	Average	1	1	1	2 g
Saturated Fat	Average	1	1	1	2 g
Trans Fat	Average	0	0	0	0.07 g
Cholesterol	Average	0 g	0 g	0 g	0 g
Carbohydrates	Average	24	31	48.5	7 g
Total Dietary Fiber	Average	18	29	41	9 g
Insoluble Fiber	Average	17	25	39	8 g
Soluble Fiber	Average	1	4	2	1 g
Ash	Average	7 g	7 g	6 g	8 g
Sodium	Average	0	0	0	40 mg
Phosphorus	Average	1750	-	1125	1150 mg
Potassium	Average	5720	-	6320	2880
Calcium	Average	170	-	150	172 mg
Iron	Average	21	-	15	8.3 mg
Calories	Average	400	387	374	446

Table 4 Allergen Declaration for Organic and Conventional Hemp Protein Powder

Component	Present in the Product?	Component	Present in the Product?
1. Barley, Rye, Oats	NO	13. Soybean (not including oil)	NO
2. Celery (not including seeds)	NO	14. Sulphites	NO
3. Corn	NO	15. Tree Nuts	NO
4. Egg or egg product	NO	16. Wheat or wheat products	NO
5. Fish	NO	17. Gluten < 10 ppm	NO
6. Milk & Milk by-product	NO	17. Yellow 5 (Tartrazine)	NO
7. Monosodium Glutamate (MSG)	NO	18. Animal Fat	NO
8. Peanuts or peanut products	NO	19. Grains containing gluten	NO
9. Seeds (Poppy, Sunflower, Cottonseed)	NO	20. Mustard/Canola	NO
10. Sesame Seeds	NO	21. Lupin	NO
11. Shell Fish & Crustaceans	NO	22. Lactose	NO
12. Soybean Oil (excluding refined soy oil)	NO		

Table 5 Amino Acid Profile for Organic and Conventional Hemp Protein Powder

(Average values for commercial product)

Nutrient	Quantity (g/100 g protein)* – Dry Process (3 Grades)			Quantity (g/100 g protein)* – Wet Process
	50%	43%	33%	
Aspartic acid	9.19	9.18	10.00	9.37
Glycine	4.03	3.99	4.30	4.03
Valine	4.38	4.39	4.79	4.44
Isoleucine	3.44	3.44	3.77	3.89
Leucine	6.08	6.06	6.58	6.77
Tryptophan	0.75	0.77	0.87	1.1
Tyrosine	2.81	2.67	2.68	2.62
Phenylalanine	4.14	4.15	4.54	4.8
Arginine	10.65	10.40	10.99	12.44
Threonine	3.13	3.11	3.35	3.98
Serine	4.57	4.52	4.85	4.88
Alanine	3.89	3.88	4.22	3.45
Glutamic acid	16.68	16.49	17.72	14.85
Cysteine	1.72	1.67	1.74	2.43
Methionine	2.24	2.15	2.21	2.58
Histidine	2.44	2.42	2.59	1.65
Lysine	3.37	3.34	3.61	3.76
Proline	3.38	3.38	3.70	4.72

* Method of analysis = Schuster, J. Chromatogr., 431:271-284; Henderson et al., Agilent Publications, 2000; Barkholt and Jensen, Anal. Biochem., 177: 318-322; AOAC 988.15

Table 6 Product Specifications and Representative Analytical Data for Organic and Conventional Hemp Protein Powder Prepared Using Dry Process

Parameter	Lot Number				
	BRAN16FO	JOHO25FC	ROSE26FO	LAMA55FO	SHME25FC
Protein	49 %	52 %	40 %	47 %	38 %
Fat	10 %	10 %	9 %	10 %	8 %
Moisture	8 %	8 %	6 %	8 %	8 %
Standard Plate Count	<10,000 cfu/g	53,920 cfu/g	<10,000 cfu/g	25,250 cfu/g	31,800 cfu/g
Total Coliforms	<10 cfu/g	310 cfu/g	<10 cfu/g	10 cfu/g	20 cfu/g
Yeast	<100 cfu/g	230 cfu/g	<100 cfu/g	<100 cfu/g	<100 cfu/g
Mold	<100 cfu/g	<100 cfu/g	<100 cfu/g	<100 cfu/g	<100 cfu/g
E. coli	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)
Salmonella	Negative	Negative	Negative	Negative	Negative
Gluten	<20 ppm	<20 ppm	<20 ppm	<20 ppm	<20 ppm
THC	<4 ppm	<4 ppm	<4 ppm	<4 ppm	<4 ppm

Table 7 Product Specifications and Representative Analytical Data for Organic and Conventional Hemp Protein Powder Prepared Using Wet Process

Parameter	Lot Number				
	161216XX	170614XW	170911XA	170213XE	170911XY
Protein	67.7 %	65.4 %	65.3 %	67.6 %	65.2 %
Moisture	4 %	4.62 %	4.4 %	4 %	4.08 %
Standard Plate Count	225,000 cfu/g	46,000 cfu/g	67,500 cfu/g	43,000 cfu/g	124,000 cfu/g
Total Coliforms	<10 cfu/g	<10 cfu/g	<10 cfu/g	<10 cfu/g	<10 cfu/g
Yeast	<10 cfu/g	<10 cfu/g	<10 cfu/g	<10 cfu/g	<10 cfu/g
Mold	<10 cfu/g	<10 cfu/g	<10 cfu/g	<10 cfu/g	<10 cfu/g
E. coli	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)	<10 cfu/g (Negative)
Salmonella	Negative	Negative	Negative	Negative	Negative
Gluten	<20 ppm	<20 ppm	<20 ppm	<20 ppm	<20 ppm
THC	<4 ppm	<4 ppm	<4 ppm	<4 ppm	<10 ppm

Table 8 Lot Analysis for Heavy Metals for Hemp Protein Powder Prepared Using Dry Process

Lot Code	Arsenic (ppm)	Cadmium (ppm)	Mercury (ppm)	Lead (ppm)
50 % Protein Grade				
ASBS16SO	<0.05	0.03	<0.05	<0.01
CHSH16NO	<0.05	0.02	<0.05	<0.01
ROBR66FO	<0.05	0.04	<0.05	<0.01
ROSH25FC	<0.05	0.01	<0.05	<0.01
WIGE65SC	<0.05	0.03	<0.05	<0.01
43% Protein Grade				
DABR64FO	<0.05	0.03	<0.05	0.01
ROSE94FO	<0.05	0.06	<0.05	0.06
DAWI84FO	<0.05	0.05	<0.05	<0.01
ROSE44FO	<0.05	0.05	<0.05	<0.01
LANE62XC	<0.05	0.06	<0.05	<0.01
33% Protein Grade				
ASBS16SO	<0.05	0.02	<0.05	<0.01
SHCH36NO	<0.05	0.01	<0.05	<0.01
SAMC16NO	<0.05	<0.01	<0.05	<0.01
ROBR36FO	<0.05	0.012	<0.05	<0.01
JOSE13FC	<0.05	0.04	<0.05	<0.01

Table 9 Lot Analysis for Heavy Metals for Hemp Protein Concentrate Prepared Using Wet Process

Lot Code	Arsenic (ppm)	Cadmium (ppm)	Mercury (ppm)	Lead (ppm)
170911XY	<0.05	0.05	<0.05	<0.01
170614XW	<0.05	0.03	<0.05	<0.01

Table 10 Lot Analysis for Aflatoxin - Organic and Conventional Hemp Protein Powder

Lot Code	Aflatoxin (ppb)
50 % Protein Grade	
ROGL14XC	<0.05
43% Protein Grade	
TOBY34XC	<0.05
33% Protein Grade	
LAWA14FC	<0.05
Wet Process	
170911XY	<0.05

Table 11 Conservative Estimation of Consumption Based on Intended Use Levels and Serving Size, All Individuals 2 Years and Older - Organic or Conventional Hemp Protein Powder

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Ages 2 and Over		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %								Mean	90th %	Mean	90th %	Mean	90th %
Whole Grains	Includes the sum of all foods in the total whole grains: Amaranth, Barley, whole Barley flour (from whole barley), Barley meal, Brown rice, Brown rice flour, Buckwheat groats, Bulgur, Corn, whole grain, Corn meal or flour, (whole grain), Millett, Oats, Oat flour, Oatmeal, Popcorn, Quinoa, Rye, whole grain, Rye flour (dark), Triticale, Wheat, Whole wheat flour, Whole grain cracked, wheat, Wild rice	24.66	49.33	1.00	9.50	20.00	0.55	5.23	11.00	55.00	0.25	0.49	2.34	4.69	4.93	9.87
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	1.98	3.97	1.00	49.50	100.00	0.55	27.23	55.00	55.00	0.02	0.04	0.98	1.97	1.98	3.97
										Total (g/person/day)	**0.27**	**0.53**	**3.32**	**6.65**	**6.91**	**13.84**

[1]Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AJ. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3]Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5]90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6] Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp protein powder would direct replace grains and soy in grain and soy products.

[7]Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 12 Conservative Estimation of Consumption Based on Intended Use Levels and Serving Size, Males 2 to 5 Years - Organic or Conventional Hemp Protein Powder

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Males 2 - 5 Years		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Maximum Use Levels (g/kg)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %									Mean	90th %	Mean	90th %	Mean	90th %
Whole Grains	Includes the sum of all foods in the total whole grains: Amaranth, Barley, whole Barley flour (from whole barley), Barley meal, Brown rice, Brown rice flour, Buckwheat groats, Bulgur, Corn, whole grain, Corn meal or flour, (whole grain), Millett, Oats, Oat flour, Oatmeal, Popcorn, Quinoa, Rye, whole grain, Rye flour (dark), Triticale, Wheat, Whole wheat flour, Whole grain cracked, wheat, Wild rice	26.65	53.30	1.00	9.50	20.00	0.55	5.23	11.00	200.00	55.00	0.27	0.53	2.53	5.06	5.33	10.66
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	0.85	1.70	1.00	49.50	100.00	0.55	27.23	55.00	1000.00	55.00	0.01	0.02	0.42	0.84	0.85	1.70
											Total (g/person/day)	**0.28**	**0.55**	**2.95**	**5.91**	**6.18**	**12.36**

[1] Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AJ. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2] U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3] Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4] U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5] 90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6] Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp protein powder would direct replace grains and soy in grain and soy products.

[7] Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 13 Conservative Estimation of consumption Based on Intended Use Levels and Serving Size, Females 2 to 5 Years - Organic or Conventional Hemp Protein Powder

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Females 2 - 5 Years		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Maximum Use Levels (g/kg)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %									Mean	90th %	Mean	90th %	Mean	90th %
Whole Grains	Includes the sum of all foods in the total whole grains: Amaranth, Barley, whole Barley flour (from whole barley), Barley meal, Brown rice, Brown rice flour, Buckwheat groats, Bulgur, Corn, whole grain, Corn meal or flour, (whole grain), Millett, Oats, Oat flour, Oatmeal, Popcorn, Quinoa, Rye, whole grain, Rye flour (dark), Triticale, Wheat, Whole wheat flour, Whole grain cracked, wheat, Wild rice	22.13	44.23	1.00	9.50	20.00	0.55	5.23	11.00	200.00	55.00	0.22	0.44	2.10	4.20	4.43	8.85
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	0.85	1.70	1.00	49.50	100.00	0.55	27.23	55.00	1000.00	55.00	0.01	0.02	0.42	0.84	0.85	1.70
											Total (g/person/day)	**0.23**	**0.46**	**2.52**	**5.04**	**5.28**	**10.55**

[1] Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AJ. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2] U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3] Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4] U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5] 90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6] Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp protein powder would direct replace grains and soy in grain and soy products.

[7] Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 14 Conservative Estimation of Consumption Based on Intended Use Levels and Serving Size, Males 6 to 11 Years - Organic or Conventional Hemp Protein Powder

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Males 6-11 Years		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %								Mean	90th %	Mean	90th %	Mean	90th %
Whole Grains	Includes the sum of all foods in the total whole grains: Amaranth, Barley, whole Barley flour (from whole barley), Barley meal, Brown rice, Brown rice flour, Buckwheat groats, Bulgur, Corn, whole grain, Corn meal or flour, (whole grain), Millett, Oats, Oat flour, Oatmeal, Popcorn, Quinoa, Rye, whole grain, Rye flour (dark), Triticale, Wheat, Whole wheat flour, Whole grain cracked, wheat, Wild rice	24.66	49.33	1.00	9.50	20.00	0.55	5.23	11.00	55.00	0.25	0.49	2.34	4.69	4.93	9.87
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	1.13	2.27	1.00	49.50	100.00	0.55	27.23	55.00	55.00	0.01	0.02	0.56	1.12	1.13	2.27
										Total (g/person/day)	0.26	0.52	2.90	5.81	6.07	12.14

[1]Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AJ. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3]Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5]90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6] Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp protein powder would direct replace grains and soy in grain and soy products.

[7]Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 15 Conservative Estimation of Consumption Based on Intended Use and Serving Size, Females 6 to 11 Years - Organic or Conventional Hemp Protein Powder

Food category[1,6]	Definition[1,2,3] Refer to Appendix 1 for examples of foods.	Consumption of food category (g/day)[4,5,6] Females 6-11 Years		Minimum % Use	Mid-Point % Use	Maximum % Use	Minimum Use levels (g/serving)	Mid-Point Use levels (g/serving)	Maximum Use levels (g/serving)	Reference Amount (g)[1,7]	Minimum Daily intake (g/person)		Mid-Point Daily intake (g/person)		Maximum Daily intake (g/person)	
		Mean	90th %								Mean	90th %	Mean	90th %	Mean	90th %
Whole Grains	Includes the sum of all foods in the total whole grains: Amaranth, Barley, whole Barley flour (from whole barley), Barley meal, Brown rice, Brown rice flour, Buckwheat groats, Bulgur, Corn, whole grain, Corn meal or flour, (whole grain), Millett, Oats, Oat flour, Oatmeal, Popcorn, Quinoa, Rye, whole grain, Rye flour (dark), Triticale, Wheat, Whole wheat flour, Whole grain cracked, wheat, Wild rice	22.68	45.36	1.00	9.50	20.00	0.55	5.23	11.00	55.00	0.23	0.45	2.15	4.31	4.54	9.07
Total Soy Products	Includes soy products: Miso, Natto, Soybean curd or tofu, Soybean flour, Soybean meal, Soybean protein, isolate and concentrate, Soy milk (soymilk), not calcium fortified, Soy nuts	1.70	3.40	1.00	49.50	100.00	0.55	27.23	55.00	55.00	0.02	0.03	0.84	1.68	1.70	3.40
										Total (g/person/day)	0.24	0.49	3.00	5.99	6.24	12.47

[1]Bowman SA, Clemens JC, Friday JE, Lynch KL, and Moshfegh AJ. 2017. Food Patterns Equivalents Database 2013-14: Methodology and User Guide [Online]. Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg Accessed August 9, 2017.

[2]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, Beltsville, Maryland, Food Patterns Equivalents Databases and Datasets. Available at: http://www.ars.usda.gov/nea/bhnrc/fsrg. Accessed August 9, 2017.

[3]Appendix 1 food examples extracted from U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Databases, 2013-2014 Food Patterns Equivalent Database per 100 grams of FNDDS 2013-2014 Foods. Available from: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/ [accessed 08/09/2017].

[4]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). FPED Data Tables, 2013-2014 Documentation: Food Patterns Equivalent Intakes from Food: Consumed per Individual, by Gender and Age. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/fped/Table_1_FPED_GEN_1314.pdf [accessed 08/09/2017].

[5]90th percentile estimated at twice the mean. WHO Offset Publication No. 87 (1985), "Guidelines for the Study of Dietary Intakes of Chemical Contaminants," WHO, Geneva.

[6] Consumption data conservatively estimates that hemp containing dairy and meat analogs would be consumed at same level as total dairy and protein foods and hemp protein powder would direct replace grains and soy in grain and soy products.

[7]Title 21 - Food and Drugs, Chapter 1 - Food and Drug Administration, Department of Health and Human Services, Subchapter B - Food for Human Consumption, Part 101 - Food Labelling, Subpart A - General Provisions, Section 101.12 Reference amounts customarily consumed per eating occasion. Accessed August 9, 2017.

Table 16 Cumulative Daily Intake of Hemp, All Individuals Age 2 Years and Older - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1]		Mid-Point Daily intake (g/person)[1]		Maximum Daily intake (g/person)[1]	
	Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	0.52	1.04	3.26	6.51	7.03	14.07
Protein Powders (inc. concentrate)	0.27	0.53	3.32	6.65	6.91	13.84
Oil	0.27	0.55	1.92	3.83	4.11	8.22
TOTAL	**1.06**	**2.12**	**8.49**	**17.00**	**18.05**	**36.12**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 17 Cumulative Daily Intake of Hemp, Males 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1] Males 2-5 Yrs		Mid-Point Daily intake (g/person)[1] Males 2-5 Yrs		Maximum Daily intake (g/person)[1] Males 2-5 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	0.43	0.85	2.71	5.43	5.86	11.71
Protein Powders (inc. concentrate)	0.28	0.55	2.95	5.91	6.18	12.36
Oil	0.16	0.32	1.12	2.24	2.40	4.81
TOTAL	**0.86**	**1.72**	**6.79**	**13.58**	**14.44**	**28.88**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 18 Cumulative Daily Intake of Hemp- Females Age 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1] Females 2-5 Yrs		Mid-Point Daily intake (g/person)[1] Females 2-5 Yrs		Maximum Daily intake (g/person)[1] Females 2-5 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.37	0.75	2.36	4.73	5.10	10.20
Protein Powders (inc. concentrate)	0.23	0.46	2.52	5.04	5.28	10.55
Oil	0.15	0.31	1.07	2.14	2.29	4.58
TOTAL	**0.76**	**1.51**	**5.95**	**11.91**	**12.67**	**25.33**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 19 Cumulative Daily Intake of Hemp - Males Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1] Males 6-11 Yrs		Mid-Point Daily intake (g/person)[1] Males 6-11 Yrs		Maximum Daily intake (g/person)[1] Males 6-11 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	0.45	0.90	2.81	5.61	6.06	12.12
Protein Powders (inc. concentrate)	0.26	0.52	2.90	5.81	6.07	12.14
Oil	0.20	0.40	1.41	2.83	3.03	6.06
TOTAL	**0.91**	**1.82**	**7.12**	**14.25**	**15.16**	**30.32**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 20 Cumulative Daily Intake of Hemp - Females Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily intake (g/person)[1] Females 6-11 Yrs		Mid-Point Daily intake (g/person)[1] Females 6-11 Yrs		Maximum Daily intake (g/person)[1] Females 6-11 Yrs	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.44	0.89	2.81	5.63	6.07	12.14
Protein Powders (inc. concentrate)	0.24	0.49	3.00	5.99	6.24	12.47
Oil	0.22	0.43	1.51	3.02	3.24	6.48
TOTAL	**0.90**	**1.81**	**7.32**	**14.65**	**15.55**	**31.10**

[1]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 21 Cumulative Daily Intake of THC, All Individuals Age 2 Years and Older - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	4.00	0.0021	0.0042	0.0130	0.0261	0.0281	0.0563
Protein Powders (inc. concentrate)	4.00	0.0011	0.0021	0.0133	0.0266	0.0276	0.0553
Oil	10.00	0.0027	0.0055	0.0192	0.0383	0.0411	0.0822
TOTAL		**0.0059**	**0.0118**	**0.0455**	**0.0910**	**0.0968**	**0.1938**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 22 Conservative Daily Intake of THC, All Individuals Aged 2 Years and Older - Organic or Conventional Hemp Protein Powder

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mcg/person)[1]		Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %
Protein Powders (inc. concentrate)	4.00	1.07	2.13	0.0011	0.0021	0.0133	0.0266	0.0276	0.0553

Table 23 Conservative Daily Intake of THC, Males Age 2 to 5 Years - Organic or Conventional Hemp Protein Powder

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Protein Powders (inc. concentrate)	4.00	0.0011	0.0022	0.0118	0.0236	0.0247	0.0494

Table 24 Conservative Daily Intake of THC, Females Age 2 to 5 Years - Organic or Conventional Hemp Protein Powder

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Protein Powders (inc. concentrate)	4.00	0.0009	0.0018	0.0101	0.0202	0.0211	0.0422

Table 25 Conservative Daily Intake of THC, Males Age 6 to 11 Years - Organic or Conventional Hemp Protein Powder

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Protein Powders (inc. concentrate)	4.00	0.0010	0.0021	0.0116	0.0232	0.0243	0.0485

Table 26 Conservative Daily Intake of THC, Females Age 6 to 11 Years - Organic or Conventional Hemp Protein Powder

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Protein Powders (inc. concentrate)	4.00	0.0010	0.0020	0.0120	0.0240	0.0249	0.0499

Table 27 Cumulative Daily Intake of THC, Males 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	4.00	0.0017	0.0034	0.0109	0.0217	0.0234	0.0468
Protein Powders (inc. concentrate)	4.00	0.0011	0.0022	0.0118	0.0236	0.0247	0.0494
Oil	10.00	0.0016	0.0032	0.0112	0.0224	0.0240	0.0481
TOTAL		**0.0044**	**0.0088**	**0.0339**	**0.0678**	**0.0722**	**0.1444**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 28 Cumulative Daily Intake of THC, Females 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seed	4.00	0.0015	0.0030	0.0094	0.0189	0.0204	0.0408
Protein Powders (inc. concentrate)	4.00	0.0009	0.0018	0.0101	0.0202	0.0211	0.0422
Oil	10.00	0.0015	0.0031	0.0107	0.0214	0.0229	0.0458
TOTAL		**0.0039**	**0.0079**	**0.0302**	**0.0605**	**0.0644**	**0.1288**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 29 Cumulative Daily Intake of THC, Males 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seed	4.00	0.0018	0.0036	0.0112	0.0224	0.0242	0.0485
Protein Powders (inc. concentrate)	4.00	0.0010	0.0021	0.0116	0.0232	0.0243	0.0485
Oil	10.00	0.0020	0.0040	0.0141	0.0283	0.0303	0.0606
TOTAL		**0.0048**	**0.0097**	**0.0370**	**0.0740**	**0.0788**	**0.1576**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 30 Cumulative Daily Intake of THC, Females 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Quality Specification for Release THC mcg/g	Minimum Daily Intake delta-9-THC (mg/person)[1]		Mid-Point Daily Intake delta-9-THC (mg/person)[1]		Maximum Daily Intake delta-9-THC (mg/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seed	4.00	0.0018	0.0035	0.0113	0.0225	0.0243	0.0486
Protein Powders (inc. concentrate)	4.00	0.0010	0.0020	0.0120	0.0240	0.0249	0.0499
Oil	10.00	0.0022	0.0043	0.0151	0.0302	0.0324	0.0648
TOTAL		**0.0049**	**0.0098**	**0.0384**	**0.0767**	**0.0816**	**0.1633**

[1]THC exposure estimated using FHF specification Limits (in accordance with Canada's Industrial Hemp Regulations and Corporate requirements).

Table 31 Conservative Daily Intake of Protein, All Individuals Age 2 Years and Older - Organic or Conventional Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Protein Content (%)	Minimum Daily Protein Intake (g/person)[1]		Mid-Point Daily Protein Intake (g/person)[1]		Maximum Daily Protein Intake (g/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	34.00	0.177	0.354	1.107	2.215	2.391	4.783
Hemp Protein Powders (including Hemp Protein Concentrate)	33-63	0.168	0.336	2.093	4.190	4.355	8.717
TOTAL		**0.345**	**0.690**	**3.200**	**6.405**	**6.745**	**13.500**

[1]Used maximum level of 63% protein (*as-is* basis) to calculate protein from Hemp Protein Powders.

Table 32 Conservative Daily Intake of Protein, Males Age 2 to 5 Years - Organic or Conventional Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Protein Content (%)	Minimum Daily Protein Intake (g/person)[1]		Mid-Point Daily Protein Intake (g/person)[1]		Maximum Daily Protein Intake (g/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	34.000	0.145	0.290	0.923	1.846	1.991	3.982
Hemp Protein Powders (including Hemp Protein Concentrate)	33-63	0.173	0.347	1.860	3.720	3.893	7.787
TOTAL		0.318	0.637	2.783	5.566	5.884	11.769

[1]Used maximum level of 63% protein (as-is basis) to calculate protein from Hemp Protein Powders.

Table 33 Conservative Daily Intake of Protein, Females Age 2 to 5 Years - Organic or Conventional Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Protein Content (%)	Minimum Daily Protein Intake (g/person)[1]		Mid-Point Daily Protein Intake (g/person)[1]		Maximum Daily Protein Intake (g/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	34.00	0.127	0.254	0.803	1.607	1.733	3.467
Hemp Protein Powders (including Hemp Protein Concentrate)	33-63	0.145	0.289	1.590	3.178	3.324	6.645
TOTAL		0.272	0.544	2.393	4.784	5.057	10.112

[1]Used maximum level of 63% protein (as-is basis) to calculate protein from Hemp Protein Powders.

Table 34 Conservative Daily Intake of Protein, Males Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Protein Content (%)	Minimum Daily Protein Intake (g/person)[1]		Mid-Point Daily Protein Intake (g/person)[1]		Maximum Daily Protein Intake (g/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	34.00	0.153	0.305	0.954	1.908	2.060	4.121
Hemp Protein Powders (including Hemp Protein Concentrate)	33-63	0.163	0.325	1.830	3.660	3.822	7.646
TOTAL		0.315	0.630	2.783	5.568	5.882	11.767

[1]Used maximum level of 63% protein (as-is basis) to calculate protein from Hemp Protein Powders.

Table 35 Conservative Daily Intake of Protein, Females Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed and Hemp Protein Powder

(Typical Nutritional Profile)

Hemp Ingredient	Typical Protein Content (%)[1]	Minimum Daily Protein Intake (g/person)		Mid-Point Daily Protein Intake (g/person)		Maximum Daily Protein Intake (g/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	34	0.1506	0.3011	0.9570	1.9139	2.0645	4.1290
Protein Powders (including concentrate)	35 - 75	0.1829	0.3657	2.2471	4.4942	4.6770	9.3540
TOTAL		**0.3334**	**0.6668**	**3.2040**	**6.4081**	**6.7415**	**13.4830**

[1]Used maximum level of 75% protein to calculate protein from Hemp Protein Powders.

Hemp Ingredient	Typical Protein Content (%)	Minimum Daily Protein Intake (g/person)[1]		Mid-Point Daily Protein Intake (g/person)[1]		Maximum Daily Protein Intake (g/person)[1]	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	34.00	0.151	0.301	0.957	1.914	2.064	4.129
Hemp Protein Powders (including Hemp Protein Concentrate)	33-63	0.154	0.307	1.888	3.775	3.929	7.857
TOTAL		0.304	0.608	2.845	5.689	5.993	11.986

[1]Used maximum level of 63% protein (as-is basis) to calculate protein from Hemp Protein Powders.

Table 36 Amino Acid Comparison - Organic or Conventional Hulled Hemp Seed and Hemp Protein Powder

Amino Acid	Hulled Hemp Seed (g/100 g protein)	50% Grade Hemp Protein Powder - Dry Process (g/100 g protein)	43% Grade Hemp Protein Powder - Dry Process (g/100 g protein)	33% Grade Hemp Protein Powder - Dry Process (g/100 g protein)	Hemp Protein Concentrate - Wet Process (g/100 g protein)	Canola Protein GRN 683 (g/100 g protein)	Oat Protein GRN 575 (g/100 g protein)	Pea Protein GRN 581 (g/100 g protein)	Soy Protein Concentrate CNF 3368[1]	Soy Protein Isolate CNF 3328[1]
Alanine	3.21	3.38	3.88	3.20	3.45	4.17	4.38	4.12	4.61	4.45
Arginine	13.39	11.22	10.40	12.81	12.44	6.32	7.13	8.52	7.99	8.27
Aspartic Acid	9.58	10.03	9.18	9.69	9.37	4.22	7.54	11.81	13.47	12.65
Cystine	1.76	2.27	1.67	1.64	2.43	3.51	2.29	0.87	1.52	1.30
Glutamic Acid	14.40	15.74	16.49	14.52	14.85	22.40	22.60	17.29	20.67	21.63
Glycine	3.56	3.76	3.99	3.71	4.03	4.83	4.17	3.97	4.62	4.47
Histidine	1.78	1.66	2.42	1.50	1.65	3.05	2.21	2.51	2.72	2.85
Isoleucine	3.94	3.78	3.44	3.97	3.89	3.52	4.50	4.76	5.06	5.27
Leucine	6.29	5.62	6.06	6.41	6.77	6.84	8.24	8.41	8.46	8.41
Lysine	4.10	3.73	3.34	4.18	3.76	6.08	3.40	7.36	6.76	6.60
Methionine	2.19	2.49	2.15	2.13	2.58	2.06	2.01	0.98	1.40	1.40
Phenylalanine	4.52	4.69	4.15	4.68	4.80	3.65	5.86	5.52	5.64	5.69
Proline	5.06	4.93	3.38	5.34	4.72	6.57	5.46	4.57	5.67	6.15
Serine	4.46	4.80	4.52	4.42	4.88	3.91	4.03	5.43	5.80	5.69
Threonine	4.01	3.88	3.11	3.91	3.98	3.73	3.12	4.05	4.26	3.89
Tryptophan	0.89	0.91	0.77	0.89	1.10	1.36	1.10	1.03	1.44	1.38
Tyrosine	2.16	2.09	2.67	1.90	2.62	1.96	3.96	3.69	3.96	3.99
Valine	4.43	4.68	4.39	4.54	4.44	4.69	5.93	5.03	5.27	5.08

1 CNF, Canadian Nutrient File. https://food-nutrition.canada.ca/cnf-fce/index-eng.jsp Accessed October 26, 2017.

Table 37 Detection of Cannabinoids in Urine

Drug Testing Program	Cut Off Limit
US Department of Defense	15 ng/ml
US Federal Workplace Drug Testing	15 ng/ml
World Anti-Doping Agency	150 ng/ml

Table 38 Daily THC Exposure at Maximum Specification Levels and Monte Carlo Modelling of Daily THC Exposure - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014)					THC EXPOSURE FROM HEMP MATERIAL CONSUMED AT MAXIMUM FRESH HEMP FOODS LTD. SPECIFICATION LIMITS (mg/Day) *Hulled Hemp Seed = NMT 4 µg/g THC *Hemp Protein Powder = NMT 4 µg/g THC *Hemp Oil = NMT 10 µg/g THC					THC EXPOSURE FROM HEMP MATERIAL CONSUMED USING MONTE CARLO MODEL AND HISTORICAL TEST DATA (mg/Day) *Hulled Hemp Seed = Mean of 0.29 µg/g THC *Hemp Protein Powder = Mean of 0.31 µg/g THC *Hemp Oil = Mean of 4.95 µg/g THC				
	2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years		2 Years & Older	2 to 5 Years		6 to 11 Years	
	Males & Females	Males	Females	Males	Females	Males & Females	Males	Females	Males	Females	Males & Females	Males	Females	Males	Females
HULLED HEMP SEED GRN XXX	14.07 (Table 16)	11.71 (Table 17)	10.2 (Table 18)	12.12 (Table 19)	12.14 (Table 20)	0.0563 (Table 21)	0.0468 (Table 27)	0.0408 (Table 28)	0.0485 (Table 29)	0.0486 (Table 30)	0.0213 (Figure 7)	0.0178 (Figure 15)	0.0155 (Figure 23)	0.0184 (Figure 31)	0.0184 (Figure 40)
HEMP PROTEIN POWDER GRN XXX	13.84 (Table 16)	12.36 (Table 17)	10.55 (Table 18)	12.14 (Table 19)	12.47 (Table 20)	0.0553 (Table 21)	0.0494 (Table 27)	0.0422 (Table 28)	0.0485 (Table 29)	0.0499 (Table 30)	0.0164 (Figure 5)	0.0147 (Figure 13)	0.0126 (Figure 21)	0.0145 (Figure 29)	0.0149 (Figure 37)
HEMP OIL GRN XXX	8.22 (Table 16)	4.81 (Table 17)	4.58 (Table 18)	6.06 (Table 19)	6.48 (Table 20)	0.0822 (Table 21)	0.0481 (Table 27)	0.0458 (Table 28)	0.0606 (Table 29)	0.0648 (Table 30)	0.0772 (Figure 9)	0.0451 (Figure 17)	0.0431 (Figure 25)	0.0566 (Figure 33)	0.0605 (Figure 44)
CUMMULATIVE	**36.12 (Table 16)**	**28.88 (Table 17)**	**25.33 (Table 18)**	**30.32 (Table 19)**	**31.1 (Table 20)**	**0.1938 (Table 21)**	**0.1444 (Table 27)**	**0.1288 (Table 28)**	**0.1576 (Table 29)**	**0.1633 (Table 30)**	**0.1049 (Figure 3)**	**0.0698 (Figure 11)**	**0.0651 (Figure 19)**	**0.0794 (Figure 27)**	**0.0834 (Figure 35)**

Table 39 Estimated Infant THC Exposure

Estimated THC food daily intake mg	Maternal THC plasma Cmax µg/L	Maternal 11-OH-THC plasma Cmax µg/L	Breast Milk THC Cmax µg/L B/P 8.4	Breast Milk 11-OH-THC Cmax µg/L B/P 8.4	Infant THC Exposure µg/kg/day[3]	Infant 11-OH-THC Exposure µg/kg/day
0.0968	<0.02	<0.04	<0.17	<0.34	<0.03	<0.05
0.1938	<0.04	<0.07	<0.34	<0.59	<0.05	<0.09
0.1025	<0.02	<0.04	<0.17	<0.34	<0.03	<0.05
5.4[1]	<1.2	<2	<10.1	<16.8	<1.5	<2.5
0.39[2]	ND	ND				
0.47[2]	ND	ND				

[1]Stott et al 2013 oral mucosa THC dose; [2]Gustafson et al 2014 oral THC dose
[3]150 mL/kg/day infant breast milk dose

Table 40 Literature Review – Oral THC Administration, Urine THCCOOH Excretion Data, Blood/Plasma/Serum THC Concentrations and Effects

Amount of THC dosed (mg/dose)	# Doses per Day (d)	Total THC per Day (mg/day)	Delivery Form	Study Duration (# Days)	# Subjects (S)	Urine Cmax (µg/L)	Urine Cutoff Level (µg/L)	# Pos Subjects; % pos urine ≥ 15µg/L	# Days Subject Tested Positive at Cutoff	Reference
NA	NA	NA	Oral hemp oil	2	7	<1.8-78.6 8h post	15	3	2 of 5 participants pos 2 d	Costantino 1997
15	1	15.0	Marinol	6	4	189 - 362	15	4; 44-54%	2 to 5 d	ElSohly 2001
16.5	1	16.5	Oral hemp oil	6	3	Up to 431	15	6 for 2.5d; 2 for 5.5d; no%given	2.5-5.5	Lehmann 1997
33	1	33.0	Oral hemp oil	6	3	Up to 378	15	See above; doses not separated	2.5-5.5	Lehmann 1997
20	1	20.0	Marinol & oral hemp oil	3	18	NA	50 screen & 15 confirm	18; 60%	NA NA	Grauwiler 2008
22.4	1	22.4	Brownie	Until negative urine	5	~325	5	5	Mean 6 d	Cone 1988
44.8	1	44.8	Brownie	Until negative urine	5	~436	5	5	Mean 6.5 d	Cone 1988
50.6	1	50.6	Brownie	2.5	9 O	116 - 667	5	9; median 84.6% (27.3-100%)	2	Huestis 135
50.6	1	50.6	Brownie	2.5	7O	181 - 766	5	7; median 88.9 (50-100)%	2	Huestis 135-5
50.6	1	50.6	Brownie	3	11 F	243 - 2010	5	11: median 100%	3	Huestis 135
50.6	1	50.6	Brownie	3	8 F	133 – 736	5	8; median 100%	3	Huestis 135-5
0.09 d X 10d	1	0.09	Oral hemp & canola oil	10	15	<5.2	50 screen & 15 confirm	0;0%	0	Leson 2001
0.19 X 10d	1	0.19	Oral hemp & canola oil	10	15	<5.2	50 screen & 15 confirm	0;0%	0	Leson 2001
0.29 X 10d	1	0.29	Oral hemp & canola oil	10	15	<5.2	50 screen & 15 confirm	0;0%	0	Leson 2001
0.45 X 10d	1	0.45	Oral hemp & canola oil	10	15	<5.2	50 screen & 15 confirm	0;0%	0	Leson 2001
0.60 X 10d	1	0.6	Oral hemp & canola oil	10	2	<5.2	15	0;0%	0	Leson 2001
0.10 d X 7d	1	0.10	Oral hemp oil capsules	14	1	5.2	15	0;0%	0	Bosy & Cole 2000
0.17 d X 7d	1	0.17	Oral hemp oil	14	1	1.8	15	0;0%	0	Bosy & Cole 2000
0.32 d X 7d	1	0.32	Oral hemp oil	14	1	13.9	15	0;0%	0	Bosy & Cole 2000
0.54 d X 7d	1	0.54	Oral hemp oil	14	1	21.1	15	1;5.3%	1d after last dose	Bosy & Cole 2000
0.55 d X 7d	1	0.55	Oral hemp oil	14	1	13.1	15	0%	0	Bosy & Cole 2000
1.8 d X 7d	1	1.8	Oral hemp oil	14	1	48	15	1; 50% in 14 d	2d after last dose	Bosy & Cole 2000
0.39 d X 5d	1	0.39	Oral hemp oil	15	7	Mean 19.8; (7.3-38.2)	15	4; mean 2.6%	1.5 mean	Gustafson 2003
0.47 d X 5d	1	0.47	Oral hemp oil	15	7	Mean 12.2; (5.4-31.0)	15	2; mean 2.3%	0.5 mean	Gustafson 2003
7.5 d X 5d	1	7.5	Marinol	15	7	Mean 146; (26.0-436)	15	7; mean 37.8%	2.5	Gustafson 2003
14.8 d X 5d	1	14.8	Oral hemp oil	15	7	Mean 116; (19.0-264)	15	7; mean 31.9%	2.5	Gustafson 2003
Unknown	2	Unknown	Oral hemp oil	7.4	1	68	15	1; most during dosing	5	Struempler 1997
2.7	6	16.2	Sativex	Dosed 30 d	8	61.3 ± 27.5	25	8; 1 urine each month	NA	Indorato 2016
2.7	6	16.2	Sativex	Dosed 90 d	12	59.8±23.6 @ 1 mo, 62.6±25.2 @2 mo, 63.2±24.8 @ 3 mo	25	12; 1 urine each month	NA	Indorato 2016

Table 41 Upper Bound Estimate of THC Exposure Based on Body Weight

	THC EXPOSURE BASED ON BODY WEIGHT AT MAXIMUM SPECIFICATION LEVELS (µg/kg Body Weight)[1,2] *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014) *Hulled Hemp Seed = NMT 4 µg/g THC *Hemp Protein Powder = NMT 4 µg/g THC *Hemp Oil = NMT 10 µg/g THC						THC EXPOSURE BASED ON BODY WEIGHT USING MONTE CARLO MODELLING FROM FIGURES 2 to 41 (µg/kg Body Weight)[1,2] *Highest Level of Inclusion per Food Category *90% Percentile Consumption Level (NHANES 2013-2014) *Hulled Hemp Seed = Mean of 0.29 µg/g THC *Hemp Protein Powder = Mean of 0.31 µg/g THC *Hemp Oil = Mean of 4.95 µg/g THC						TOLERABLE DAILY INTAKE RECOGNIZED BY OTHER REGULATORY AUTHORITIES (µg/kg Body Weight)					
	2 Years & Older		2 to 5 Years		6 to 11 Years		2 Years & Older		2 to 5 Years		6 to 11 Years		Germany	Switzerland	Australia	New Zealand	Canada	Austria
	Males (Mean BW = 88.8 kg)	Females (Mean BW = 76.4 kg)	Males (Mean BW = 14.2 kg)	Females (Mean BW = 13.3 kg)	Males (Mean BW = 23.9 kg)	Females (Mean BW = 23.8 kg)	Males (Mean BW = 88.8 kg)	Females (Mean BW = 76.4 kg)	Males (Mean BW = 14.2 kg)	Females (Mean BW = 13.3 kg)	Males (Mean BW = 23.9 kg)	Females (Mean BW = 23.8 kg)						
Hulled Hemp Seed GRN XXX	0.634 (Table 43)	0.737 (Table 43)	3.299 (Table 44)	3.067 (Table 45)	2.029 (Table 46)	2.041 (Table 47)	0.240	0.279	1.254	1.165	0.770	0.773	5	7	6	6	Not Set	1-2
Hemp Protein Powder GRN XXX	0.623 (Table 43)	0.724 (Table 43)	3.482 (Table 44)	3.172 (Table 45)	2.031 (Table 46)	2.096 (Table 47)	0.185	0.215	1.035	0.947	0.607	0.626						
Hemp Oil GRN XXX	0.925 (Table 43)	1.075 (Table 43)	3.387 (Table 44)	3.444 (Table 45)	2.536 (Table 46)	2.723 (Table 47)	0.869	1.010	3.176	3.241	2.368	2.542						
CUMMULATIVE	**2.182 (Table 43)**	**2.536 (Table 43)**	**10.168 (Table 44)**	**9.684 (Table 45)**	**6.596 (Table 46)**	**6.86 (Table 47)**	**1.181**	**1.373**	**4.915**	**4.895**	**3.322**	**3.504**						

[1] Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States. 2011-2014. National center for Health Statistics. Vital Health Stats 3(39). 2016

[2] Assumes that children would eat all the same foods as an adult.

Table 42 Summary of Standards Adopted by Other Regulatory Bodies for Cumulative THC Exposure from Uses of Industrial Hemp[1]

Country	Recognized Tolerable Daily Intake (µg/kg Body Weight)	Regulated THC Limit - Hulled Hemp Seed (µg /g)	Regulated THC Limit - Hemp Protein Powder (µg /g)	Regulated THC Limit - Hemp Oil (µg /g)
Germany	5	No specific guidance	No specific guidance	5
Switzerland	7	1	No specific guidance	2
Australia	6	5	No specific guidance	10
New Zealand	6	5	No specific guidance	10
Canada	Not set	10	10	10
Austria	1-2	Not to exceed 1-2 µg/kg bw/day	Not to exceed 1-2 µg /kg bw/day	Not to exceed 1-2 µg/kg bw/day

[1] Table 40 was completed with information from the report by Nova Institute titled, *Scientifically Sound Guidelines for THC in Food in Europe* July 2015 (available at http://eiha.org/media/2015/08/15-07-24-Report-Scientifically-Safe-Guidelines-THC-Food-nova-EIHA.pdf (lasted visited February 26, 2018)).

Table 43 Daily Intake of THC Based on Body Weight, All Individuals Age 2 Years and Older - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]				Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]				Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]			
	Male - Adult 20 Years and Older Mean BW = 88.8 kg		Female - Adult 20 Years and Older Mean BW = 76.4 kg		Male - Adult 20 Years and Older Mean BW = 88.8 kg		Female - Adult 20 Years and Older Mean BW = 76.4 kg		Male - Adult 20 Years and Older Mean BW = 88.8 kg		Female - Adult 20 Years and Older Mean BW = 76.4 kg	
	Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.02344	0.24775	0.02725	0.28796	0.14664	0.29339	0.17043	0.34101	0.31671	0.63367	0.36812	0.73652
Protein Powders (inc. concentrate)	0.01200	0.24775	0.01395	0.28796	0.14968	0.29962	0.17397	0.34825	0.31135	0.62324	0.36188	0.72440
Oil	0.03083	0.24775	0.03584	0.28796	0.21583	0.43175	0.25086	0.50182	0.46250	0.92517	0.53757	1.07533
TOTAL	**0.06627**	**0.74324**	**0.07703**	**0.86387**	**0.51214**	**1.02475**	**0.59527**	**1.19107**	**1.09056**	**2.18208**	**1.26757**	**2.53624**

[1]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD).

[2]Highly conservative - assumes a person would consume all sources of hemp per day.

Table 44 Daily Intake of THC Based on Body Weight, Males Age 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]	
	Male 2 years[2] Mean BW = 14.2 kg		Male 2 years[2] Mean BW = 14.2 kg		Male 2 years[2] Mean BW = 14.2 kg	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.1202	0.2405	0.7646	1.5292	1.6494	3.2989
Protein Powders (inc. concentrate)	0.0775	0.1549	0.8317	1.6635	1.7408	3.4820
Oil	0.1129	0.2258	0.7902	1.5804	1.6933	3.3866
TOTAL	**0.3106**	**0.6212**	**2.3865**	**4.7732**	**5.0835**	**10.1675**

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016

[2]Highly conservative - assumes a person would consume all sources of hemp per day and assumes a child would consume same foods as an adult.

Table 45 Daily Intake of THC Based on Body Weight, Females Age 2 to 5 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]	
	Female 2 years[2] Mean BW = 13.3 kg		Female 2 years[2] Mean BW = 13.3 kg		Female 2 years[2] Mean BW = 13.3 kg	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.1124	0.2249	0.7105	1.4212	1.5334	3.0672
Protein Powders (inc. concentrate)	0.0691	0.1381	0.7588	1.5169	1.5868	3.1720
Oil	0.1148	0.2296	0.8037	1.6074	1.7222	3.4444
TOTAL	**0.2963**	**0.5926**	**2.2730**	**4.5455**	**4.8423**	**9.6836**

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016

[2]Highly conservative - assumes a person would consume all sources of hemp per day and assumes a child would consume same foods as an adult.

Table 46 Daily Intake of THC Based on Body Weight, Males Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]	
	Male 6 years[2] Mean BW = 23.9 kg		Male 6 years[2] Mean BW = 23.9 kg		Male 6 years[2] Mean BW = 23.9 kg	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.0751	0.1502	0.4695	0.9393	1.0142	2.0287
Protein Powders (inc. concentrate)	0.0432	0.0864	0.4860	0.9724	1.0152	2.0311
Oil	0.0845	0.1691	0.5917	1.1836	1.2680	2.5362
TOTAL	**0.2028**	**0.4056**	**1.5473**	**3.0952**	**3.2974**	**6.5960**

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016

[2]Highly conservative - assumes a person would consume all sources of hemp per day and assumes a child would consume same foods as an adult.

Table 47 Daily Intake of THC Based on Body Weight, Females Age 6 to 11 Years - Organic or Conventional Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil

Hemp Ingredient	Minimum Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Mid-Point Daily Intake THC based on Body Weight (mcg/kg BW)[1]		Maximum Daily Intake THC based on Body Weight (mcg/kg BW)[1]	
	Female 6 years[2] Mean BW = 23.8 kg		Female 6 years[2] Mean BW = 23.8 kg		Female 6 years[2] Mean BW = 23.8 kg	
	Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	0.0744	0.1488	0.4730	0.9461	1.0205	2.0410
Protein Powders (inc. concentrate)	0.0410	0.0819	0.5035	1.0071	1.0481	2.0961
Oil	0.0908	0.1815	0.6353	1.2706	1.3613	2.7227
TOTAL	**0.2062**	**0.4123**	**1.6119**	**3.2238**	**3.4299**	**6.8598**

[1]Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011–2014. National Center for Health Statistics. Vital Health Stat 3(39). 2016

[2]Highly conservative - assumes a person would consume all sources of hemp per day and assumes a child would consume same foods as an adult.

Figure 1 Manufacturing Flow Chart - Dry Process

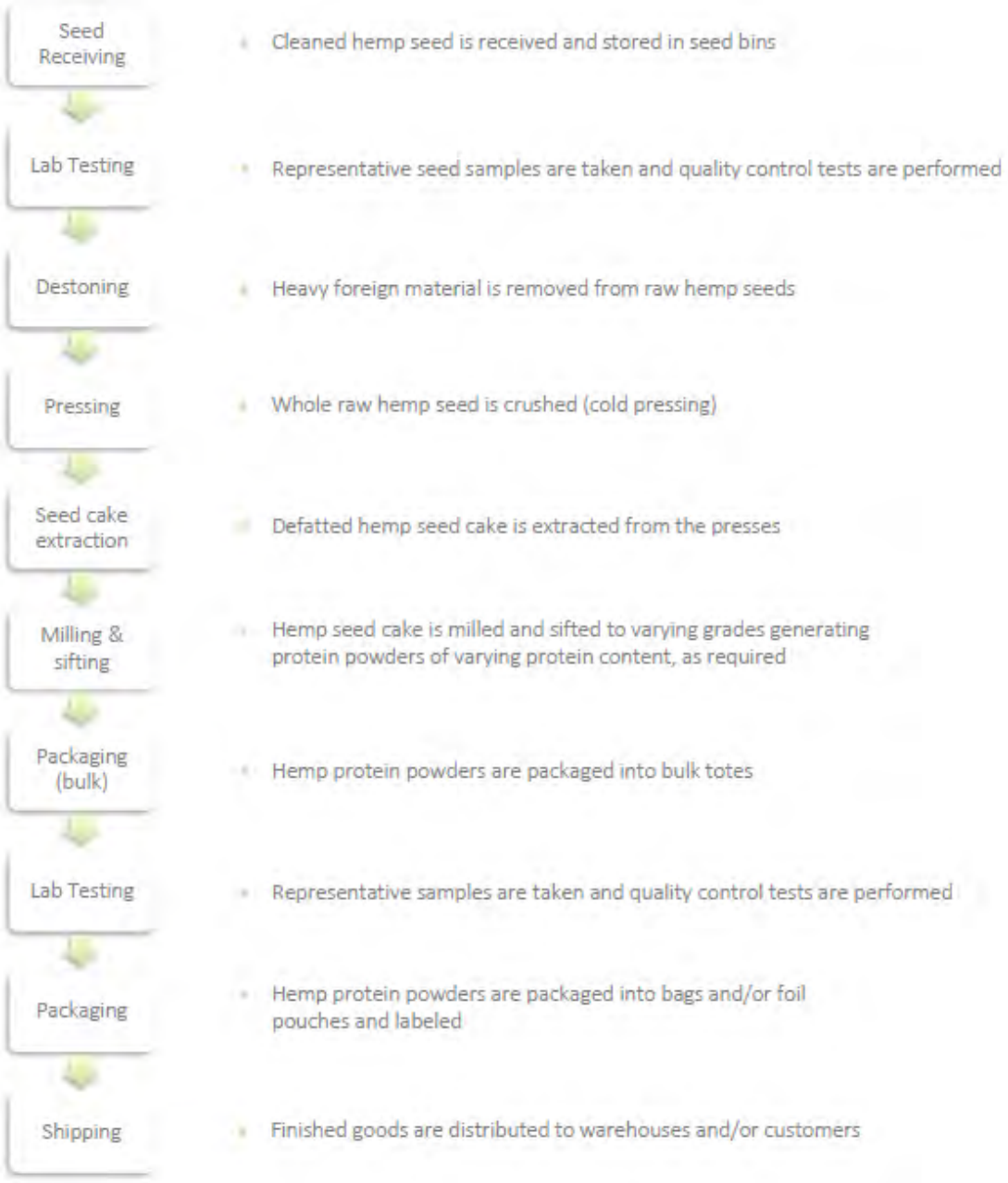


Figure 2 Manufacturing Flow Chart - Wet Process

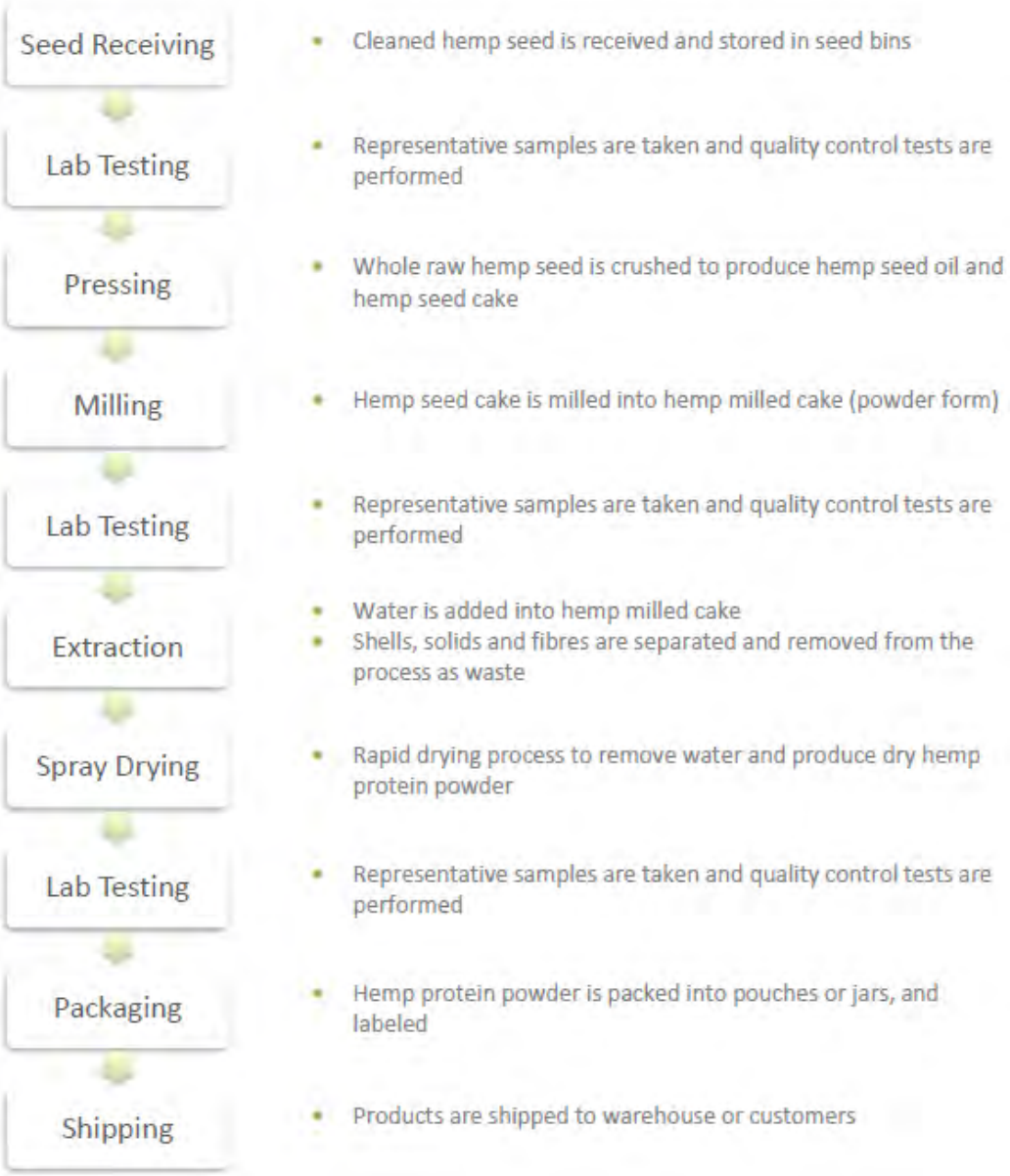
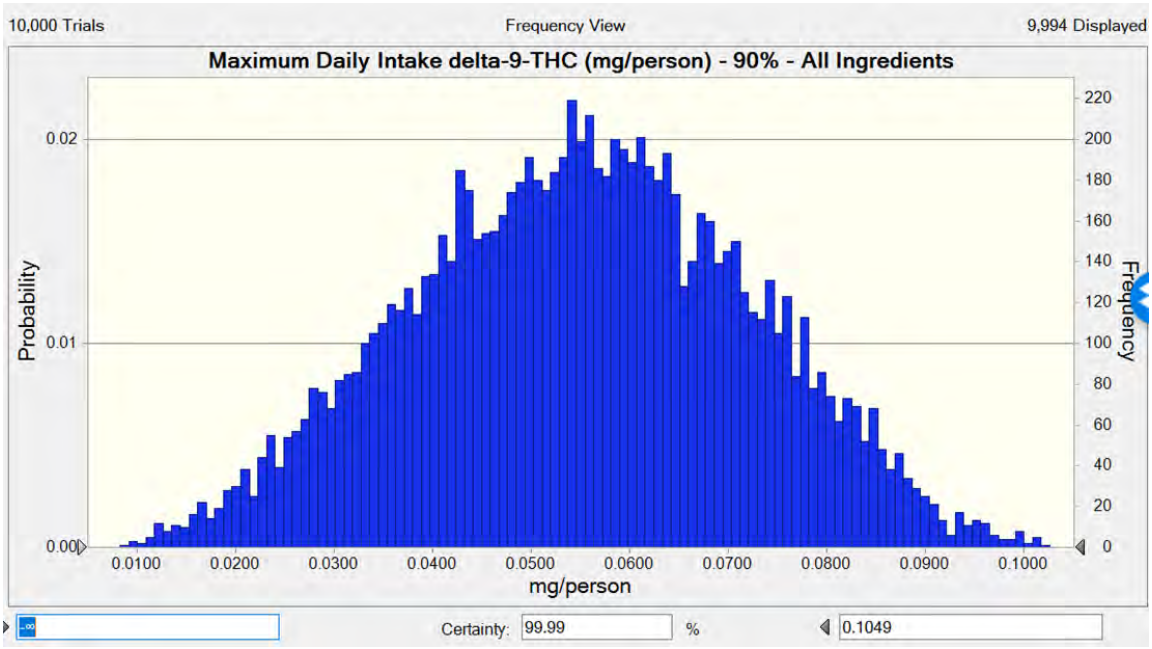


Figure 3 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – All Individuals Age 2 Years and Older

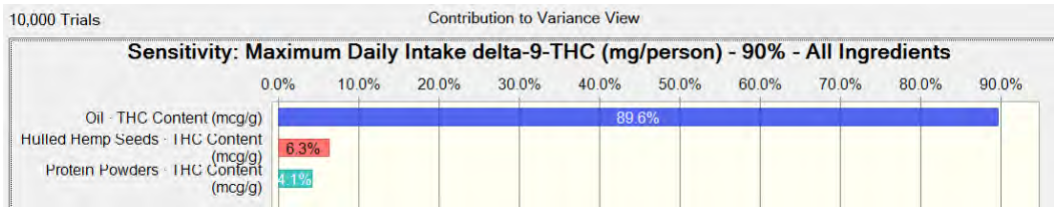


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.1049 mg/person/day.

Figure 4 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile - All Individuals Age 2 Years and Older

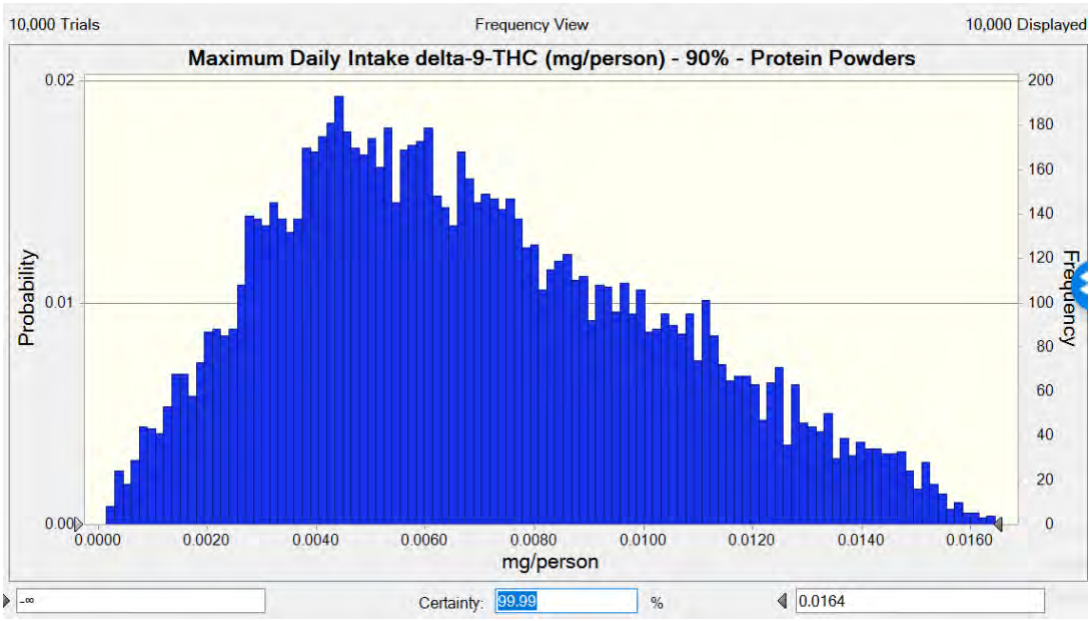
Statistic	Forecast values
Trials	10,000
Base Case	0.0490
Mean	0.0550
Median	0.0552
Mode	---
Standard Deviation	0.0170
Variance	0.0003
Skewness	-0.0190
Kurtosis	2.55
Coeff. of Variation	0.3093
Minimum	0.0063
Maximum	0.1061
Mean Std. Error	0.0002

Percentile	Forecast values
0%	0.0063
10%	0.0323
20%	0.0400
30%	0.0456
40%	0.0507
50%	0.0552
60%	0.0597
70%	0.0642
80%	0.0701
90%	0.0775
100%	0.1061



Variability in THC within Hemp Oil makes up 89.6% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 6.3% and Protein Powders make up 4.1%

Figure 5 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – All Individuals Age 2 Years and Older



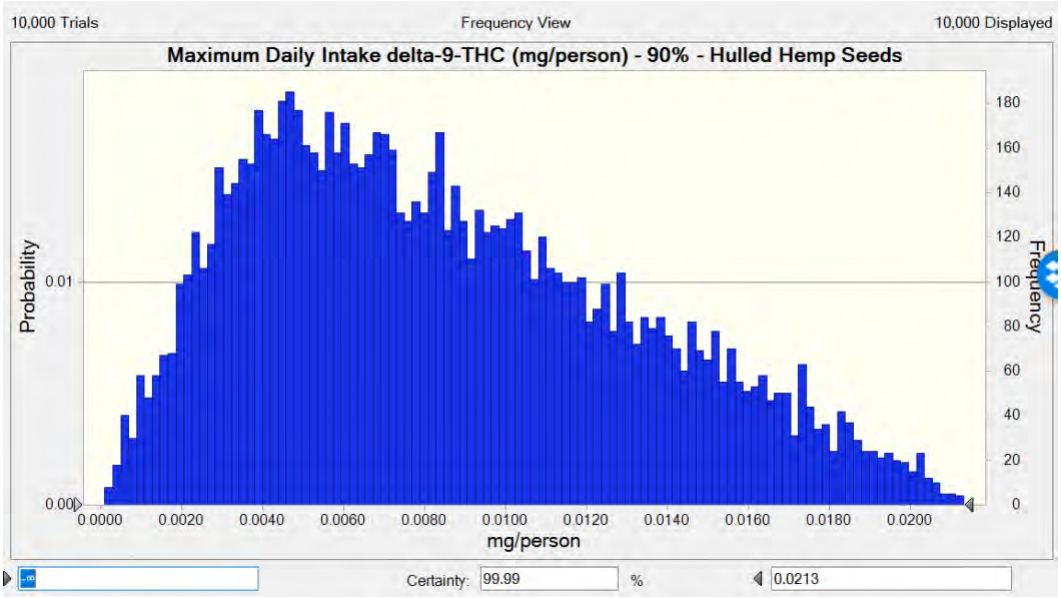
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0164 mg/person/day.

Figure 6 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile - All Individuals Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0043
Mean	0.0069
Median	0.0064
Mode	---
Standard Deviation	0.0035
Variance	0.0000
Skewness	0.4205
Kurtosis	2.44
Coeff. of Variation	0.5019
Minimum	0.0001
Maximum	0.0164
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0027
20%	0.0038
30%	0.0046
40%	0.0055
50%	0.0064
60%	0.0074
70%	0.0086
80%	0.0101
90%	0.0119
100%	0.0164

Figure 7 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – All Individuals Age 2 Years and Older



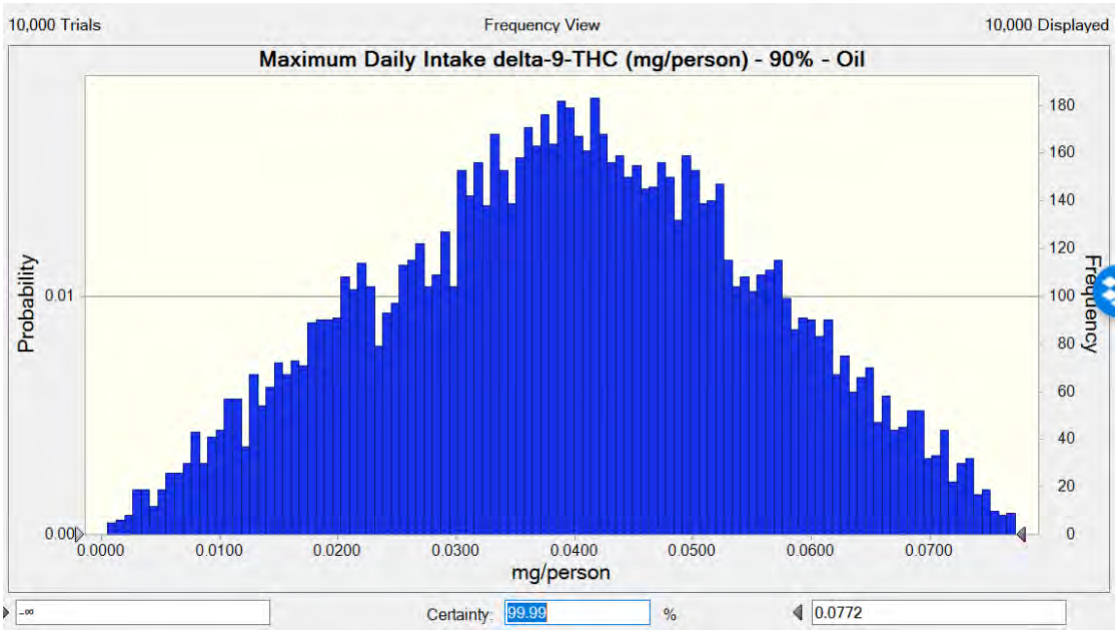
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0213 mg/person/day.

Figure 8 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile - All Individuals Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0041
Mean	0.0085
Median	0.0078
Mode	---
Standard Deviation	0.0047
Variance	0.0000
Skewness	0.4952
Kurtosis	2.42
Coeff. of Variation	0.5508
Minimum	0.0001
Maximum	0.0213
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0029
20%	0.0042
30%	0.0053
40%	0.0065
50%	0.0078
60%	0.0092
70%	0.0108
80%	0.0128
90%	0.0154
100%	0.0213

Figure 9 Monte Carlo Model – Hemp Oil - THC Exposure at 90th Percentile – All Individuals Age 2 Years and Older



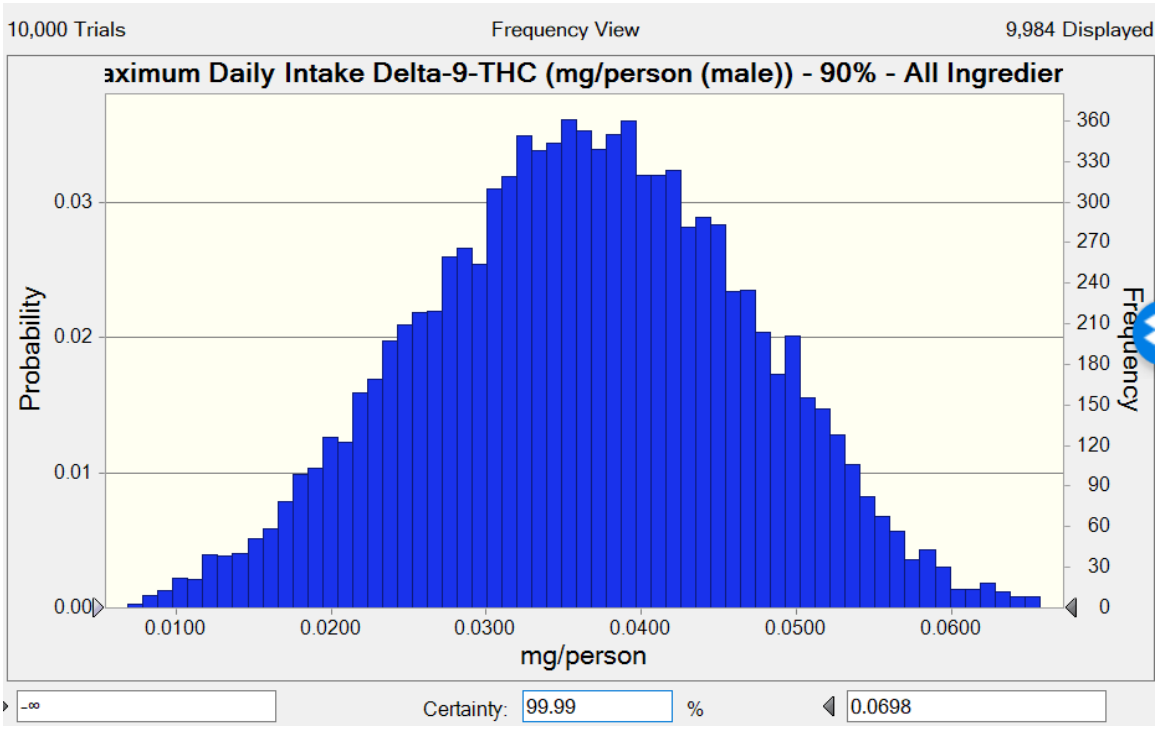
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0772 mg/person/day.

Figure 10 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile - All Individuals Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0407
Mean	0.0396
Median	0.0398
Mode	---
Standard Deviation	0.0160
Variance	0.0003
Skewness	-0.0429
Kurtosis	2.39
Coeff. of Variation	0.4029
Minimum	0.0005
Maximum	0.0772
Mean Std. Error	0.0002

Percentile	Forecast values
0%	0.0005
10%	0.0178
20%	0.0251
30%	0.0310
40%	0.0357
50%	0.0398
60%	0.0440
70%	0.0488
80%	0.0538
90%	0.0609
100%	0.0772

Figure 11 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years

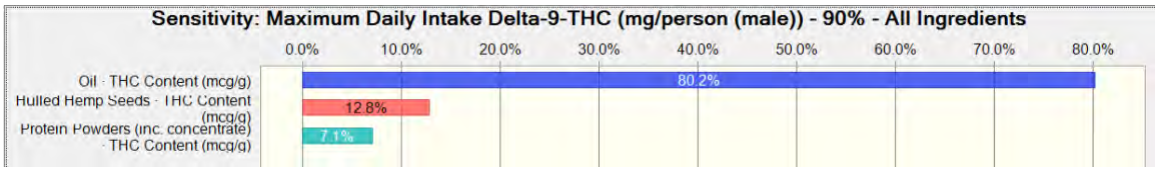


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.0698 mg/person/day.

Figure 12 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile – Males Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0310
Mean	0.0363
Median	0.0364
Mode	---
Standard Deviation	0.0105
Variance	0.0001
Skewness	-0.0238
Kurtosis	2.68
Coeff. of Variation	0.2891
Minimum	0.0048
Maximum	0.0724
Mean Std. Error	0.0001

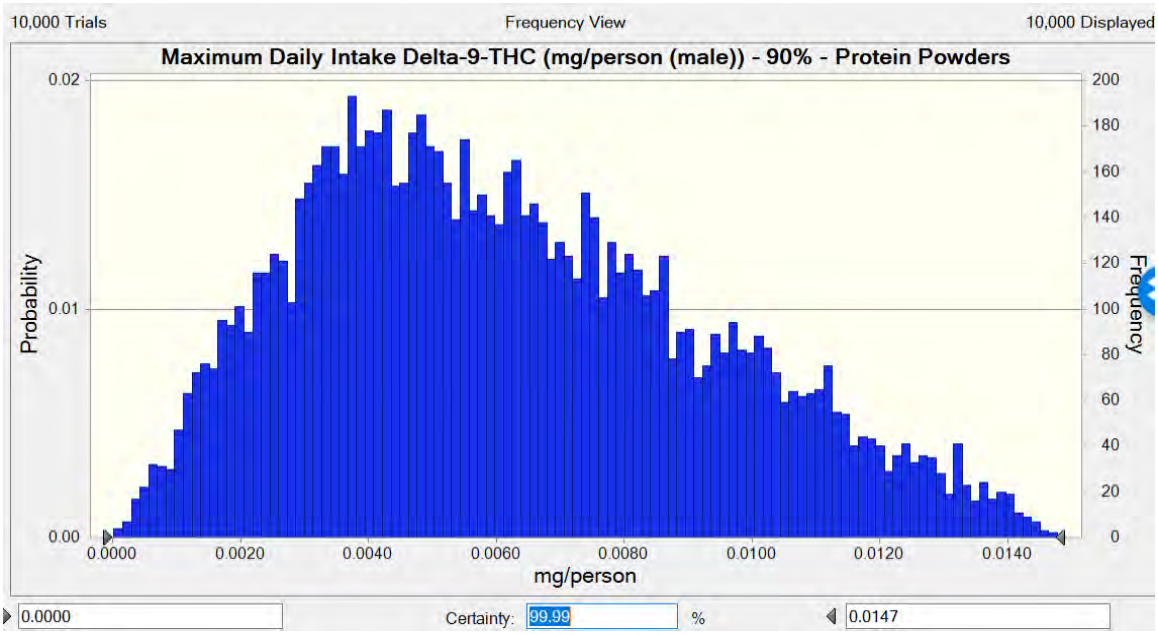
Percentile	Forecast values
0%	0.0048
10%	0.0225
20%	0.0272
30%	0.0307
40%	0.0336
50%	0.0364
60%	0.0392
70%	0.0421
80%	0.0454
90%	0.0499
100%	0.0724



Variability in THC within Hemp Oil makes up 80.2% of the variability in our Maximum Daily

Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 12.8% and Protein Powders make up 7.1%.

Figure 13 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years



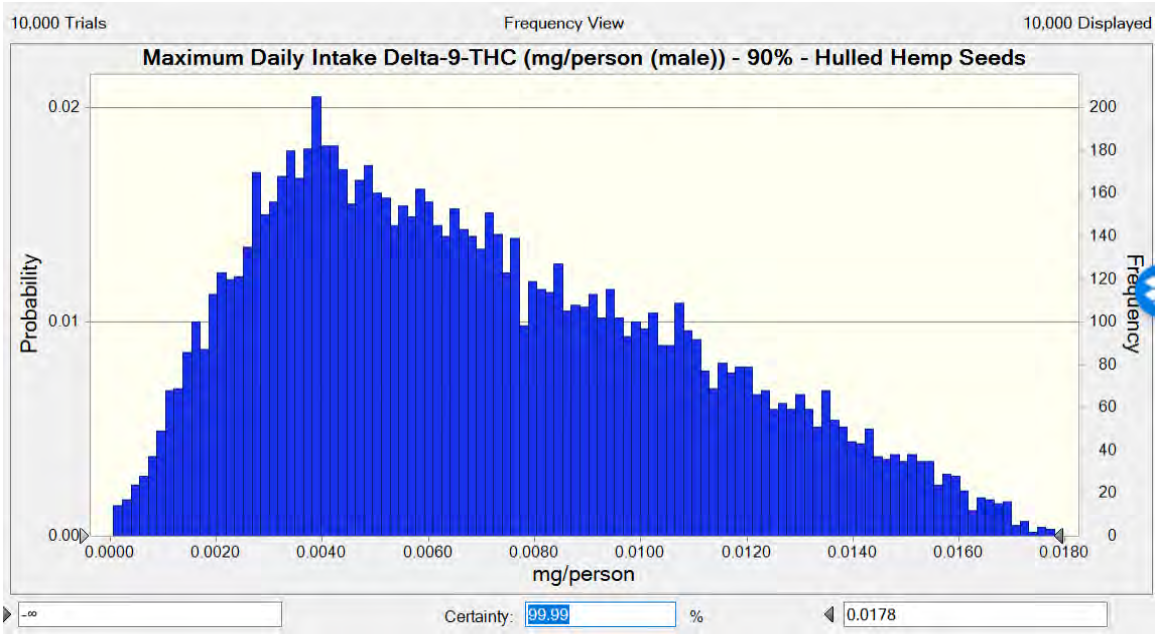
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0147 mg/person/day.

Figure 14 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile – Males Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0038
Mean	0.0062
Median	0.0058
Mode	---
Standard Deviation	0.0031
Variance	0.0000
Skewness	0.4352
Kurtosis	2.46
Coeff. of Variation	0.5051
Minimum	0.0000
Maximum	0.0148
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0000
10%	0.0024
20%	0.0033
30%	0.0041
40%	0.0049
50%	0.0058
60%	0.0067
70%	0.0077
80%	0.0090
90%	0.0107
100%	0.0148

Figure 15 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years



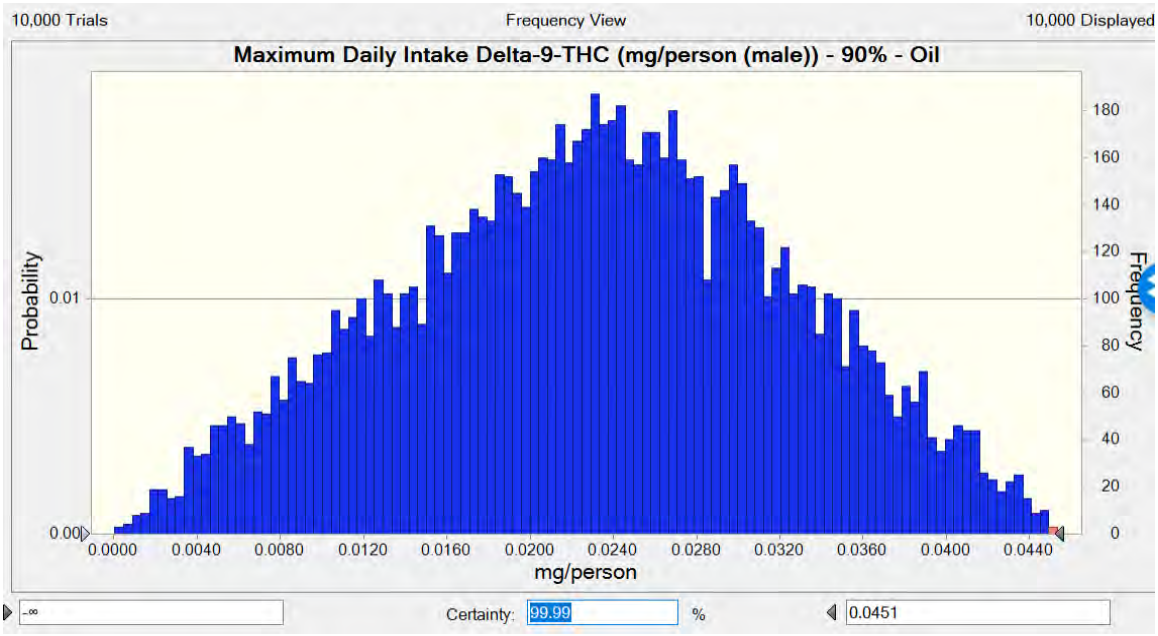
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0178 mg/person/day.

Figure 16 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile – Males Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0034
Mean	0.0070
Median	0.0064
Mode	---
Standard Deviation	0.0039
Variance	0.0000
Skewness	0.4921
Kurtosis	2.40
Coeff. of Variation	0.5487
Minimum	0.0001
Maximum	0.0178
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0024
20%	0.0035
30%	0.0044
40%	0.0054
50%	0.0064
60%	0.0076
70%	0.0090
80%	0.0107
90%	0.0128
100%	0.0178

Figure 17 Monte Carlo Model – Hemp Oil Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years



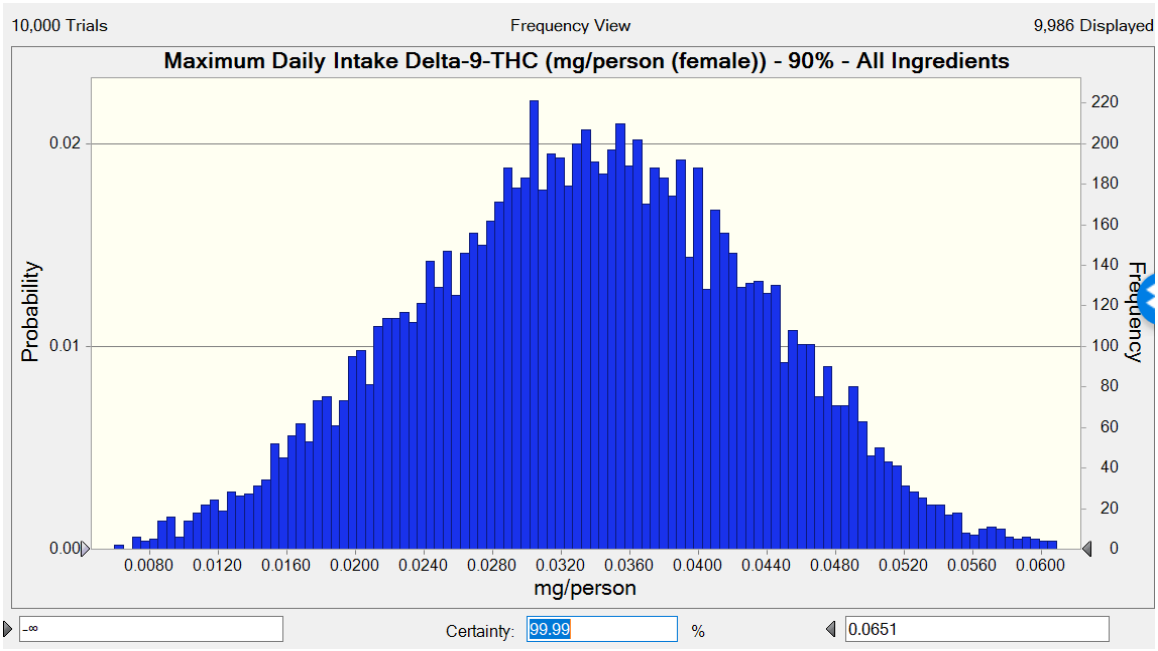
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0451 mg/person/day.

Figure 18 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile – Males Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0238
Mean	0.0231
Median	0.0233
Mode	---
Standard Deviation	0.0093
Variance	0.0001
Skewness	-0.0540
Kurtosis	2.41
Coeff. of Variation	0.4026
Minimum	0.0001
Maximum	0.0453
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0001
10%	0.0104
20%	0.0147
30%	0.0181
40%	0.0208
50%	0.0233
60%	0.0257
70%	0.0283
80%	0.0313
90%	0.0355
100%	0.0453

Figure 19 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – Females Age 2 to 5 Years

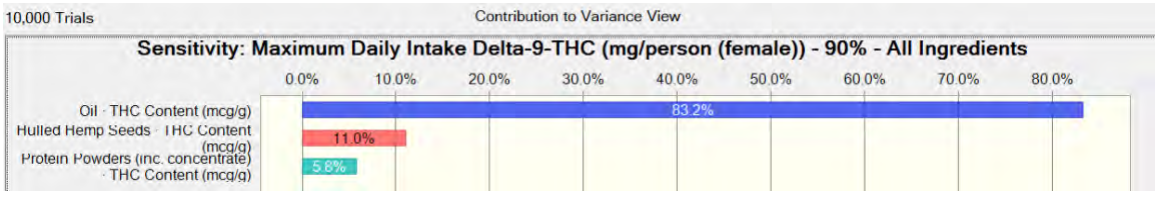


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.0651 mg/person/day.

Figure 20 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile – Females Age 2 to 5 Years

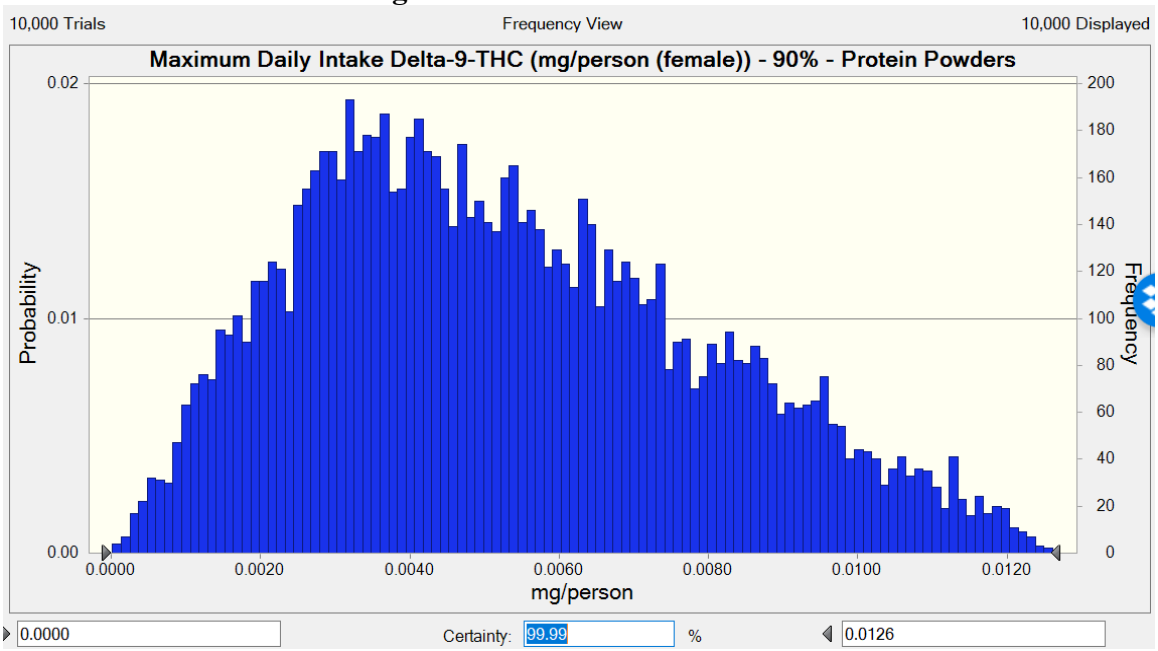
Statistic	Forecast values
Trials	10,000
Base Case	0.0289
Mean	0.0334
Median	0.0335
Mode	---
Standard Deviation	0.0098
Variance	0.0001
Skewness	-0.0324
Kurtosis	2.65
Coeff. of Variation	0.2935
Minimum	0.0042
Maximum	0.0663
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0042
10%	0.0203
20%	0.0248
30%	0.0282
40%	0.0309
50%	0.0335
60%	0.0361
70%	0.0388
80%	0.0420
90%	0.0462
100%	0.0663



Variability in THC within Hemp Oil makes up 83.2% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 11% and Protein Powders make up 5.8%

Figure 21 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – Females Age 2 to 5 Years



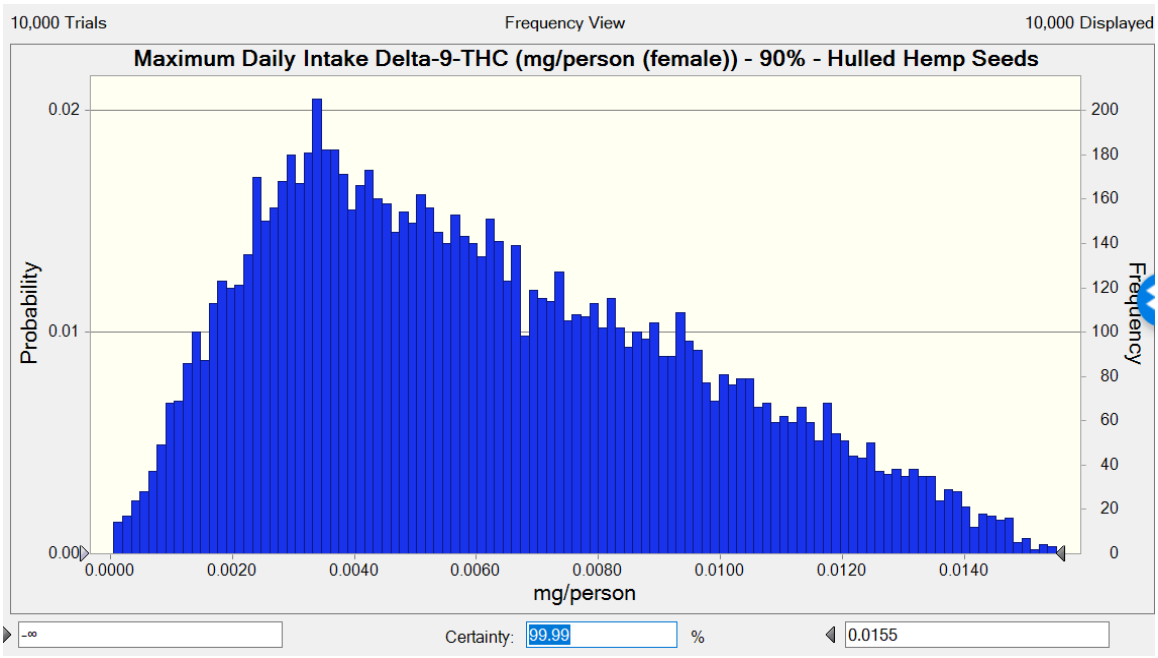
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0126 mg/person/day**.**

Figure 22 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile – Females Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0033
Mean	0.0053
Median	0.0049
Mode	---
Standard Deviation	0.0027
Variance	0.0000
Skewness	0.4352
Kurtosis	2.46
Coeff. of Variation	0.5051
Minimum	0.0000
Maximum	0.0126
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0000
10%	0.0020
20%	0.0029
30%	0.0035
40%	0.0042
50%	0.0049
60%	0.0057
70%	0.0066
80%	0.0077
90%	0.0091
100%	0.0126

Figure 23 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – Females Age 2 to 5 Years



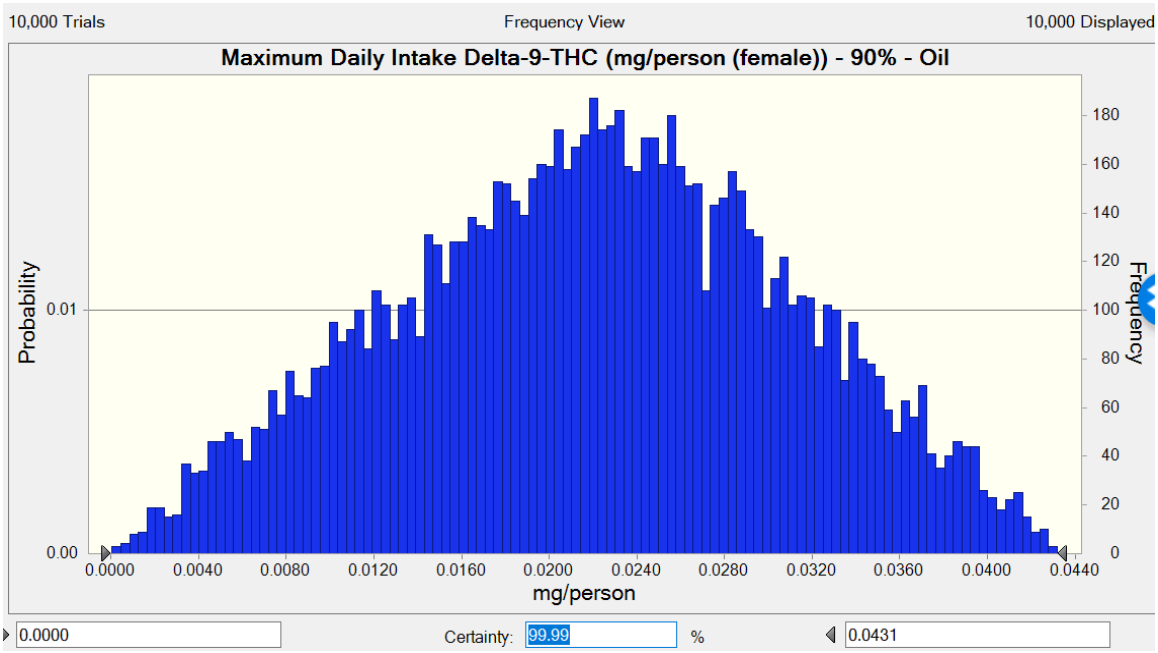
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0155 mg/person/day.

Figure 24 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile – Females Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0030
Mean	0.0061
Median	0.0056
Mode	---
Standard Deviation	0.0034
Variance	0.0000
Skewness	0.4921
Kurtosis	2.40
Coeff. of Variation	0.5487
Minimum	0.0001
Maximum	0.0155
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0021
20%	0.0030
30%	0.0038
40%	0.0047
50%	0.0056
60%	0.0066
70%	0.0079
80%	0.0093
90%	0.0111
100%	0.0155

Figure 25 Monte Carlo Model – Hemp Oil Consumption - THC Exposure at 90th Percentile – Males Age 2 to 5 Years



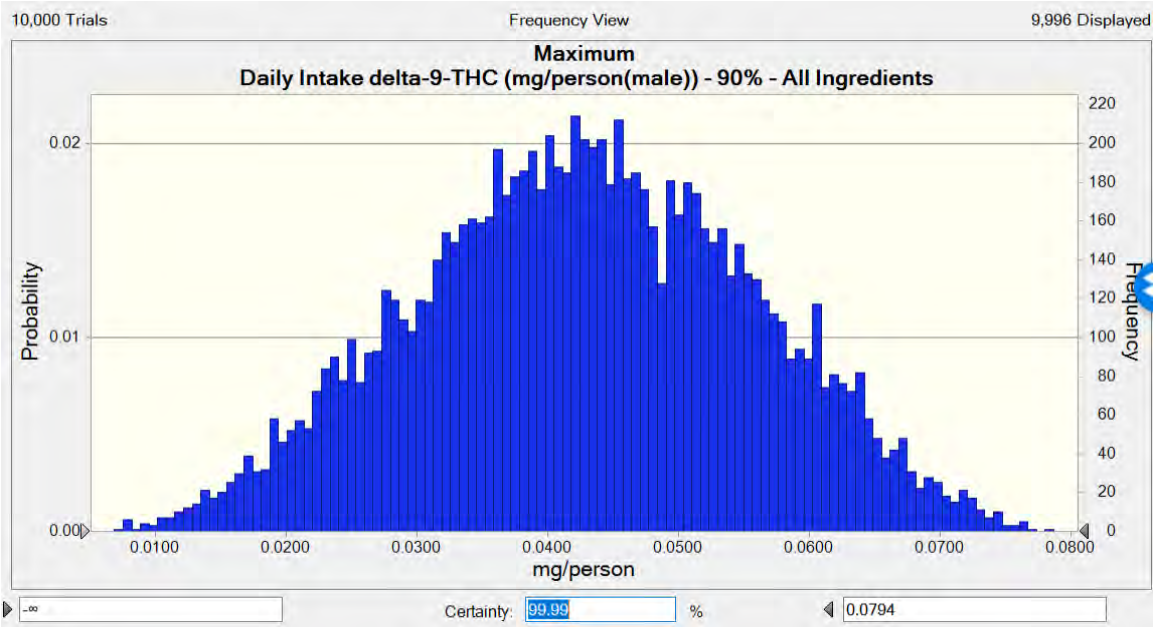
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0431 mg/person/day.

Figure 26 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile – Females Age 2 to 5 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0227
Mean	0.0220
Median	0.0222
Mode	---
Standard Deviation	0.0089
Variance	0.0001
Skewness	-0.0540
Kurtosis	2.41
Coeff. of Variation	0.4026
Minimum	0.0000
Maximum	0.0432
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0000
10%	0.0099
20%	0.0140
30%	0.0172
40%	0.0198
50%	0.0222
60%	0.0245
70%	0.0269
80%	0.0298
90%	0.0338
100%	0.0432

Figure 27 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years

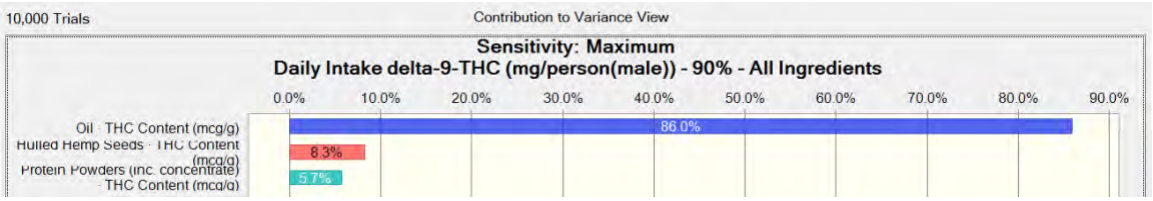


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.0794 mg/person/day.

Figure 28 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile – Males Age 6 to 11 Years

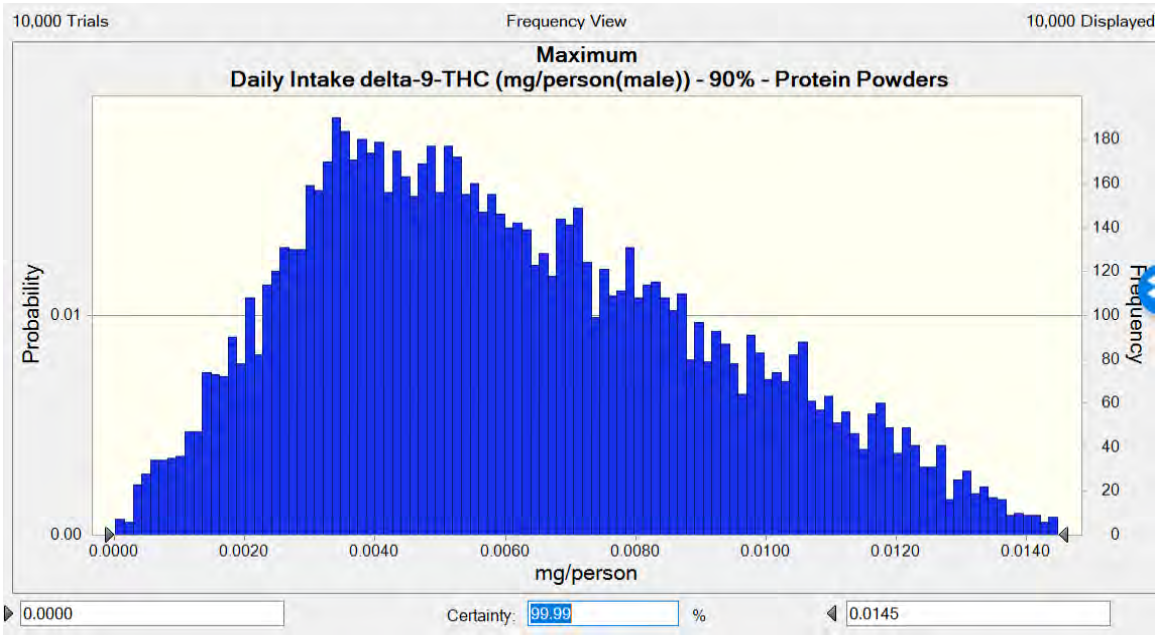
Statistic	Forecast values
Trials	10,000
Base Case	0.0373
Mean	0.0428
Median	0.0427
Mode	---
Standard Deviation	0.0128
Variance	0.0002
Skewness	-0.0172
Kurtosis	2.54
Coeff. of Variation	0.2998
Minimum	0.0048
Maximum	0.0804
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0048
10%	0.0256
20%	0.0316
30%	0.0358
40%	0.0393
50%	0.0427
60%	0.0461
70%	0.0500
80%	0.0542
90%	0.0599
100%	0.0804



Variability in THC within Hemp Oil makes up 86% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 8.3% and Protein Powders make up 5.7%.

Figure 29 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years



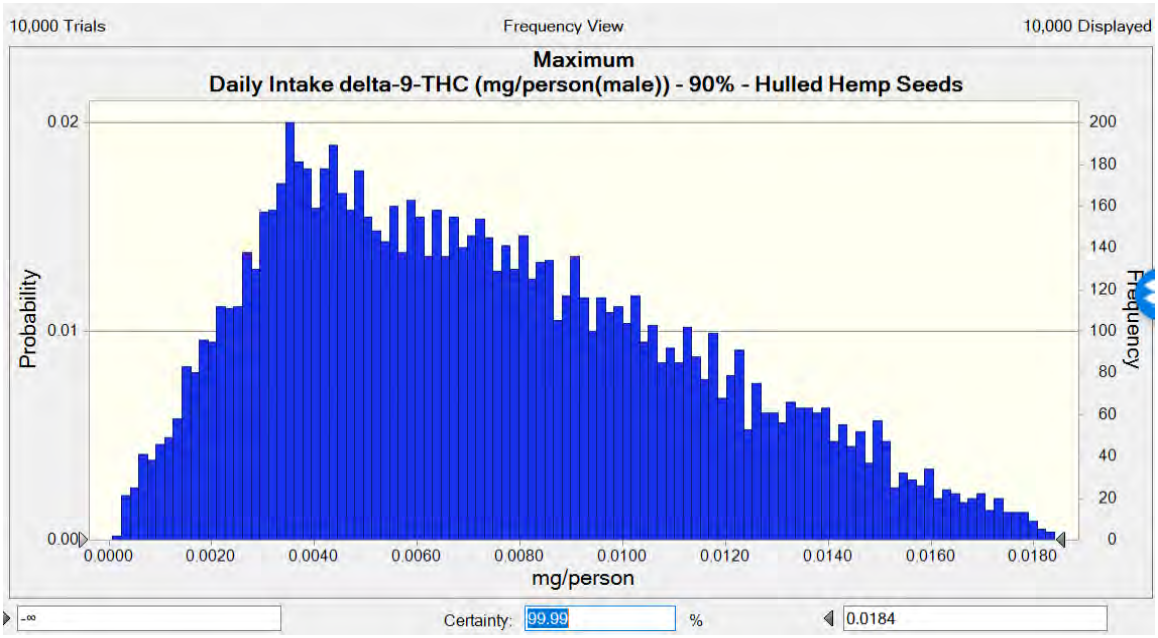
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0145 mg/person/day.

Figure 30 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0038
Mean	0.0061
Median	0.0057
Mode	---
Standard Deviation	0.0031
Variance	0.0000
Skewness	0.4176
Kurtosis	2.42
Coeff. of Variation	0.5008
Minimum	0.0000
Maximum	0.0145
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0000
10%	0.0024
20%	0.0033
30%	0.0041
40%	0.0049
50%	0.0057
60%	0.0067
70%	0.0077
80%	0.0089
90%	0.0106
100%	0.0145

Figure 31 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years



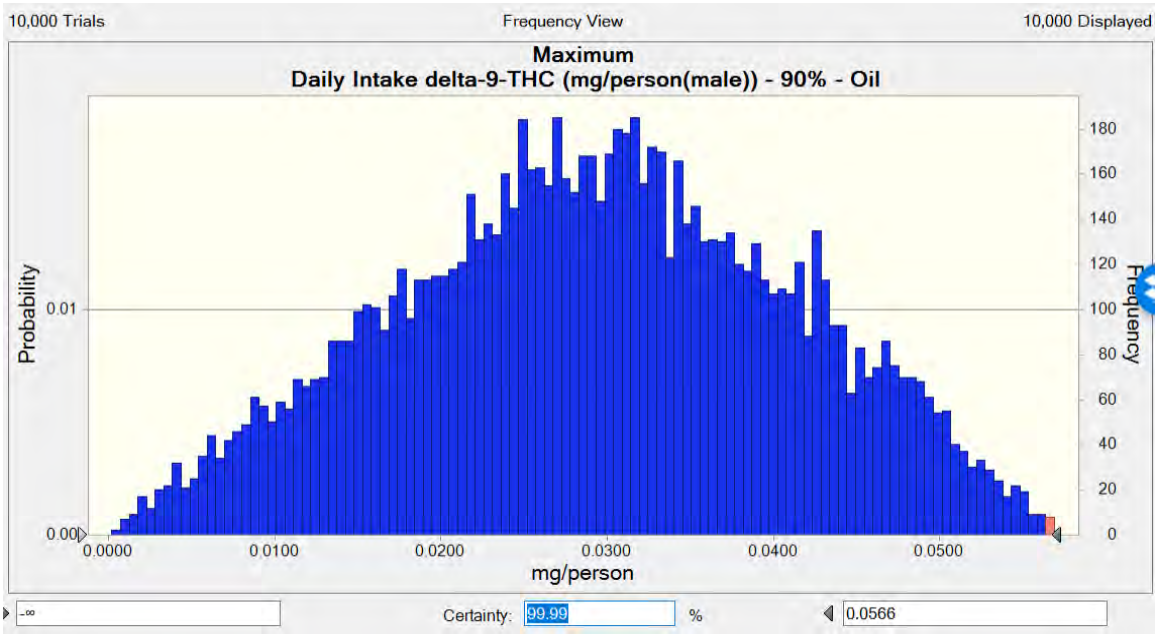
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0184 mg/person/day.

Figure 32 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0035
Mean	0.0074
Median	0.0069
Mode	---
Standard Deviation	0.0040
Variance	0.0000
Skewness	0.4788
Kurtosis	2.44
Coeff. of Variation	0.5382
Minimum	0.0001
Maximum	0.0184
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0026
20%	0.0037
30%	0.0046
40%	0.0057
50%	0.0069
60%	0.0080
70%	0.0094
80%	0.0110
90%	0.0132
100%	0.0184

Figure 33 Monte Carlo Model – Hemp Oil Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years



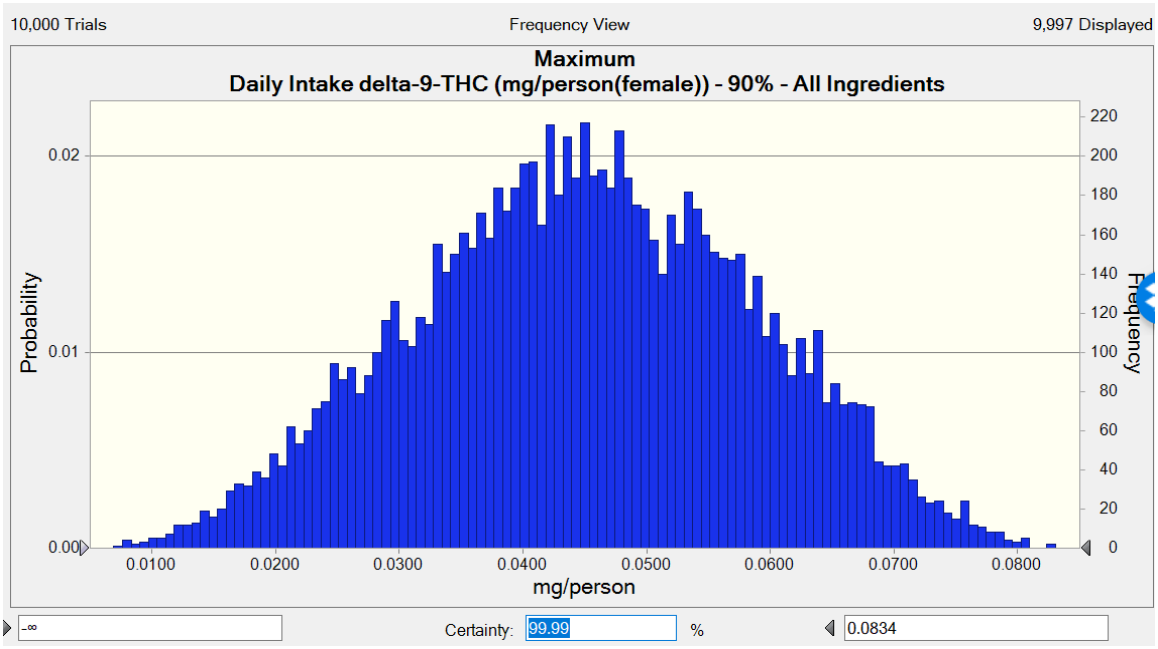
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0566 mg/person/day.

Figure 34 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0300
Mean	0.0293
Median	0.0294
Mode	---
Standard Deviation	0.0118
Variance	0.0001
Skewness	-0.0449
Kurtosis	2.38
Coeff. of Variation	0.4024
Minimum	0.0002
Maximum	0.0569
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0002
10%	0.0134
20%	0.0187
30%	0.0229
40%	0.0262
50%	0.0294
60%	0.0324
70%	0.0359
80%	0.0400
90%	0.0452
100%	0.0569

Figure 35 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure at 90th Percentile – Females Age 6 to 11 Years

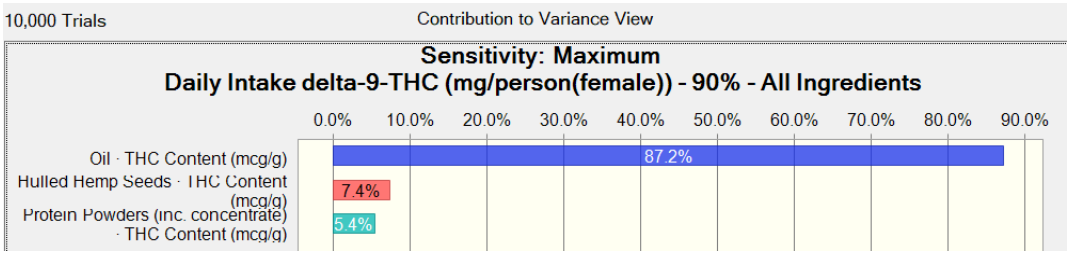


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 0.0834 mg/person/day.

Figure 36 Cumulative Hemp Consumption - THC Exposure Forecast at 90th Percentile – Females Age 6 to 11 Years

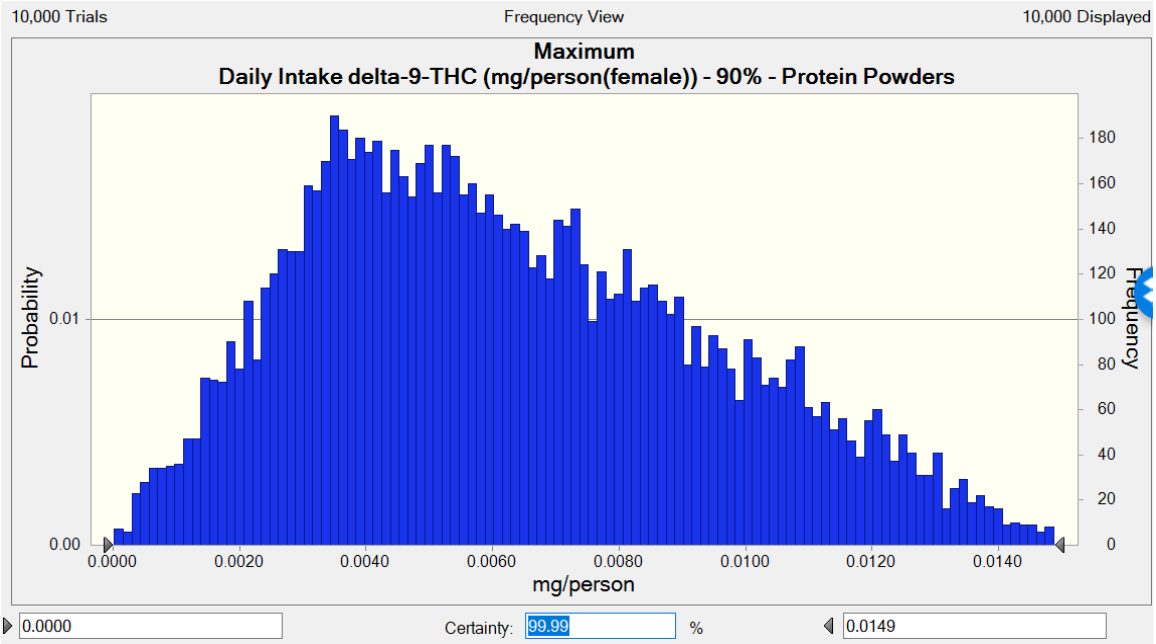
Statistic	Forecast values
Trials	10,000
Base Case	0.0395
Mean	0.0450
Median	0.0449
Mode	---
Standard Deviation	0.0136
Variance	0.0002
Skewness	-0.0203
Kurtosis	2.52
Coeff. of Variation	0.3023
Minimum	0.0050
Maximum	0.0843
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0050
10%	0.0267
20%	0.0331
30%	0.0376
40%	0.0414
50%	0.0449
60%	0.0485
70%	0.0527
80%	0.0571
90%	0.0631
100%	0.0843



Variability in THC within Hemp Oil makes up 87.2% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 7.4% and Protein Powders make up 5.4%

Figure 37 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure at 90th Percentile – Females Age 6 to 11 Years



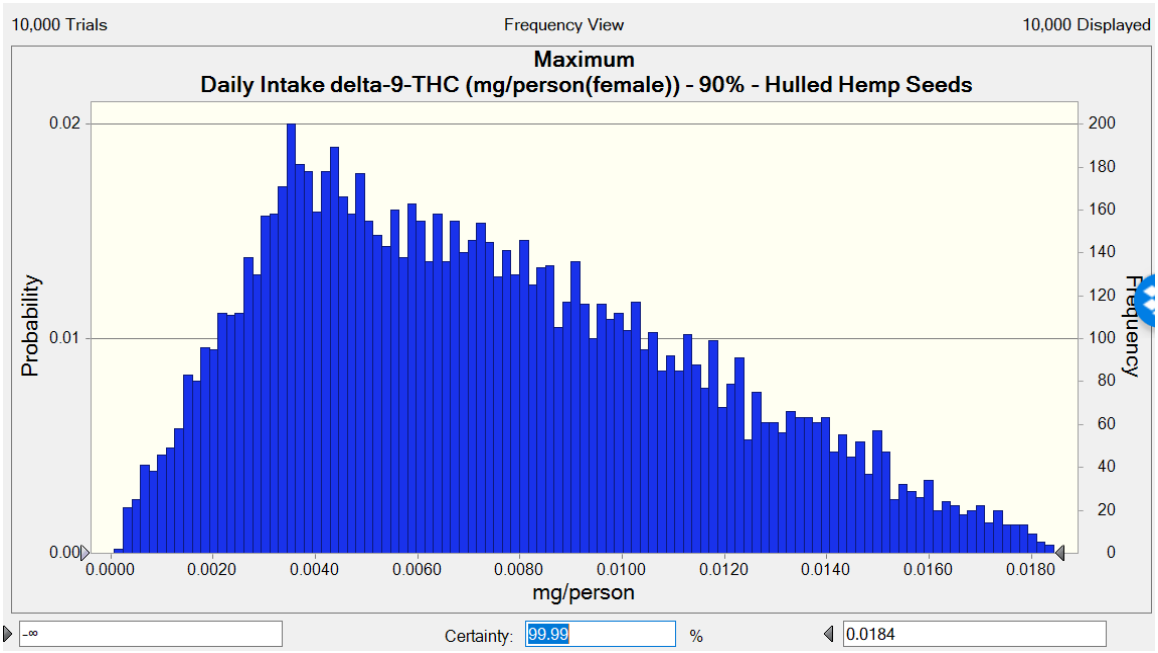
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.0149 mg/person/day.

Figure 38 Hemp Protein Powder Consumption - THC Exposure Forecast at 90th Percentile – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0039
Mean	0.0063
Median	0.0059
Mode	---
Standard Deviation	0.0032
Variance	0.0000
Skewness	0.4176
Kurtosis	2.42
Coeff. of Variation	0.5008
Minimum	0.0000
Maximum	0.0149
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0000
10%	0.0025
20%	0.0034
30%	0.0042
40%	0.0050
50%	0.0059
60%	0.0068
70%	0.0079
80%	0.0092
90%	0.0109
100%	0.0149

Figure 39 Monte Carlo Model – Hulled Hemp Seed Consumption - THC Exposure at 90th Percentile – Females Age 6 to 11 Years



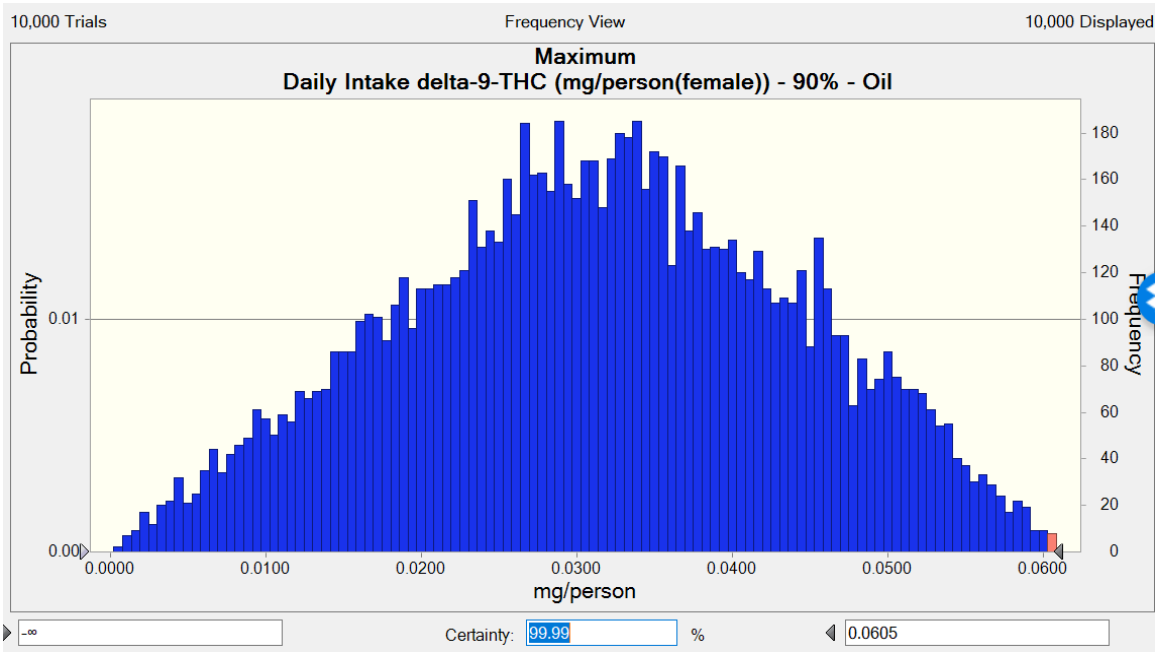
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.0184 mg/person/day.

Figure 40 Hulled Hemp Seed Consumption - THC Exposure Forecast at 90th Percentile – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0035
Mean	0.0074
Median	0.0069
Mode	---
Standard Deviation	0.0040
Variance	0.0000
Skewness	0.4788
Kurtosis	2.44
Coeff. of Variation	0.5382
Minimum	0.0001
Maximum	0.0184
Mean Std. Error	0.0000

Percentile	Forecast values
0%	0.0001
10%	0.0027
20%	0.0037
30%	0.0046
40%	0.0057
50%	0.0069
60%	0.0081
70%	0.0094
80%	0.0110
90%	0.0133
100%	0.0184

Figure 41 Monte Carlo Model – Hemp Oil Consumption - THC Exposure at 90th Percentile – Males Age 6 to 11 Years



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.0605 mg/person/day.

Figure 42 Hemp Oil Consumption - THC Exposure Forecast at 90th Percentile – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.0321
Mean	0.0313
Median	0.0314
Mode	---
Standard Deviation	0.0126
Variance	0.0002
Skewness	-0.0449
Kurtosis	2.38
Coeff. of Variation	0.4024
Minimum	0.0002
Maximum	0.0608
Mean Std. Error	0.0001

Percentile	Forecast values
0%	0.0002
10%	0.0143
20%	0.0200
30%	0.0244
40%	0.0280
50%	0.0314
60%	0.0346
70%	0.0383
80%	0.0428
90%	0.0483
100%	0.0608

List of References

Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci 1995, 56 (23–24):2097–2102.

Abrams RM, Cook CE, Davis KH, Niederreither K, Jaeger MJ, Szeto HH. Plasma delta-9-tetrahydrocannabinol in pregnant sheep and fetus after inhalation of smoke from a marijuana cigarette. Alcohol Drug Res 1985–1986, 6:361–369.

Ahmad GR, Ahmad N. Passive consumption of marijuana through milk: a low level chronic exposure to delta-9-tetrahydrocannabinol(THC). J Toxicol Clin Toxicol 1990;28(2):255–260.

Alaniz VI, Liss J, Metz TD, Stickrath E. Cannabinoid hyperemesis syndrome: a cause of refractory nausea and vomiting in pregnancy. Obstet Gynecol. 2015;125(6):1484-6.

Alt A, Reinhardt G. Positive cannabis results in urine and blood samples after consumption of hemp food products. J Anal Toxicol 1998;22:80–1.

Aluko, R.E. Chapter 7. Hemp Seed (*Cannabis sativa* L.) Proteins: Composition, Structure, Enzymatic Modification, and Functional or Bioactive Properties. In: Sustainable Protein Sources. New York: Elsevier, 2017. Pg 125. Print.

American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk Pediatrics 2001;108(3):776-789.

Angelova V., Ivanova R., Delibaltova V. Ivanov K. Bio-Accumulation and Distribution of Heavy Metals in Fibre Crops (Flax, Cottone, Hemp). Industrial Crops and Products. 2004;19:197-205.

Armentia A, Herrero M, Martin-Armentia B et al. Molecular diagnosis in cannabis allergy. J Allergy Clin Immunol Pract 2014;2:351–352.

Asero R, Mistrello G, Roncarolo D et al. A case of allergy to beer showing cross-reactivity between lipid transfer proteins. Ann Allergy Asthma Immunol 2001;87:65–67.

Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. Neurotoxicol Teratol 1990;12(2):161–168.

Astwood JD, Leach JN, Fuchs RL. Stability of food allergens to digestion in vitro. Nat Biotechnol. 1996;14(10):1269–73.

Bailey JR, Cunny HC, Paule MG, Slikker W Jr. Fetal disposition of delta 9-tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey. Toxicol Appl Pharmacol 1987, 90:315–321.

Baňas B, Beitzke, Carus B, Kerstin Iffland, Kruse D, Sarmento L, Sfrija D. Position paper of the European Industrial Hemp Association (EIHA) on: Reasonable guidance values for THC (Tetrahydrocannabinol) in food products. Nova-Institute, Hürth
(available online at www.eiha.org). 2017.

Bannon GA. What makes a food protein an allergen? Curr Allergy Asthma Rep. 2004;4(1):43–6.

Battista N, Sergi M, Montesano C, Napoletano S, Compagnone D, Maccarrone M. Analytical approaches for the determination of phytocannabinoids and endocannabinoids in human matrices. Drug Testing Analysis 2014;6:7–16.

Beal, J. E. et al. (1997): Efficacy and Safety of Dronabinol for Acquired Immunodeficiency Syndrome-Associated Anorexia, J. of Pain and Symptom Management Vol.14, No. 1, July 1997: 7-14.

Bergeria CL, Heil SH, Surveying Lactation Professionals Regarding Marijuana Use and Breastfeeding. Breastfeeding Medicine 2015;10(7):377-380.

Berlin CM, Briggs GG. Drugs and chemicals in human milk. Seminars in Fetal & Neonatal Medicine. 2005;10:149e159.

Beezhold DH, Hickey VL, Kostyal DA et al. Lipid transfer protein from Hevea brasiliensis (Hev b 12), a cross-reactive latex protein. Ann Allergy Asthma Immunol 2013;90:439–445.

Bortolin, Kristen & Ben-Shoshan, Moshe & Kalicinsky, Chrystyna & Lavine, Elana & Lejtenyi, Christine & Warrington, Richard & Pitt, Tracy. Case Series of 5 Patients with Anaphylaxis to Hemp Seed Ingestion. Journal of Allergy and Clinical Immunology. 137. AB239. 10.1016/j.jaci.2015.12.969.

Bosy TZ, Cole KA. Consumption and quantitation of delta-9-tetrahydrocannabinol in commercially available hemp seed oil products. J Anal Toxicol 2000;24:562–6.

Brenneisen R, Egli A, Elsohly MA, et al. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int J Clin Pharmacol Ther 1996; 34 (10): 446-52.

Brooks E, Gundersen DC, Flynn E, Brooks-Russell A, Bull S. The clinical implications of legalizing marijuana: Are physician and non-physician providers prepared? Addictive Behaviors 72 (2017) 1–7.

Burns L, Mattick RP, Cooke M. The use of record linkage to examine illicit drug use in pregnancy. Addiction 2006;101(6):873–882.

Callaway JC, Weeks RA, Raymon LP, Walls HC, Hearn WL. A positive THC urinalysis from hemp (Cannabis) seed oil. J Anal Toxicol 1997;21:319–20.

Carnes J, De Larramendi CH, Ferrer A et al. Recently introduced foods as new allergenic sources: sensitisation to Goji berries (Lycium barbarum). Food Chem 2013;137:130–135

Chesher, G.B. et al. (1990): The effects of orally administered delta-9-trahydrocannabinol in man on mood and performance measures: a dose-response study, Pharmacol. Biochem. Behav. 1990 Apr; 35(4):861-4.

Cone EJ, Johnson RF, Paul BD, Mell LD, Mitchell J. Marijuana-laced brownies: Behavioral effects, physiologic effects, and urinalysis in humans following ingestion. J Anal Toxicol 1988;12:169-175.

Costantino A, Schwartz RH, Kaplan P. Hemp oil ingestion causes positive urine tests for 9-tetrahydrocanabinol carboxylic acid. J Anal Toxicol 1997;21:482–5.

Crew S. Hemp Oil Canada Inc., Ste. Agathe, MB, Canada. Development of hemp food products and processes. Report prepared for the Agricultural Research and Development Initiative (ARDI), Winnipeg, MB, Canada, 2000).

Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. Neurotoxicol Teratol 2011;33(1):129–136.

Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy.
Arch Dis Child 1986, 61 (5):502–505.

De Larramendi CH, Carnes J, Garcia-Abujeta JL et al Sensitization and allergy to Cannabis sativa leaves in a population of tomato (Lycopersicon esculentum)-sensitized patients. Int Arch Allergy Immunol 2008:146:195–202

DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P et al. Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. Biol Psychiatry 2011;70(8):763–769.

Dotters-Katz SK, Smid MC, Manuck TA, Metz TD. Risk of neonatal and childhood morbidity among preterm infants exposed to marijuana. J Matern Fetal Neonatal Med. 2017;30(24):2933-2939.

Ebo D, Swerts S, Sabato V et al. New food allergies in a european non-mediterranean region: is Cannabis sativa to blame? Int Arch Allergy Immunol 2013;161:220–228.

Ebo DG, Stevens WJ. IgE-mediated food allergy—extensive review of the literature. Acta Clin Belg 2001;56:234–247

Egger M, Hauser M, Mari A et al. The role of lipid transfer proteins in allergic diseases. Curr Allergy Asthma Rep 2010;10:326–335

El Marroun H, Hudziak JJ, Tiemeier H, Creemers H, Steegers EA, Jaddoe VW et al. Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. Drug Alcohol Depend 2011;118(2-3):470–474.

El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatry 2009;48(12):1173–1181.

ElSohly MA, deWit H, Wachtel SR, Feng S, Murphy TP. Delta-9- tetrahydrocannabivarin as a marker for the ingestion of marijuana versus Marinol: results of a clinical study. J Anal Toxicol 2001; 25:565–71.

Escuder-Vieco D, Garcia-Algar Ó, Joya X, Marchei E, Pichini S, Pacifici R, Pallás-Alonso CR. Breast Milk and Hair Testing to Detect Illegal Drugs, Nicotine, and Caffeine in Donors to a Human Milk Bank. Journal of Human Lactation 2016;32(3):542-5.

Escuder-Vieco D, Garcia-Algar Ó, Pichini S, Pacifici R, García-Lara NR, Pallás-Alonso CR. Validation of a screening questionnaire for a human milk bank to determine the presence of illegal drugs, nicotine, and caffeine. J Pediatr. 2014;164(4):811-4.

Faber, Margriet & Van Gasse, Athina & Sabato, Vito & Hagendorens, Margo & Bridts, Chris & Clerck, Luc & Ebo, Didier. Marihuana Allergy: Beyond the Joint. Journal of investigational allergology & clinical immunology. 2015a;25. 70-2.

Faber MA, Sabato V, Bridts CH et al. Clinical relevance of the lipid transfer protein Hev b 12 of Hevea brasiliensis. J Allergy Clin Immunol 2015b;pii: S0091-6749(14)03747-6.

Foeller ME, Lyell DJ. Marijuana Use in Pregnancy: Concerns in an Evolving Era. J Midwifery Womens Health 2017;62:363–367.

Food Standards Australia New Zealand Supporting Document 1 Updated Estimates of Dietary Exposure to 9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) from Foods Containing Low THC Hemp Seed (at Approval) – Proposal P1042 Low THC Hemp Seeds as Food Executive Summary

Fortner N, Fogerson R, Lindman D, Iversen T, Armbruster D. Marijuana-positive urine test results from consumption of hemp seeds in food products. J Anal Toxicol 1997;21:476–81.

Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 1999;21(5):513–525.

Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2003;25(4):427–436.

Frytak S, Moertel CG, Rubin J. Metabolic studies of delta-9-tetrahydrocannabinol in cancer patients. Cancer Treat Rep 1984; 68 (12): 1427-31.

Fu T, Abbott UR, Hatzos C. Digestibility of food allergens and nonallergenic proteins in simulated gastric fluid and simulated intestinal fluid-a comparative study. J Agric Food Chem. 2002;50(24):7154–60.

Garry A, Rigourd V, Amirouche A, Fauroux V, Aubry S, Serreau R. Cannabis and Breastfeeding. J Toxicol. 2009:596149.

Gaylor DW. The use of Haber's law in standard setting and risk assessment. Toxicology 2000, 149 (1):17–19.

Gamboa P, Sanchez-Monge R, Sanz ML et al. Sensitization to Cannabis sativa caused by a novel allergenic lipid transfer protein, Can s 3. J Allergy Clin Immunol 2007;120:1459–1460

Gleason KA, Birnbaum SG, Shukla A, Ghose S. Susceptibility of the adolescent brain to cannabinoids: long-term hippocampal effects and relevance to schizophrenia. Transl Psychiatry 2012;2:e199.

Godding V, Bonnier C, Fiasse L, Michel M, Longueville E, Lebecque P et al. Does in utero exposure to heavy maternal smoking induce nicotine withdrawal symptoms in neonates? Pediatr Res 2004;55(4):645–651.

Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. Neurotoxicol Teratol 2000;22(3):325–336.

Goldschmidt L, Richardson GA, Willford JA, Severtson SG, Day NL. School achievement in 14-year-old youths prenatally exposed to marijuana. Neurotoxicol Teratol 2012; 34(1):161–167.

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

Gustafson RA, Levine B, Stout PR, Klette KL, George MP, Moolchan ET and Huestis MA. Urinary cannabinoid detection times following controlled oral administration of delta-9-tetrahydrocannabinol to humans. *Clinical Chemistry*, 2003 Jul; 49(7):1114-1124.

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.

Hale TW. Medications and Mother's Milk, 15th ed. Plano, TX: Hale Publishing, 2012.

Health Canada Industrial Hemp Regulations (http://laws-lois.justice.gc.ca/PDF/SOR-98-156.pdf); Health Canada Industrial Hemp Technical Manual (https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/hc-ps/alt_formats/hecs-sesc/pdf/pubs/precurs/hemp-indus-chanvre/tech-man/hemp-tech-manual-eng.pdf).

Herman RA, Woolhiser MM, Ladics GS, et al. Stability of a set of allergens and non-allergens in simulated gastric fluid. Int J Food Sci Nutr. 2007;58(2):125–41.

Hollister LE, Gillespie HK, Ohlsson A, et al. Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? J Clin Pharmacol 1981; 21 (8-9 Suppl.):171S-7S.

Hotham N, Hotham E. Drugs in breastfeeding. Australian Prescriber. 2015;38;5:156-160.

House JD, Neufeld J, Leson G. Evaluating the quality of protein from hemp seed (Cannabis sativa L.) products through the use of the protein digestibility-corrected amino acid score method. Journal of Agriculture and Food Chemistry. 2010;58(22):11801-11807.

Howlett AC. Pharmacology of cannabinoid receptors. Annu Rev Pharmacol Toxicol 1995, 35:607–
634.

Huestis MA, Abulseoud O, Sempio C, Andersson M, Newmeyer MN, (unpublished urine data following smoked, vaporized and oral administration of 50.6 mg THC).

Huestis MA, Mazzoni I, Rabin O. Cannabis in Sport: Anti-Doping Perspective. Sports Med. 2011 Nov; 1; 41(11): 949-966.

Hutchings DE, Martin BR, Gamagaris Z, Miller N, Fico T. Plasma concentrations of delta-9-tetrahydrocannabinol in dams and fetuses following acute or multiple prenatal dosing in rats. Life Sci 1989, 44 (11):697–701.

Indorato F, Liberto A, Ledda C, Romano G, Barbera N. The therapeutic use of cannabinoids: Forensic aspects. Forensic Science International 2016;265:200–203.

Interpretation of listing of “tetrahydrocannabinol” in Schedule I [Interpretive Rule]. Federal Register 2001;195:51530–44.

Jansson LM, Bunik M, Bogen DL. Lactation and the Marijuana-Using Mother Breastfeeding Medicine 2015;10(6):1.

Jarlenski M, Zank J, Tarr J, Chang JC. Public health messages about perinatal marijuana use in an evolving policy context. Substance Abuse. 2017;38(1):48-54.

Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, Abdel-Latif ME, Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology 2014;34:417–424.

Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, Abdel-Latif ME, Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology 2014;34(6):417-24.

Jegou S, Douliez JP, Molle D et al. Purification and structural characterization of LTP1 polypeptides from beer. J Agric Food Chem 2000;48:5023–5029.

Jenkins JA, Breiteneder H, Mills EN. Evolutionary distance from human homologs reflects allergenicity of animal food proteins. J Allergy Clin Immunol. 2007;120(6):1399–405.

Kacew S Adverse effects of drugs and chemicals in breast milk on the nursing infant. J Clin Pharmacol. 1993;33(3):213-21.

Khare M, Taylor AH, Konje JC, Bell SC. Delta 9-tetrahydrocannabinol inhibits cytotrophoblast cell proliferation & modulates gene transcription. Mol Hum Reprod 2006;12(5):321–333.

Klonoff-Cohen H, Lam-Kruglick P. Maternal and paternal recreational drug use and sudden infant death syndrome. Arch Pediatr Adolesc Med 2001;155(7):765–770.

Larramendi CH, Lopez-Matas MA, Ferrer A et al. Prevalence of sensitization to Cannabis sativa. Lipid-transfer and thaumatin-like proteins are relevant allergens. Int Arch Allergy Immunol 2013;162:115–122

Law B, Mason PA, Moffat AC, et al. Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin. J Pharm Pharmacol 1984; 36 (5):289-94.

Lehmann T, Sager F, Brenneisen R. Excretion of cannabinoids in urine after ingestion of cannabis seed oil. J Anal Toxicol 1997;21:373–5.

Leson G, Pless P, Grotenhermen F, Kalant H, ElSohly MA. Evaluating the impact of hemp food consumption on workplace drug tests. J Anal Toxicol 2001;25:691–8.

Liston J. Breastfeeding and the use of recreational drugs – alcohol, caffeine, nicotine and marijuana. Breastfeeding Review 1998;6(2):27-30.

Manitoba Agriculture, Province of Manitoba. Agriculture Mycotoxins. https://www.gov.mb.ca/agriculture/food-safety/at-the-food-processor/print,mycotoxins.html. Accessed 12/18/2017.

Marchei E, Escuder D, Pallas CR, Garcia-Algar O, Gómez A, Friguls B, Pellegrini M, Pichini S. Simultaneous analysis of frequently used licit and illicit psychoactive drugs in breast milk by liquid chromatography tandem mass spectrometry. J Pharm Biomed Anal. 2011;55(2):309-16.

Martin BR, Dewey WL, Harris LS, Beckner JS. 3H-delta 9-tetrahydrocannabinol distribution in pregnant dogs and their fetuses. Res Commun Chem Pathol Pharmacol 1977, 17:457–470.

Masilamani, M, Commins, S, ShrefflerW. Determinants of Food Allergy. Immunol. Allergy Clin. North Am.2012;32(1)11-33.

Matsuda LA. Molecular aspects of cannabinoid receptors. Crit Rev Neurobiol 1997, 11:143–166.

Metz TD, Allshouse AA, Hogue CJ, Goldenberg RL, Dudley DJ, Varner MW, Conway DL, Saade GR, Silver RM. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. Am J Obstet Gynecol. 2017;217(4):478.e1-478.

Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. Am J Obstet Gynecol. 2015;213(6):761-78.

Mills E, Madsen C, Shewry P. Food allergens of plant origin–their molecular and evolutionary relationships. Trends in Food Science and Technology. 2003;(14):145–56.

Mölleken and H. Husmann. Cannabinoids in seed extracts of Cannabis sativa cultivars. J. Int. Hemp Assoc. 4: 1, 76–79 (1997).

Mourh J, Rowe H. Marijuana and Breastfeeding: Applicability of the Current Literature to Clinical Practice. Breastfeed Med. Epub 2017 Sep 5.

Murphy LL, Munoz RM, Adrian BA, Villanu´ a MA. Function of cannabinoid receptors in the neuroendocrine regulation of hormone secretion. Neurobiol Dis 1998;5(6PtB):432–446.

Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M et al. Metabolic effects of chronic cannabis smoking. Diabetes Care 2013;36(8):2415–2422.

Nayak AP, Green BJ, Sussman G et al. Characterization of Cannabis sativa allergens. Ann Allergy Asthma Immunol 2013;111:32–37

Neugebauer R, Kline J, Stein Z, Shrout P, Warburton D, Susser M. Association of stressful life events with chromosomally normal spontaneous abortion. Am J Epidemiol 1996;143:588–596.

Newton ER & Hale TW. Drugs in Breast Milk. Clinical Obstetrics and Gynecology. 2015;58(4):868–884.

Odani S and Odani SIolation and Primary Structure of a Methionine and Cysteoine Richseed protein of *Cannabis sativa*. Bioscience, Biotechnology and Biochemistry. 1998. 62:650-654.

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther. 1980 Sep;28(3):409-16.

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma levels of delta 9-tetrahydrocannabinol after intravenous, oral, and smoke administration. NIDA Res Monogr. 1981 Feb;34:250-6.

Ohlsson A, Agurell S, Lindgren JE, Gillespie HK, Hollister LE. Pharmacokinetic studies of delta-1-tetrahydrocannabinol in man. In Pharmacokinetics and pharmacodynamics of psychoactive drugs. Barnett G and Chiang CN (Eds). 1985 Mosby Yearbook, Inc. Volume 4 Pages 75-92.

Perez-Reyes M, Lipton MA, Timmons MC, Wall ME, Brine DR, Davis KH. Pharmacology of orally administered delta-9-tetrahydrocannabinol. Clinical Pharmacology Therapeutics 1973;14:48-55.

Perez-Reyes M, Wall ME. Presence of delta 9-tetrahydrocannabinol in human milk. N Engl J Med 1982; 307(13): 819–820.

Pertwee R. Cannabinoid Receptors. Academic Press, London, United Kingdom, 1995.

Petro, D. J., Ellenberger, C. Jr. (1981): Treatment of human spasticity with delta 9-tetrahydrocannabinol, J Clin Pharmacol. 1981 Aug-Sep;21(8-9 Suppl): 413S-416S.

Quadri MI, Nasserullah . Hb Bart's levels in cord blood in Hb H disease: follow-up of cases with "probable" Hb H disease. Ann Saudi Med 2001;21:357–358

Reece-Stremtan S, Marinelli KA. The Academy of Breastfeeding Medicine. ABM Clinical Protocol #21: Guidelines for Breastfeeding and Substance Use or Substance Use Disorder, Revised 2015. Breastfeeding Medicine 2015:10(3);135-141.

Reisner SH, Eisenberg NH, Stahl B, Hauser GJ. Maternal medications and breast-feeding. Dev Pharmacol Ther. 1983;6(5):285-304.

Research, Health Protection Branch, Health Canada. Industrial hemp technical manual: TPP-BDS-004 – Basic method for determination of THC in hempseed oil, 1992.

Rihs HP, Rueff F, Lundberg M et al. Relevance of the recombinant lipid transfer protein of Hevea brasiliensis: IgE-binding reactivity in fruit-allergic adults. Ann Allergy Asthma Immunol 2006;97:643–649.

Sadler BM, Wall ME, Perez-Reyes M. The pharmacokinetics of delta-9 -tetrahydrocannabinol after simultaneous intravenous and oral administration. In: Agurell S, Dewey WL, Willette RE, eds. The cannabinoids: chemical, pharmacologic, and therapeutic aspects. New York: Academic Press, 1984:227–38.

Sharma P, Murthy P, Bharath MMS. Chemistry, Metabolism, and Toxicology of Cannabis: Clinical Implications. Iran J Psychiatry 2012;7(4):149-156.

Sipsma A, Divney AA, Magriples U, Hansen N, Gordon D, Kershaw T. Breastfeeding Intentions Among Pregnant Adolescents and Young Adults and Their Partners. Breastfeeding Medicine 2013;8(4):374-380.
adolescents: Initiation, duration, and exclusivity. J Adolesc Health. 2013;53(3):394–400.

Sipsma A, Magriples U, Divney AA, Gordon D, Gabzdyl,E, Kershaw T. Breastfeeding behavior among
Warner TD, Roussos-Ross D, Behnke M. It's Not Your Mother's Marijuana: Effects on Maternal-Fetal Health and the Developing Child. Clin Perinatol. 2014;41(4):877–894.

Smithers LG, Lynch JW, Yang S, Dahhou M, Kramer MS. Impact of neonatal growth on IQ and behavior at early school age. Pediatrics 2013;132(1):e53–e60.

Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. Neurotoxicol Teratol 2006;28(2):286–295.

Sporkert F, Pragst F, Ploner CJ, Tschirch A, Stadelmann AM. Pharmacokinetic investigations and delta-9-tetrahydrocannabinol and its metabolites after single administration of 10 mg Marinol in attendance of a psychiatric study. The Annual Meeting of The International Association of Forensic Toxicologists, Prague, Czech Republic. 2001.

Stadtmauer G, Beyer K, Bardina L et al. Anaphylaxis to ingestion of hempseed (Cannabis sativa). J Allergy Clin Immunol 2003;112:216–217

Strasser, F. et al. (2006): Comparison of Orally Administered Cannabis Extract and Delta-9-Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome: A Multicenter, Phase III, Randomized, Double-Blind,
Placebo-Controlled Clinical Trial From the Cannabis-In-Cachexia-Study-Group, J. Clin. Oncology, 24 (21), July 20 (2006): 3394-3400.

Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray.
Eur J Clin Pharmacol. 2013 May;69(5):1135-47. doi: 10.1007/s00228-012-1441-0. Epub 2012 Nov 22.

Struempler RE, Nelson G, Urry FM. A positive cannabinoids workplace drug test following the ingestion of commercially available hemp seed oil. J Anal Toxicol 1997;21:283–5.

The American College of Obstetricians and Gynecologists. Committee on Obstetric Practice. Marijuana Use During Pregnancy and Lactation. 2015;126(1):234-8.

Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. AIDS Res Hum Retroviruses 1997; 13 (4):305-15.

Van Gasse AL et al. L'allergie au cannabis: bien plus qu'un voyage stupéfiant. Rev Fr Allergol. doi:10.1016/j.reval.2014.01.022

Van Loon LC (1999) Occurrence and properties of plant pathogenesis-related proteins. In: Datta SK, Muthukrishnan S (eds) Pathogenesis-related proteins in plants. CRC Press LLC, Boca Raton, pp 1–19

Wall ME, Perez-Reyes M. The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man. J Clin Pharmacol 1981; 21 (8-9 Suppl.): 178S-89S.

Wall ME, Sadler BM, Brine D, et al. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol, in men and women. Clin Pharmacol Ther 1983; 34 (3): 352-63.

Wang GS Pediatric Concerns Due to Expanded Cannabis Use: Unintended Consequences of Legalization. J. Med. Toxicol. 2017 Mar;13(1):99-105.

Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. In utero marijuana exposure associated with abnormal amygdala dopamine D2 gene expression in the human fetus. Biol Psychiatry 2004;56(12):909–915.

Warner TD, Roussos-Ross D, Behnke. It's not your mother's marijuana: effects on maternal-fetal health and the developing child. Clin Perinatol. 2014;41(4):877-94.

Zajicek, J. P.et al. (2003): Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised
placebo-controlled trial, Lancet 2003 Nov. 8; 362(9395): 1517-26.

Zajicek; J. P. et al. (2005): Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow-up, J. Neurol. Neurosurg. Psychiatry 2005; 76: 1664-69.

Appendix
Expert Review & Resume

Appendix: Expert Review and Commentary on Literature and Expert Resume

Huestis & Smith Toxicology, LLC
683 Shore Road
Severna Park, MD 21146
Phone (410) 544-2456
huestis.smithtoxicologyllc@gmail.com

Professor Dr. Dr. (h.c.) Marilyn A. Huestis
President

Michael L. Smith, PhD, F-ABFT
Vice President

December 30, 2017

Virginia Savoie
Ryan Bracken
Fresh Hemp Foods
Manitoba, Canada

Huestis report on the general safety, potential for a positive urine cannabinoid test, and transfer of ∆9-tetrahydrocannabinol (THC) into human breast milk and infants during breastfeeding after oral THC ingestion

Dear Ms. Savoie and Mr. Bracken,
I conducted a thorough literature search for data related to ingestion of THC-containing foods and liquids, and also on the transfer of THC from the mother to the infant during breastfeeding. I addressed general safety data, possible positive urine cannabinoid test data, and infant THC-exposure from breastfeeding based on oral THC-exposure data from estimated combined daily ingestion of 4 Fresh Hemp Foods products, hulled hemp seed, hemp protein powder, hemp protein concentrate and hemp oil. The mean combined THC dose from all 4 Fresh Hemp Foods Products is estimated at 0.0968 mg/day, and the 90th percentile THC dose is estimated at 0.1938 mg/day.

Executive Summary

Ingestion of a mean daily amount of 0.0968 mg THC from intake of all 4 Fresh Hemp Foods products is too low to produce THC's psychoactive, cognitive and physiological effects. Even at the highly conservative 90th percentile THC dose of 0.1938 mg/day, no effects should be produced based on numerous controlled THC oral administration studies.

Based on 11-nor-9-carboxy-THC (THCCOOH) urine concentrations following controlled oral THC administration, it is highly unlikely that a positive urine cannabinoid test (≥15 µg/L) would be produced following ingestion of a mean total of 0.0968 mg THC from consumption of all four Fresh Hemp Foods hemp products. Based on the studies of Bosy and Cole 2000, Leson et al 2001, and Gustafson et al 2004. In the Bosy and Cole 2000 study, there were no positive urine specimens ≥15 µg/L following the 0.10, 0.17, 0.32, and 0.55 mg THC/d for 7 daily doses. The 0.54 mg and 1.8 mg THC/d doses produced a small number of positive urine specimens ≥15 µg/L. Leson et al 2001 administered four daily THC doses, 0.09, 0.19, 0.29, and 0.45 mg THC in hemp oil for 10 consecutive days each. No positive urine samples were obtained. An individual who ingested a daily THC dose of

0.6 mg produced the highest urine THCCOOH concentration of 5.2 µg/L, well below the 15 µg/L confirmation cutoff of federal drug testing programs. Gustafson et al 2003 determined urinary THCCOOH excretion by GC/MS analysis in 4381 urine specimens collected before, during, and after 5 oral daily 0.39, 0.47, 7.5, and 14.8 mg THC/day to 7 participants. All urine voids were collected over the 10-week study. At the two lowest doses that were 2-5 times higher than the mean or 90th percentile total THC dose if all 4 Fresh Hemp Foods hemp products were ingested, a mean of 2.7 urine samples per subject over 10 days were positive; maximum THC concentrations ranged from 5.4-38.2 µg/L by GC-MS. Therefore, it is highly unlikely that ingestion of all 4 hemp food products would produce a positive urine cannabinoid test.

Based on studies administering known quantities of oral THC and blood/plasma/serum concentrations, we can estimate the blood concentrations that would result from intake of 0.0968 (mean daily mg THC from 4 Fresh Hemp Foods, Ltd products) to 0.1938 (90th percentile daily mg THC from 4 Fresh Hemp Foods, Ltd. Products) mg oral THC. Stott et al 2013 administered two Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses (total 5.4 mg THC) to adults. There are no infant THC administration data. The mean plasma Cmax was <1.2 µg/L THC and <2 µg/L 11-OH-THC. The mean daily amount (0.0968 mg) and 90th percentile (0.1938) of THC exposure from ingesting all 4 Fresh Hemp Foods, Ltd. Products is 55- and 27-fold lower than this exposure, respectively. These data would estimate the plasma Cmax in the breastfeeding mother assuming a 0.0968 mg daily dose as <0.02 µg/L THC and <0.04 µg/L 11-OH-THC, and if the highly conservative 0.1938 mg THC dose is assumed, plasma Cmax in the mother of <0.04 µg/L THC and <0.07 µg/L 11-OH-THC.

In a single maternal plasma and breast milk pair, the THC plasma to breast milk ratio was 8.4. Based on this ratio and the mean-90th percentile maternal plasma THC concentrations, the maximum THC concentration in the breast milk would be between 0.17-0.34 µg/L. There are no data on 11-OH-THC breast milk/plasma ratios, but if one assumed a similar distribution for 11-OH-THC into breast milk, maximum 11-OH-THC concentrations in breast milk would be 0.34-0.59 µg/L.

The estimate of daily breast milk intake is 150 mL/kg/day. Our estimates of maximum THC concentration in breast milk and daily intake would suggest THC intake of 0.05 – 0.09 µg/kg/day THC. As 11-OH-THC is equipotent to THC, assuming the breast milk to plasma ratio is also 8.4, the total active cannabinoids exposure for the infant is estimated to be <0.08-0.14 µg/kg/day. Gustafson et al 2014 administered 0.39 and 0.47 mg THC per day for 5 days, resulting in non-detectable THC concentrations in human plasma. These doses are 2-4 times the dose a breastfeeding mother would consume with all 4 hemp products. This low-level exposure is not expected to produce adverse developmental outcomes in the infant whose mother consumes the maximum amount of all 4 Fresh Hemp Foods, Ltd. per day.

Furthermore, Stott et al 2013 also administered the 5.4 mg THC/day dose for 9 consecutive days and showed that THC and 11-OH-THC concentrations did not accumulate over time. This also demonstrates that daily use of the 4 Fresh Hemp Foods,

Ltd doses that are much lower than the 5.4 mg Stott dose should not accumulate. At birth, a 10 lb. (4.55 kg) infant would receive about 0.14-0.23 µg/day THC and 0.23-0.41 µg/day 11-OH-THC. The total active cannabinoid dose would be approximately 0.37-0.64 µg/day. The oral bioavailability of THC and 11-OH-THC is low, estimated to be 6-12% in adults; bioavailability could be different in the infant although first pass metabolism would still reduce active cannabinoid exposure. This low concentration of active cannabinoids should not produce adverse developmental effects.

General Safety Data following oral THC doses (blood/serum/plasma data)

Early reports on blood/plasma/serum THC concentrations after oral THC administration were primarily related to the abuse potential and detection of use after this route of administration. There are many more reports of blood/plasma/serum concentrations than urine concentrations. These data are useful for determining the bioavailability of the oral route of administration (especially when evaluating transfer of drugs to breast milk in breastfeeding women) and for comparison of oral doses to the Fresh Hemp Foods Ltd. daily oral doses. Later pharmacokinetic studies of oral THC administrations were focused more on the therapeutic uses of THC, for instance in AIDS wasting disease or other indication. There also are data from Sativex oromucosal studies of THC and cannabidiol (CBD) that are relevant but could have slightly higher bioavailability due to bypass of first metabolism for some portion of the administered dose. There were a number of studies evaluating whether or not hemp oil or hemp food products produce positive urine cannabinoid tests. Although many studies administered known quantities of THC in hemp products and quantified 11-nor-9-carboxy-THC (THCCOOH) in urine by GC-MS or LC-MS/MS, some did not quantify the administered THC dose, and therefore, are less informative.

Factors determining individual response to oral cannabis administration include the dose of total THC and THC precursor acid, the degree of conversion of THC precursor acid to THC prior to ingestion, the rate of absorption of THC from the gastrointestinal system that is influenced by the vehicle used, and degree of first-pass THC metabolism. Perez-Reyes et al. 1973 reported that the speed and degree of THC absorption is greatly influenced by the administration vehicle, and based on cumulative urinary excretion data over 72 h, THC absorption rate was affected by the nature of the vehicle, but not the total amount of absorption.

Perez Reyes et al, 1973 administered 35 mg oral THC (containing 50 µc tritium THC) in five different vehicles (ethanol, sesame oil, 5.5% sodium glycholate, 5.5% sodium glycholate and ethanol, and Tween-80) to 40 individuals after fasting, showing that absorption speed and bioavailability was highly dependent upon the vehicle utilized. Plasma, urine and feces were analyzed over 72 h. Total radioactivity of thin layer chromatography bands were used to quantify results. The vehicles providing the highest concentrations in plasma were from highest to lowest bioavailability 5.5% sodium glycholate, sesame oil, Tween-80, ethanol and combined glycholate and ethanol, with peak concentrations between 1-2 h. In addition, with the same vehicle and dose, a large 4.8 inter-individual variability in peak plasma THC concentrations was observed. The

radioactivity represented total THC and metabolite concentrations. The percentage of total radioactivity excreted in the urine in 24 h ranged from 14.1 to 17%, in 48 h from 3.1-4.7%, and in 72 h 1.2 to 2.2%. Total percent of the 35-mg dose excreted in the urine in the sodium glycholate vehicle was 21.9% or 7.7 mg in 72 h. A greater percentage (53.0±5.0% or 18.6 mg) of the 35-mg dose was excreted in the feces over 72 h in 3 subjects receiving the drug in sodium glycholate. For these same 3 subjects, urinary excretion with this vehicle was 22.4±4.3%. The urinary percentage was for all THC and metabolites in the urine, rather than only the THCCOOH metabolite, the current urine target. Separation of the different cannabinoid analytes in urine was not possible with thin layer chromatography. This was one of the only studies that determined THC percentages excreted in urine and feces, and established that about 22% of the dose is excreted in urine and more than 50% in feces.

Ohlsson et al 1980, 1981, Wall and Perez 1981, Hollister et al, 1981 and Ohlsson et al 1985 administered 20 mg oral THC in a chocolate cookie, 10 mg smoked THC, and 5 mg intravenous (IV) THC in 95% ethanol over 2 min to 11 males. Plasma was analyzed from 3 to 240 min (4 h) for smoked and IV doses and from 30 to 360 min (6 h) after oral dosing. THC was analyzed by GC-MS. Maximum plasma THC concentrations (Cmax) after the 20-mg oral dose were 4.4-11 µg/L with time of peak concentration (Tmax) between 60 and 300 min. Compared to the IV dose, bioavailability of the oral dose was 6±3% (4-12%), with slow and irregular absorption. This is one of the only studies administering THC by both the oral and IV routes enabling determination of oral THC bioavailability estimated to be 6-12% in most studies.

THC and Metabolites in Human Plasma Following Oral Administration of 20 mg THC by GC-MS (Wall and Perez-Reyes 1981)

Time minutes	THC µg/L	11-OH-THC µg/L	THCCOOH µg/L
45	0.8±0.4	1.0±0.5	6±4
60	3.8±2.9	3.4±1.6	14±9
75	4.7±3.4	3.7±1.7	22±11
90	5.7±3.5	4.7±1.5	30±10
105	4.9±2.6	5.8±1.7	41±14
120	4.3±0.6	7.2±1.8	54±18
135	7.9±3.6	8.3±1.3	49±6
150	6.6±3.5	8.4±2.1	64±13
165	6.4±3.8	8.3±2.0	65±16
180	7.1±4.9	8.5±2.0	62±17
360	9.3±3.5	8.8±1.7	46±11
1440	1.3±0.4	1.1±0.5	21±8

Wall et al 1983 intravenously administered THC laced with tritium-labeled THC over 15 to 25 min with a mean of 2.2 mg THC to six women and 4.0 mg to 6 men.

Time h	Plasma concentrations		
Women n=6	THC µg/L	11-OH-THC	THCCOOH
0.5	4.8 ± 4.6	1.4±1.3	4.1 ± 3.9
0.75	9.0 ± 8.4	3.8 ± 4.2	15 ± 10
1	7.7 ± 5.9	3.7 ± 2.8	27 ± 18
1.25	8.4 ± 5.3	4.2 ± 2.6	41 ± 21
1.5	9.1 ± 4.7	5.5 ± 2.6	48 ± 28
1.75	9.4 ± 4.5	5.9 ± 2.8	62 ± 28
2	7.4 ± 2.2	5.3 ± 1.6	68 ± 20
2.5	7.2 ± 3.8	4.5 ± 2.-S	64 ± 10
3	6.8 ± 3.1	4.4 ± 2.9	51 ± 14
4	6.2 ± 3.2	2.5 ± 1.7	48 ± 8.0
6	5·.4 ± 4.2	1.6 ± 0.9	38 ± 8.6
8	3.8 ± 2.3	1.2 ± 0.5	39 ± 13
12	3.2 ± l.9	0.9 ± 0.5	28 ± 6.4
24	l.9 ± 0.6	0.7 ± 0.5	21 ± 6.4
30	l.5 ± 1.0	-	15 ± 2.6
48	0.9 ± 0.5	-	12 ± 7.4
72	0.8 ± 0.9	-	8.4 ± 5.3
Men n=6			
0.75	9.1±4.0	2.7 ±0.8	2.7±0.8
1	8.0 ± 7.3	3.4 ± 3.1	23 ± 12
1.25	11 ± 9.3	3.8 ± l.9	47 ± 22
1.5	11 ± 6.6	5.2 ± 1.7	66 ± 32
1.75	13 ± 7.5	5.1 ± 2.1	82 ± 39
2	13 ± 9.1	6.6 ± 3.4	89 ± 40
2.5	14 ± 9.7	5.9 ± 3.0	80 ± 39
3	11 ± 8.2	5.6 ± 3.2	82 ± 37
4	11 ± 6.6	5.6 ± 3.6	82 ± 36
6	10 ± 6.0	4.0 ± 1.8	62 ± 31
8	8.4 ± 4.8	3.4 ± 2.3	51 ± 21
11-12	6.4 ± 3.9	1.9 ± 1.3	37 ± 18
24	3.3 ± 2.4	1.3 ± 1.2	29 ± 14
30	3.2 ± 2.1	0.8 ± 0.6	23 ± 8
48	2.2 ± 1.7	0.6 ± 0.5	14 ± 6
72	1.0 ± 0.6	-	8 ± 5

Four subjects received 20 mg THC in a meat sandwich with plasma collected for up to 5 days and analyzed by high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA) (Law et al 1984).

Mean (n=4) plasma cannabinoid concentrations after 20 mg oral THC (Law et al 1984).

Time h	THC µg/L	THCCOOH µg/L	THCCOOH-glucuronide µg/L
1	1.5±0.2	6.6±2.1	3.4±1.1
2	3.9±1.1	23±6.3	26±3.4
4	6.9±1.4	38±10	107±16
6	3.0±0.9	29±4.7	99±8.3
8	1.8±0.4	24±5.6	80±10
24	0.5±0.1	14±2.5	31±1.3
48	0.2±0.1	6±2.0	17±3.9
72	0.1±0.1	3.3±0.9	9.1±2.7

In a controlled cannabinoid administration study of THC-containing hemp oils and dronabinol, the pharmacokinetics and pharmacodynamics of oral THC were evaluated (Goodwin et al 2005). Up to 14.8 mg THC was ingested by six volunteers each day in three divided doses with meals for five consecutive days. There was a 10-day washout phase between each of the five dosing sessions. THC was quantified in plasma by GC/MS. THC and 11-OH-THC were not detected in plasma following the two lowest doses of 0.39 and 0.47 mg/day THC, while peak plasma concentrations of <6.5 µg/L THC, <5.6 µg/L 11-OH-THC, and <43.0 µg/L THCCOOH were achieved after the two highest THC doses of 7.5 and 14.8 mg/day. This is important because the mean daily THC dose for all four Fresh Hemp Foods products combined is 0.0968 mg. Interestingly, THCCOOH concentrations after the 7.5 mg/day dronabinol dose were greater than or equal to those of the high potency 14.8 mg/day hemp oil dose. Two possible reasons for the higher THC bioavailability in dronabinol are greater protection from degradation in the acidic environment of the stomach due to encapsulation and improved absorption of THC from the sesame oil formulation. Analytes were detectable in plasma 1.5 h after initiating dosing with the 7.5 mg THC/day regimen and 4.5 h after starting the 14.8 mg THC/day sessions. THCCOOH was detected 1.5 h after the first dose, except for the 0.47mg THC/d session, which required 4.5 h for concentrations to reach the LOQ 0.5 µg/L. Plasma THCCOOH concentrations peaked at 3.1 µg/mL during dosing with the low-dose hemp oils. Plasma THC and 11-OH-THC concentrations were negative for all participants at all doses within 15.5 h after the last THC dose. Plasma THCCOOH persisted (LOQ 1 µg/L) for at least 39.5 hours after the end of dosing and at much higher concentrations (up to 43.0 ng/mL). After oral and sublingual administration of THC, THC-containing food products, or cannabis-based extracts, THC and 11-OH-THC concentrations were much lower than after smoked administration.

Since 2013, Nabiximols, an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD in each 100 µL spray was approved in Italy for the treatment of Multiple Sclerosis.
Low blood concentrations were produced by Nabiximols administration, more than 10 times lower than the blood concentrations known to produce psychotropic effects (Indorato et al 2016). Whole venous blood for THC analysis was collected immediately before and at fixed intervals after Nabiximols administration (15, 30 and 60 min). THC and CBD were detected in the blood a few minutes after administration. Fifteen min after administration of 2.7 mg THC (a single puff), THC blood concentrations ranged from 0.2

to 1.2 µg/L. THC Cmax was 1.3 µg/L 30 min after Nabiximol intake. Blood Cmax ranges between 2.5 and 2.9 µg/L after administration of 10.8 mg of THC (four puffs of Nabiximol). Blood samples from 20 patients treated with Nabiximols for short (28 days) or long-term treatment (60 or 90 days) were analyzed. Treatment consisted of one puff 6 times/day of 100 µL containing 2.7 mg of THC and 2.5 mg CBD. 20 patients provided informed consent to participate in short (less than 28 days) or long-term 90 days treatment. The THC blood concentrations of all samples ranged from not detected to 1.3 µg/L with a lower limit of quantification (LOQ) of 0.20 µg/L. Oromucosal administration has a better bioavailability than oral administration due to a lower first pass effect.

THC blood concentrations at 0, 15, 30 and 60 min after the administration of one puff of Nabiximols. 2.7 mg THC, 2.5 mg CBD (Indorato et al 2016)

	THC µg/L 0	THC µg/L 15 min	THC µg/L 30 min	THC µg/L 60 min
N	20	20	20	20
Pos Samples	0	20	18	14
Mean ± SD	<LOQ 0.2	0.47 ± 0.27	0.52 ± 0.30	0.22 ± 0.11

THC blood concentrations at 0, 15, 30 and 60 min after the administration of 1 puff of 2.7 mg THC 6 times a day (Nabiximols) for short term (<28 days) or long term (>28 days) therapy.

	THC µg/L 0	THC µg/L 15 min	THC µg/L 30 min	THC µg/L 60 min
N	20	20	20	20
Short therapy	<LOQ	0.34 ± 0.16	0.26 ± 0.12	0.14 ± 0.07
Long therapy	<LOQ	0.55 ± 0.30	0.69 ± 0.26	0.27 ± 0.10

The following studies contain only blood/plasma/serum data without simultaneous urine results. These data are valuable because they provide information on THC bioavailability after oral THC in food products, including data needed to estimate THC exposure in breastfeeding infants.

Frytak et al 1984 dosed 6 cancer patients with 15 mg oral THC during 5-Fluoruracil and semustine chemotherapy for gastrointestinal malignancy. Median peak plasma concentrations were 3.7 for THC, 6.7 for 11-OH-THC and 62.5 µg/L THCCOOH at 2, 2 and 3 h, respectively. Three additional patients received multiple 15 mg THC doses 2 h prior to chemotherapy and 2 and 8 h after chemotherapy. Peak plasma concentrations (µg/L) ranged from 3.6 - 6.3 for THC, 8.6-15.6 for 11-OH-THC and 98.2-203 for THCCOOH at median times of 1, 2 and 8 h after the first dose. THC and 11-OH-THC concentrations did not appear to accumulate, but THCCOOH plasma concentrations were higher after multiple doses than after the single dose 24 h after dosing. There was erratic gastrointestinal absorption in these patients who had variable gastrointestinal function.

Timpone et al 1997 conducted a randomized, open-label, multicenter study to assess the safety and pharmacokinetics of dronabinol (Marinol) tables for treatment of HIV wasting

syndrome. Twenty patients received dronabinol 2.5 mg twice/day and had a mean peak THC plasma concentration of 2.0 µg/L (0.6 – 12.5) at a mean of 2.1 h (0.7 -8.3). 11-OH-THC mean peak plasma concentration was 4.6 µg/L (0.5 - 37.5) at 2.1 h (0.5 - 8). The LOQ for THC and 11-OH-THC were 0.1 µg/L. Serious adverse events assessed as related to dronabinol included CNS events including confusion, anxiety, emotional lability, euphoria, and hallucinations.

Sporkert et al 2001 investigated the pharmacokinetics of a single 10 mg THC dose in 10 females and 7 males before and up to 24 h after dosing. Plasma THC Cmax µg/L was 4.7 ± 3.0 and Tmax was 60 - 120 min. Mean bioavailability was 7.0±3.0% (2-14%). There was no correlation of THC concentrations and age, sex, body weight and body height.

Maximum plasma concentrations (µg/L) of THC, 11-OH-THC and THCCOOH after 10 mg THC (Sporkert et al 2001).

Subject	THC µg/L Cmax	THC h Tmax	11-OH-THC µg L Cmax	11-OH-THC Tmax h	THCCOOH µg/L Cmax	THCCOOH µg/L Tmax
1	7.3	2	12.8	2	33.2	2
2	3.1	1	4.0	2	45.8	2
3	4.2	1	3.5	1	38.9	2
4	2.5	1	2.1	2	24.7	3
5	2.2	1	1.7	1	29.6	2
6	6.6	2	3.5	3	23.0	3
7	4.6	1	5.6	1	43.5	1
8	4.4	1	1.6	2	24.2	2
9	4.3	1	1.9	1	25.6	1
10	3.1	1	1.7	1	19.2	1
11	12.7	1	4.6	1	14.5	2
12	1.3	1	1.3	1	21.7	2
13	9.8	1	9.4	1	66.8	2
14	3.2	2	5.2	2	45.5	2
15	1.5	1	1.5	2	23.5	3
16	2.6	1	2.8	2	24.6	2
17	5.5	3	5.3	2	38.8	2

Stott et al 2013 administered single Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses as 2 (5.4 mg THC), 4 (10.8 mg THC), 8 (21.6 mg THC) sprays, or multiple sprays (2, 4 or 8 sprays) for 9 consecutive days. With increasing single and multiple doses of THC/CBD spray, the mean plasma Cmax increased for all analytes. There was evidence of dose-proportionality in the single but not the multiple dosing data. The bioavailability of THC was greater than CBD at single and multiple doses, and there was no evidence of accumulation for any analyte with multiple dosing. Inter-subject variability ranged from moderate to high for all pharmacokinetic parameters in this study. Plasma Tmax was longest for all analytes in the 8-spray group, but was similar in the 2 and 4 spray groups. The mean Cmax values (<12 µg/L) recorded in this study were well below those reported

in patients who smoked/inhaled cannabis, which is associated with significant psychoactivity. There was also no evidence of accumulation on repeated dosing.

Since 2013, Nabiximols, an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD in each 100 µL spray was approved in Italy for the treatment of Multiple Sclerosis. Low blood concentrations were produced by Nabiximols administration, more than 10 times lower than the blood concentrations known to produce psychotropic effects (Indorato et al 2016). Blood THC Cmax concentrations after a single 2.7 mg THC oromucosal spray were 0.52 ± 0.30 µg/L. Blood samples from 20 patients treated with Nabiximols for short (28 days) or long-term treatment (60 or 90 days) were analyzed. Treatment consisted of one puff 6 times/day of 100 µL containing 2.7 mg of THC and 2.5 mg CBD. THC blood concentrations of all samples ranged from not detected to 1.3 µg/L with a lower limit of quantification (LOQ) of 0.20 µg/L. These doses of THC are higher than the daily 0.1938 mg THC limit (90^{th} percentile) for Fresh Hemp Foods, Ltd, indicating that consumers would not have psychotropic effects following the mean combined daily THC dose for the 4 hemp products.

In Timpone et al 1997, 20 HIV patients received 2.5 mg Marinol (synthetic THC) twice/day for treatment of HIV wasting syndrome. Mean peak THC plasma concentration was 2.0 µg/L (0.6 – 12.5) at a mean of 2.1 h (0.7 -8.3). 11-OH-THC mean peak plasma concentration was 4.6 µg/L (0.5 - 37.5) at 2.1 h (0.5 - 8). Serious adverse events assessed as related to dronabinol included CNS events of confusion, anxiety, emotional lability, euphoria, and hallucinations.

Stott et al, 2013 administered single Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses as 2 (5.4 mg THC), 4 (10.8 mg THC), 8 (21.6 mg THC) sprays, or multiple sprays (2, 4 or 8 sprays) for 9 consecutive days. With increasing single and multiple doses of THC/CBD spray, the mean plasma Cmax increased for all analytes. There was evidence of dose-proportionality in the single but not the multiple dosing data. There was no evidence of accumulation for any analyte with multiple dosing. The mean Cmax values (<12 µg/L) recorded in this study were well below those reported in patients who smoked/inhaled cannabis, which is associated with significant psychoactivity. In terms of safety, THC/CBD spray was well tolerated in all phases of the study, with no serious AEs or withdrawals due to AEs. All but three AEs were of mild severity, with three of moderate severity. All AEs resolved without sequelae, but most were considered to be related to the study treatment. The most common AEs were dizziness and somnolence. As expected, there was a direct relationship between increasing doses of THC/CBD spray and the frequency of AEs, with all subjects receiving eight sprays of THC/CBD spray experiencing at least one AE.

Treatment-emergent adverse events with a subject incidence of 1 or more (Stott et al 2013)

	2 sprays 5.0 mg THC n = 6		4 sprays 10.0 mg THC n = 12		8 sprays 20.0 mg THC n = 7	
Primary system organ class	# Events	# (%) patients	# Events	# (%) patients	# Events	# (%) patients
Single dose						
Nervous system disorders						
Dizziness	0	0	0	0	3	3 (43)
Headache	2	2 (33)	0	0	1	1 (14)
Somnolence	1	1 (17)	1	1 (8)	1	1 (14)
Disturbance in attention	0	0	0	0	2	2 (29)
Psychiatric disorders						
Disorientation	0	0	0	0	2	2 (29)
Euphoric mood	0	0	1	1 (8)	1	1 (14)
General disorders & administration site conditions						
Feeling abnormal	0	0	1	1 (8)	1	1 (14)
Multiple doses						
Nervous system disorders						
Dizziness	0	0	1	1 (8)	4	3 (50)
Headache	2	2 (33)	1	1 (8)	1	1 (17)
Somnolence	0	0	4	3 (25)	3	3 (50)
General disorders and administration site conditions						
Feeling abnormal	0	0	1	1 (8)	2	1 (17)
Gastrointestinal disorders						
Dry mouth	1	1 (17)	1	1 (8)	2	2 (33)
Psychiatric disorders						
Abnormal dreams	2	1 (17)	1	1 (8)	0	0
Euphoric mood	0	0	4	2 (17)	1	1 (17)

There are few data on THC effects following low oral doses. The Stott data above, are most relevant to the Fresh Hemp Foods comparison for the single 2 spray 5.0 mg THC dose, although this dose is more than 52 times the size of the mean daily THC dose for 4 Fresh Hemp Foods products. In addition, low daily THC doses did not appear to accumulate in blood. These data illustrate that the number of adverse events are low and of minor or moderate severity at much higher THC doses.

Law et al 1984 administered 5.0-5.2 mg THC in a meat sandwich to 5 subjects. None of the subjects reported any psychological effects or any reaction associated with cannabis administration. One of 5 subjects had poor pallor and felt faint.

Brenneisen et al 1996 administered 10 mg Marinol (synthetic THC) to Patient A and 15 mg THC to Patient B for four consecutive days. Peak THC concentrations varied from 2.1-6.9 µg/L in patient A and 2.7-16.9 µg/L in patient B. There were improvements in mobility, walking ability and rigidity in both patients, one patient showed no change in concentration and mood, while the other patient showed mixed changes at the higher 15 mg oral dose.

Bosy & Cole 2000 administered 7 daily doses of hemp oils containing 0.10 and 1.8 mg THC/day. No psychoactive effects were experienced by any of the subjects during the course of the experiment.

Can consumption of mean and 90% percentile THC amounts of all Fresh Hemp Foods products in a single day produce a positive urine cannabinoid test ≥15 µg THCCOOH/L?

The goal was to determine if oral ingestion of combined daily mean or 90% percentile THC amounts of all Fresh Hemp Foods products (hulled hemp seed, hemp protein powder, hemp protein concentrate and hemp oil) could produce positive urine cannabinoid tests. We determined the mean daily THC amounts in each product and daily amounts of THC in all products combined. Fresh Hemp Foods Ltd provided the data on mean and 90th percentile total daily amounts of the 4 products. The THC calculations are based on the new Fresh Hemp Foods, Ltd standards for ≤4 µg THC/g as verified by the Quality Department for hulled hemp seed, hemp protein powder and hemp protein concentrate. The Fresh Hemp Foods, Ltd standard for hemp oil will be the same as the Canadian Industrial Hemp Regulations requirement of ≤10 µg THC/g product. These values were used in determining daily THC intake if the recommended dose of all products were consumed each day. We determined the mean total daily THC amount as 0.0968 mg THC and the total amount based on the 90th percentile of ingestion of all 4 hemp food products as 0.1938 mg.

We reviewed all clinical studies that administered THC by the oral route and measured urine cannabinoids, preferably by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS), although many reports include immunoassay screening data, generally at a 50 µg/L cutoff concentration. The number of studies that included both the dose of THC administered and urine concentrations were limited; therefore, I also surveyed most of the studies administering known quantities of THC and blood/plasma/serum concentrations to help estimate the blood concentrations that would result from intake of 0.0968 (mean daily mg THC from 4 Fresh Hemp Foods, Ltd products) to 0.1938 (90th percentile daily mg THC from 4 Fresh Hemp Foods, Ltd. Products) mg oral THC.

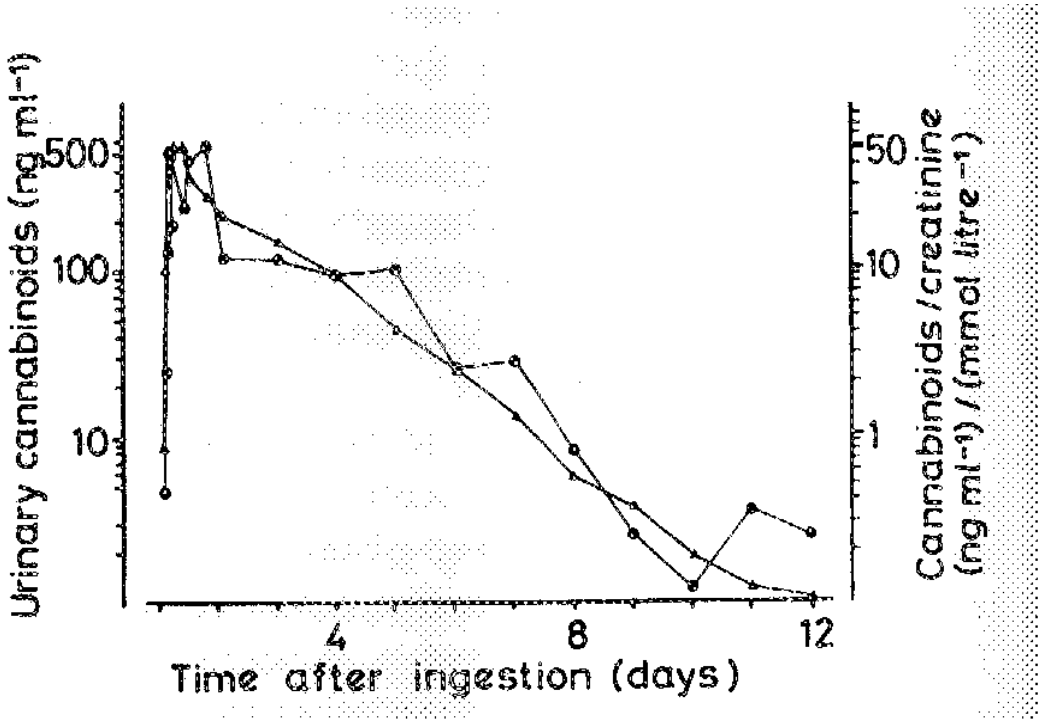
Following oral dosing with 5 mg THC, urinary cannabinoids peaked at 112-210 µg/L at 8-10 h after ingestion by RIA, with positive urine tests for 7 days (Law et al 1984). After the

20-mg dose, urine concentrations increased to 185-1063 µg/L cross reacting cannabinoids 6 h after ingestion, with positive results for 12 days. This was the first report of the importance of the THCCOOH-glucuronide metabolite in plasma and urine and of its instability in urine at higher pH's and after 12 and 90-day room temperature storage. Urine concentrations determined by RIA as compared to GC-MS or LC-MS/MS will be elevated because the radioactivity is for multiple analytes rather than just THCCOOH.

Sadler et al 1984 simultaneously administered 0.141 mg/123 µCi ^{3}H THC intravenous tracer and 20 mg oral THC in sesame oil to 6 males to determine oral THC bioavailability. After 72 h, 21±1% of the tracer was in the urine and 40±2% was in the feces. A low bioavailability of 13% was found due to an extensive first pass effect in the liver.

Five males ingested cannabis-laced brownies in a double-blind crossover study to evaluate urinary cannabinoid excretion (Cone et al. 1988). On three occasions, each subject consumed two brownies containing 1.6 g of cannabis plant material. Placebo cannabis (0% THC) was mixed with 2.8% THC cannabis plant material to produce doses of 0, 22.4 mg THC, and 44.8 mg THC. All urine specimens were collected throughout the study. Urinalyses by EMIT® daub. assay (20 µg/L cutoff) and Abuscreen® RIA for cannabinoids (5 µg/L cutoff) and GC/MS (LOQ 2 µg/L) for THCCOOH indicated that cannabinoid-related metabolites were excreted over a period of 3 to 14 days.

GC/MS Urine THCCOOH results µg/L for one subject following ingestion of 22.2 and 44.4 mg THC in a brownie (left y axis) and µg/mmol THCCOOH creatinine (Cone et al 1988).



GC-MS produced overall results similar to the assay profiles of cannabinoid excretion by EMIT 20 Assay and Abu screen® RIA. With a 5 µg/L THCCOOH cutoff, mean times ± SE to the first negative urine sample were 94.5 ± 26.8 h and 114 ± 33.8 h and mean times ± SE to last positive urine sample were 149 ± 36.2 h and 156 ± 49 h after administration of the 22.4 mg and 44.8 doses, respectively. Individual peak concentrations of total THCCOOH varied from 108 to 325 µg/L (mean± SE= 180 ± 39) and 177 to 436 µg/L (mean± SE= 312 ± 48) after the low and high doses, respectively. An estimation of the cumulative dose of total THCCOOH excreted in urine after both cannabis doses was 1.3% of the administered dose. Excretion of detectable amounts of cannabinoid metabolites occurred for approximately 6 days (range 3-11 days) after 22.4 mg THC, and for slightly longer periods of time (range 3-14.5 days) after the 44.8 mg dose.

Brenneisen et al 1996 dosed 2 participants with organic spasticity with multiple oral THC doses every 24 h and determined plasma concentrations by GC-MS. After four daily 10 mg THC oral doses, THC plasma concentrations of Subject A were detectable from 1 to 8 h with a mean peak concentration of 3.5 ± 2.3 µg/L (2.1 - 6.9 µg/L) at 2.0 ± 1.3 h (range

Table IV. GC/MS and Abuscreen RIA Assay of Specimens from Subjects Who Ingested Marijuana-Laced Brownies

Subject	Dose equivalent (cigarettes)	GC/MS* Time to first negative (h)	GC/MS* Time to last positive (h)	GC/MS* Peak concn (ng/ml)	GC/MS* Time to peak concn (h)	GC/MS* THCCOOH Cumulative dose (0/a)	RIA** Time to first negative (h)	RIA** Time to last positive (h)
H	1	73.1	131.8	156	9.4	1.21	93.3	159.5
	2	85.7	110.8	436	14.0	1.43	113.3	127.5
K	1	53.5	74.3	121	7.4	1.16	53.5	74.3
	2	56.2	100.2	234	5.5	1.07	117.1	132.0
L	1	84.4	243.0	191	21.3	1.83	86.1	144.3
	2	106.0	147.2	392	21.2	1.70	130.2	217.5
M	1	199.5	223.5	325	12.6	1.74	199.5	247.4
	2	245.6	346.8	323	25.4	1.52	245.6	346.8
N	1	61.8	72.2	108	6.5	0.63	61.8	76.1
	2	77.7	76.6	177	7.5	0.80	77.7	127.5
Mean±SE	1	94.5±26.8	149.0±36.2	180±39	11.4±2.7	1.31 ±0.22	98.8±26.2	140.3±31.9
	2	114.2±33.8	156.3±49	312±48	14.7 ±3.8	1.30±0.16	136.8±28.6	190.3±42.7

"Cutoff = 5 ng/ml THCCOOH.
•• Cutoff = 10 ng/ml THCCOOH equivalents.

1 to 4 h). Mean peak THCCOOH concentration for Subject A was 79.6 µg/L at 5.5 ± 3.0 h (2 - 8 h). Subject B received four daily oral doses of 15 mg THC with a mean peak THC concentration of 7.2 µg/L (2.7 to 16.9 µg/L) THC at 5.0 ± 3.5 h (range 2 - 8 h). Mean peak THCCOOH concentration for Subject B was 185 ± 42.0 µg/L (146 – 244 µg/L) at 6.5 h (2 - 8 h). There was little THC accumulation with multiple doses of the 10 and 15 mg THC. This is important for our understanding of the excretion of daily Fresh Hemp Foods Ltd h products that entail a much lower mean daily dose of 0.0938 mg THC. Concentrations were less than the THC LOQ (0.5 µg/L) between 4 and 24 h.

Several studies reported that ingestion of hemp oil causes positive urine tests for cannabinoids. Lehmann et al. 1997 reported THC concentrations of 3–1500 µg/g in 25 hemp oil samples. Six individuals ingested one or two tablespoons of hemp oil containing 1500 µg/g THC (11 and 22 g of hemp oil, or 16.5 – 33 mg THC). Positive urine specimens were observed with a 50 µg/L cannabinoid immunoassay cutoff and a 15 µg/L THCCOOH GC/MS cutoff for up to 6 days. Morning urine samples were collected for 6 days and screened by immunoassay, and THCCOOH determined by GC-MS. Urine samples were positive for cannabinoids up to 6 days with the Abuscreen OnLine immunoassay with a 50 µg/L cutoff and THCCOOH concentrations were 5 to 431 µg/L. All subjects reported THC-specific psychotropic effects. All urine samples were positive at a 15µg/L GC-MS cutoff from 12 to 60 h and at 84 h except for 1 participant. Two participants' urine samples were greater than 15 µg/L for 132 h after the single dose.

Table II. Urine THCCOOH Concentrations (ng/ml) after Ingestion of 11 g and 22 g of Cannabis Seed Oil as Analyzed by GC-MS*

Time after in2estion (h)	Subjects					
	1	2	3	4	5	6
0	0	0	0	0	0	0
12	298	378	280	81	431	281
36	154	186	121	104	242	263
60	65	71	77	54	57	213
84	35	30	78	10	49	69
108	12	13	31	13	12	46
132	11	9	24	6	5	30

•subjects 1-3 ingested 22 g cannabis seed oil, and subjects 4-6 ingested 11g cannabis seed oil.

A commercially available health food product of cold-pressed hemp seed oil was ingested by one volunteer twice a day for 4 1/2 days (135 mL total) (Struempler et al 1997). Urine specimens collected from the volunteer were subjected to standard workplace urine drug testing procedures, and the following concentrations of THCCOOH were detected: 41 µg/L THCCOOH at 45 h, 49 µg/L at 69 h, and 55 µg/L at 93 h. Ingestion was discontinued after 93 h, and the following concentrations were detected: 68 µg/L at 108 h, 57 µg/L at 117 h, 31 µg/L at 126 h, and 20 µg/L at 142 h. The first specimen that tested negative (50 µg/L initial immunoassay test, 15 µg/L confirmatory GC-MS was at 146 h, which was 53 h after the last hemp seed oil ingestion. Four subsequent specimens taken to 177 h were also negative. This study indicates that a workplace urine drug test positive for cannabinoids may arise from the consumption of commercially available cold-pressed hemp seed oil.

In a 1997 survey of hemp oils in the US, THC concentrations between 11-117µg/g were noted (Mölleken and Husmann 1997). These oils were produced from imported Chinese seeds. Presence of THC in hemp seed products is predominantly caused by external contact of the seed hull with cannabinoid-containing resins in bracts and leaves during maturation, harvesting, and processing. The seed kernel is not entirely THC-free but contains, depending on the hemp variety, less than 0.5 µg/g of THC. These studies also showed that the use of low-THC cultivars and thorough seed cleaning is effective in reducing THC levels in the main products currently made from the seed kernel for human

consumption, that is, oil and hulled seeds (Leson et al, 2001). Since 1998, more thorough seed drying and cleaning appears to have considerably reduced THC levels in seeds and oil available in the U.S. Results from the mandatory THC analysis of seeds and oil produced in Canada and a study evaluating the effectiveness of various dry and wet cleaning methods show typical THC concentrations of 5 and 2 µg/g, respectively, in oil and hulled seeds from Canada (Crew 2000).

ElSohly et al. 2001 administered a single 15-mg dronabinol dose to four individuals over 3 sessions in a within-subject, crossover design, with a 1 week washout period between sessions. Each subject received, in separate sessions and in randomized order, an oral dose of Marinol (15 mg), a smoked dose of THC (16.9 mg) or a smoked dose of 17 mg THC and 1 mg THCV. Every urine sample was collected for 24 h, and then samples were collected once a day for 6 days. The limits of detection for THC and THCV were 1 µg/L. THCCOOH concentrations for the 4 subjects after the 15-mg oral THC dose ranged from 2.4 - 362 µg/L, with 43.1% of urine samples (22 of 51) ≥15µg/L up to one week after ingesting the drug.

Grauwiler et al 2008 evaluated the sensitivity and specificity of the CEDIA and FPIA immunoassays to detect cannabinoids with a 50 µg/L cutoff and a 15 µg/L LC-MS/MS cutoff (LOQ for THCCOOH 1 µg/L) in urine samples from volunteers receiving 20 mg oral synthetic THC (Marinol) or five different Cannabis sativa extracts. Urine samples were collected in an open, randomized, single-center, three-period crossover study in 18 healthy male volunteers. Urine samples were collected from all volunteers at 0, 4, 12, 24, 48, and 72 h after cannabinoid administration. Urine samples were analyzed with and without hydrolysis.

Sensitivity and specificity using 50 µg/L CEDIA/FPIA and 15 µg/L LC-MS/MS cutoffs for urine samples collected after 20 mg Marinol and 5 different cannabis extracts, each containing 20 mg THC (Grauwiler et al 2008).

		LC-MS/MS Hydrolyzed THCCOOH			LC-MS/MS Nonhydrolyzed THCCOOH & THCCOOH-gluc		
		Neg	Pos	% Pos	Neg	Pos	% Pos
CEDIA	Neg	105	34		105	34	
	Pos	22	164	61%	27	160	60%
CEDIA hydrolyzed	Neg	104	57		114	56	
	Pos	17	146	63%	21	141	59%
FPIA	Neg	100	18		102	16	
	Pos	16	171	62%	22	165	59%
FPIA hydrolyzed	Neg	102	19		102	18	
	Pos	14	179	63%	19	172	61%

The data above document that almost 60% of urine samples were positive following ingestion of 20 mg THC in 6 different formulations. Also, the immunoassays showed similar positive results between hydrolyzed and non-hydrolyzed urine samples.

Nabiximols deliver 2.7 mg THC and 2.5 mg CBD in each 100 µL oromucosal spray (Indorato et al 2016). Urine samples from 20 patients treated with Nabiximols for short (28 days) or long-term treatment (60 or 90 days) were analyzed. Positive urine test results (cut-off 25 µg/L) by the Drug-Screen-THC immunoassay occurred in all patients during the three months of follow-up, despite low concentrations in blood samples. Treatment consisted of one puff 6 times/day of 100 µL containing 2.7 mg of THC and 2.5 mg CBD. Urine samples were analyzed before and after starting the treatment and once a month for the 3 months of treatment. THCCOOH (cut-off: 25 µg/L) confirmation in urine was performed by GC–MS. Oromucosal administration has a better bioavailability than oral administration due to a lower first pass effect.

THCCOOH urine concentrations before starting therapy (T0) and after 1, 2, 3 months of Nabiximols therapy. Daily THC intake was 2.7 mg X 6 per day = 16.2 mg THC per day

Duration	THCCOOH µg/L Before drug	THCCOOH µg/L 1 month	THCCOOH µg/L 2 months	THCCOOH µg/L 3 months
Short therapy	<LOQ	61.3±27.5	-	-
Long therapy	<LOQ	59.8±23.6	62.6±25.2	63.2±24.8

In our last cannabinoid administration study at the National Institute on Drug Abuse, we administered 50.6 mg THC by the smoked, vaporized and oral routes to 11 chronic frequent and 9 occasional cannabis users (Huestis, unpublished data). The chronic frequent cannabis users had high residual cannabinoid concentrations and will not be included here. However, occasional cannabis users' urine THC-glucuronide, THCCOOH, THCCOOH-glucuronide concentrations were quantified by LC-MS/MS. The maximum analyte urine concentration (Cmax), time of maximum concentration (Tmax), concentration of the last positive sample (Clast) and time of the last positive sample (Tlast) are presented after oral administration of 50.6 mg THC.

	Median	Range
THC-glucuronide		
Cmax (ug/L)	3.3	2.4 – 23
Tmax (h)	5.5	3.2 – 14.2
Clast (≥1ug/L)	1.4	1.0 - 20.6
Tlast (h)	10	5 – 37
THCCOOH		
Cmax (ug/L)	10.6	1.6 - 28
Tmax (h)	9.4	5.5 - 21
Clast (≥0.5ug/L)	0.8	0.6 - 1.7
Tlast (h)	51	44 - 55.3
THCCOOH-gluc		
Cmax (ug/L)	354	116 - 667

Tmax (h)	6.7	5.5 - 24.9
Clast (ug/L)	20.7	12.2-34.1
Tlast (h)	52.9	48.9-59.9

%Pos (THCCOOH + THCCOOH-gluc) ≥ 15 ug/L up to 54 h

Sessions 1-4	84.6	27.3-100% up to 54 h

The most relevant oral THC administration studies for predicting the possibility of a positive urine cannabinoid test following oral THC ingestion were published by Bosy & Cole 2000, Leson et al 2001, and Gustafson et al 2004.

The purpose of the Bosy and Cole 2000 study was to quantify THC concentrations by GC-MS in commercially available hemp oils and to determine THCCOOH urine concentrations following 7 daily 15-g doses of hemp oil products containing from 11.5 to 117.5 µg/g THC. This represents daily THC doses of 0.17 to 1.8 mg. These doses exceeded the mean and were close to the 90% percentile of the combined 4 Fresh Hemp Foods products daily THC amounts and are highly relevant. Urine samples were tested by the Abbott AxSYM® FPIA and Roche On-line® KIMS immunoassays and by GC-MS to determine THCCOOH concentrations before and 6 h after each dose. After the last dose of oil, urine samples were collected for one week to determine the length of time an individual remains positive after this dosing regimen. Volunteers selected to participate in this study were required to submit three pre-study urine samples to verify no recent THC use. The 15-g quantity was selected because it approximates one tablespoon, a dose that was frequently recommended by manufacturers. One volunteer consumed two 1000-mg Health from the Sun Hemp 1000 gel caps which is the recommended dose indicated on the product. Urine samples were collected for one week after the last dose of oil to determine an excretion profile and the time when the subjects' urine drops below the screening positive cutoff. Peak THCCOOH concentrations in the participants' urine ranged from 1.8 to 48.7 µg/L. There were no positive urine specimens ≥15 µg/L following the 0.10, 0.17, 0.32, and 0.55 mg THC/d for 7 daily doses. The 0.54 mg and 1.8 mg THC/d doses produced positive urine specimens ≥15 µg/L.

Subjects ingesting low doses of THC (0.10, 0.17 & 0.32 mg THC/d) had immunoassay results well below the 50-µg/L immunoassay positive cutoff. Subjects ingesting medium doses of THC in hemp oil (0.54 & 0.55 mg THC/d) produced positive immunoassay screen results in the third and fourth days of ingestion. These two subjects had negative immunoassays within 24 h after ingestion ceased. The subject ingesting a high dose (1.8 mg THC/d) screened positive on the first day and was immunoassay negative within 72 h after last ingestion.

The impact of extended daily ingestion of THC via hemp oil on urine concentrations of THCCOOH for four daily THC doses (0.09, 0.19, 0.29, and 0.45 mg THC) was determined (Leson et al 2001). Fifteen THC-naïve adults ingested, over 4 successive 10-day periods, single daily THC doses. Websar Laboratories, Inc. (Ste. Anne, MB, Canada) quantified total THC concentration in the oil in triplicate by the method used to meet regulatory requirements in Canada (Research, Health Protection Branch, Health Canada 1992).

Hemp oil results were 6.2 ± 0.5, 13.3 ± 0.8, 20.7 ± 1.2, and 31.7 ± 1.4 µg THC/g; the corresponding actual doses per 15-mL aliquots, using a specific density of 0.95 for all four oil blends, were 0.09, 0.19, 0.29, and 0.45 mg THC. The Subjects self-administered THC in 15-mL aliquots (20 mL for the 0.6-mg dose) of four different blends of hemp and canola oils. Urine specimens were collected prior to the first ingestion of oil, on days 9 and 10 of each of the four study periods, and 1 and 3 days after the last ingestion. All specimens were confirmed for THCCOOH by GC–MS, and analyzed for creatinine to identify dilute specimens. None of the subjects who ingested daily doses of 0.45 mg THC screened positive and only one specimen screened positive at the 50 µg/L cutoff at a daily THC dose of 0.6 mg. The highest THCCOOH concentration was 5.2 µg/L, well below the 15 µg/L confirmation cutoff of federal drug testing programs. A THC intake of 0.6 mg/day is equivalent to the consumption of approximately 125 mL of hemp oil containing 5 µg/g of THC or 300 g of hulled seeds at 2 µg/g. These THC concentrations are now typical in Canadian hemp seed products. Concentrations were sufficiently low to prevent confirmed positives from the extended and extensive consumption of hemp foods with low THC content. A summation of these results found no positive urine specimens ≥15 µg/L, in fact all below 5.5 µg/L after 4 daily doses of up to 0.6 mg/day, and only a single specimen positive by RIA at 50 µg/L.

Tables below include the calculated THC doses and the immunoassay and GC-MS urine results after hemp oil administration.

Table II. Summary of Urine Analyses by Radioimmunoassay and GC–MS

THC dose (mg/day)	#ofSpecimens *n*	GC–MS		RIA				
		″2.5ng/mL	>2.5ng/mL*	< 10 ng/mL	< 20 ng/mL	< 50 ng/mL	< 100 ng/mL	% Specimens ≥ 20 ng/mL
Baseline	15	15	0	15	0	0	0	0
0.09	29	29	0	28	1	0	0	0
0.19	30	30	0	21	8	1	0	3
0.29	30	28	2	17	9	4	0	13
0.45 (0.6)†	22 (6)	16 (6)	6 (0)	8 (3)	4 (1)	10 (2)	0 (0)	43
Washout day 1†	11 (3)	10 (2)	1 (1)	6 (2)	2 (0)	3 (0)	0 (1)	29
Washout day 3†	10 (3)	10 (3)	0 (0)	10 (3)	0 (0)	0 (0)	0 (0)	0
Total number of specimens including baseline	159	149	10	113	25	20	1	13
Total number of specimens excluding baseline	144	134	10	98	25	20	1	15

* Maximum GC–MS value measured 5.2 ng/mL.
† Values in parentheses refer to 0.6 mg/day dose in Period 4.

Gustafson et al 2003 determined urinary THCCOOH excretion by GC/MS analysis in 4381 urine specimens collected before, during, and after 5 oral daily 0.39, 0.47, 7.5, and 14.8 mg THC/day to 7 participants. All urine voids were collected over the 10-week study. At the federally mandated immunoassay cutoff (50 µg/L), mean detection rates were <0.2% during ingestion of the two low doses typical of current hemp oil THC concentrations. These low oral THC data are 2-4 times higher than the mean and 90th percentile combined daily THC doses present in the 4 Fresh Hemp Food products and suggest that positive urine THCCOOH tests are possible but likely <0.05% of the mean and <0.1% of the 90% of the combined intake. Only four of 7 participants produced a mean of 3.1 positive urine

THCCOOH specimens after the 0.39 mg/day and 2 of 7 had a mean of 2.4 positive samples during and for the 10 days following 5 daily doses, range 0-13 total specimens). Positive cannabinoid urine tests ≥15 µg/L occurred as early as 14.6 h and as late as 110.5 h after the start of 5 daily doses. Mean detection rate for the 0.39 mg THC/d was 2.6% positive tests with a range of 0 to 10.3% positive tests at ≥15 µg/L. Mean detection rate for the 0.47 mg THC/d was 2.3% positive tests with a range of 0 to 8.7% positive tests at ≥15 µg/L. Maximum metabolite concentrations were 5.4 – 38.2 µg/L for the low THC/day doses. The two high doses produced mean detection rates of 23 – 46% with intermittent positive tests up to 118 h with an LOQ of 2.5 µg/L. Maximum metabolite concentrations were 19.0 – 436 µg/L for the high THC/day doses. Urine tests have a high likelihood of being positive after Marinol therapy. The high 14.8 mg dose was prepared from a high THC content hemp oil of 347 µg/g, and the 0.47 mg dose was from a 92 µg/g hemp oil. Individuals absorbed enough drug from hemp oils containing high THC concentrations to produce a positive sample by the first urine void.

% Positive urine samples at 15 µg/L GC-MS THCCOOH cutoff (Gustafson 2003.

THC dose mg/day	0	0.39	0.47	7.5	14.8
Specimens ≥15 µg/L					
Mean # (SD)	0	3.1 (4.6)	2.4 (0.7)	33.7 (14.0)	31.7 (14.4)
Range		0–13	0–9	10–48	7–47
Detection rate % over 15 d					
Mean	0	2.6 (3.7) %	2.3 (4.0)%	37.8 (19)%	31.9 (16.8)%
Range		0-10.3%	0-8.7%	10.4-62%	5.7-58.8%
1st Positive h					
Mean (SD)	0	55.9 (28.3)	19.9 (3.1)	21.1 (18.7)	23.1 (25.5)
Range		14.6-75.7	17.7-22.1	5.8-59.8	6.8-79.3
Last Positive h					
Mean (SD)	0	34.1 (28.0)	16.0	63.0 (32.4)	63.8 (18.3)
Range		13.4-66.0		23.8–111	29.5-84.2
1st Negative h					
Mean (SD)	0	2.6 (2.0)	1.7	36.1 (27.3)	22.7 (28.4)
Range		1.2-4.8		5.6-91.6	0.3-75.0
Cmax µg/L					
Mean (SD)	2.0	19.8 (13.1)	12.2 (9.6)	146 (143)	116 (93.2)
Range	0-3.5	7.3-38.2	5.4-31.0	26.0–436	19.0–264
Tmax					
Mean (SD)	0	99.9 (40)	85.9 (23.9)	97.8 (24.2)	104 (42.2)
Range		35.7-151	40.8-112	52.1-119	46.0-157

Urinary THCCOOH terminal elimination half-lives after oral THC ingestion

Table I. Urinary 11-Nor-9-Carboxy-^{9}-Tetrahydrocannabinol Terminal Elimination Half-Lives (h) after Oral ^{9}-Tetrahydrocannabinol

Subject	N*	Elimination Half-lives (h) 7.5 mg/day† (Capsule)	N	14.8 mg/day (Liquid)	N	0.47 mg/day (Capsule)	N	0.39 mg/day (Liquid)
A	12	61.5	6	64.8	12	51.7	7	44.2
C	9	79.4	6	79.3	8	59.0	9	84.1
G	12	88.8	6	25.6	6	34.7	7	31.4
H	6	23.6	8	23.9	6	11.6	6	59.8
L	9	49.4	7	81.0	7	65.0	10	45.8
N	10	82.1	8	45.0	6	58.0	10	37.6
P	7	63.2	7	45.3	6	29.5	6	48.7
Mean (± SD)	–	64.0 (22.5)	–	52.1 (21.8)	–	44.2 (19.4)	–	50.3 (17.4)

* Number of points on excretion curve used to determine terminal elimination half-life.

† Dronabinol, synthetic ^{9}-tetrahydrocannabinol, 2.5 mg THC capsules.

Table 2. Cannabinoid immunoassay data for 50 µg/L cutoff.

THC dose, mg/day	Assay	Detection rate,[a] % Mean (SD)	Detection rate,[a] % Range	First positive,[b] h Mean (SD)	First positive,[b] h Range	Last positive,[c] h Mean (SD)	Last positive,[c] h Range	First negative,[d] h Mean (SD)	First negative,[d] h Range
0	Emit II	0.0		0.0		0.0		0.0	
	DRI	0.0		0.0		0.0		0.0	
	CEDIA	0.0		0.0		0.0		0.0	
0.39	Emit II	0.2 (0.6)	0–1.6	104[e]		6.2[e]		1.2[e]	
	DRI	0.1 (0.3)	0–0.8	112.2[f]		6.2[f]		1.2[f]	
	CEDIA	0.0		0.0		0.0		0.0	
0.47	Emit II	0.7 (1.0)	0–1.9	28.5[g] (32.1)	29.5–87.1	0.0		3.1[g] (1.3)	1.8–4.3
	DRI	0.0		0.0		0.0		0.0	
	CEDIA	0.0		0.0		0.0		0.0	
7.5	Emit II	45.7 (14.1)	34.4–73.1	7.7 (5.6)	1.9–10.6	58.4 (24.3)	15.9–91.1	44.1 (25.4)	16.6–83.9
	DRI	39.4 (14.8)	21.9–66.7	13.0 (12.0)	1.9–36.8	53.6 (27.3)	15.9–87.9	30.3 (19.4)	16.3–71.0
	CEDIA	30.7 (14.4)	12.5–50.0	22.7 (17.8)	1.9–52.8	41.4 (23.5)	15.9–67.0	24.2 (11.7)	15.1–45.0
14.8	Emit II	41.2 (7.4)	32.6–54.4	7.4 (3.1)	4.0–13.0	65.6 (28.8)	19.3–117.5	32.1 (15.5)	5.7–53.9
	DRI	34.3 (9.6)	20.3–46.6	9.9 (4.4)	4.3–16.1	48.6 (20.3)	12.6–67.3	15.9 (16.0)	2.6–45.9
	CEDIA	23.5 (11.5)	5.7–37.5	17.3 (9.2)	4.3–32.5	46.6 (20.2)	12.6–67.3	13.5 (11.3)	2.6–29.0

[a] Detection rate: number of positive samples divided by total number of samples from first dose to last sample of the session × 100.

[b] First positive: time from first dose to first positive sample.

[c] Last positive: time from last dose to last positive sample.

[d] First negative: time from last dose to first negative sample.

[e] One of seven participants had two positive samples.

[f] One of seven participants had a single positive sample.

[g] Three participants had positive samples.

The results of these three studies are not consistent. Bosy and Cole 2000 found no positive urine tests after 7 daily doses of 0.10, 0.17, and 0.32 mg THC/d and testing urine samples up to 6 h after dosing and daily for 7 days. However, dosing 0.54 and 0.55 mg THC/d produced different results, with some urine samples positive after the 0.54 mg regimen and no samples positive after the 0.55 mg regimen. Only a single individual was administered each dose. Leson et al found no positive GC/MS results ≥15 µg/L following 4 daily up to 0.6 mg THC/day doses, but all urine specimens were not collected and analyzed. Gustafson et al 2003 administered 5 daily doses of 0.39 and 0.47 mg THC/d to 7 individuals and all urine specimens were collected and analyzed. Less than 0.2% of urine specimens screened positive at a 50 µg/L cutoff; however, in one subject receiving the 0.39 mg regimen, up to 10.3% of urine specimens were positive for THCCOOH ≥15 µg/L. Therefore, it is possible that individuals consuming 0.1938 mg THC/d in Fresh Hemp Foods, Ltd products (90^{th} percentile) over 5 days could screen positive for THCCOOH in urine at mandated cutoff concentrations. It is apparent that the vehicle is important for absorption, as a 0.47 mg THC/d hemp oil produced fewer positive urine specimens than the 0.39 mg THC/d dose in Gustafson et al. 2003.

The following manuscripts describe urine THCCOOH results after unknown oral THC doses.

Thirteen volunteers consumed 40 to 90 mL of hemp seed oils containing 7 to 150 µg/mL THC and others ate hemp food products (Alt et al, 1998). Some urine samples were positive for up to 80 h, and the highest serum concentrations were 6 µg/L. The total amounts ingested were not described.

Callaway et al, 1997 reported positive urine cannabinoid tests following ingestion of hemp seed oil, but the dose was unknown.

Costantino et al. 1997 reported that seven individuals ingesting 15 mL of hemp oil of an unknown THC concentration had positive urine drug tests by immunoassay at a cutoff of 20 µg/L for up to 48 h after ingestion. GC/MS analysis of urine specimens for THCCOOH, the primary urinary metabolite of THC, identified concentrations up to 78.6 µg/L. This is substantially above the federally mandated urine THCCOOH confirmation cutoff concentration of 15 µg/L. It is of concern that legitimate consumption of hemp oil may be interpreted as illicit drug exposure and that hemp oil ingestion may be used to conceal illicit cannabis use.

Commercially available snack bars and other foodstuffs prepared from pressed hemp seeds were ingested by volunteers (Fortner et al, 1997). Urine specimens were collected for 24 h after ingestion of the foodstuffs containing hemp seeds and tested for marijuana using an EMIT immunoassay and GC-MS. Specimens from individuals who ate one hemp seed bar demonstrated little marijuana immunoreactivity, and only one specimen screened positive at a 20-ng/mL cutoff. Specimens from individuals who ate two hemp seed bars showed increased immunoreactivity, and five specimens screened positive at a 20-ng/mL cutoff. A single specimen yielded a quantitative GC-MS value (0.6 µg/L), but it failed to meet reporting criteria. Several specimens from individuals who ate three

cookies made from hemp seed flour and butter screened positive at both 50- and 20-ng/mL cutoffs. Two specimens produced quantitative GC-MS values (0.7 and 3.1 ng/mL), but they failed to meet reporting criteria. Several specimens also tested positive with an FDA-approved on-site marijuana-screening device. Hemp seeds similar to those used in the foodstuffs did not demonstrate the presence of marijuana when tested by GC-MS. In this study, ingestion of hemp seed food products resulted in urine specimens that screened positive for marijuana. No specimens gave a GC-MS quantitative value above the limit of detection for marijuana.

Infant THC-exposure from breastfeeding based on estimated oral THC ingestion of 4 Fresh Hemp Foods products, hulled hemp seed, hemp protein powder, hemp protein concentrate and hemp oil by breastfeeding women.

There was a surprising lack of information related to this question in the published literature, with most articles focused on THC transfer during the perinatal period that included transfer during gestation and breastfeeding. Additional sources of data included websites and books on the topic.

The lack of controlled THC administration studies is obvious due to ethical and medical concerns with unnecessarily exposing the fetus and neonate to an exogenous compound. After extensive searching, I found no data relating ingestion of a known amount of THC by the mother and resultant breast milk THC concentrations. Neither are there controlled studies of THC administration to the infant and resultant infant plasma or urine THC concentrations. There are data estimating the volume of daily breast milk ingested by neonates and infants, effects on the fetus following in utero THC exposure and on the neonate following THC breast milk exposure. In addition, there are many reports advising for or against breastfeeding if the mother uses cannabis. The list of references reviewed for this report is included below.

A summary of the available literature on this topic is included. Data were available to estimate THC and 11-OH-THC daily exposure in breast milk. This calculation required data on plasma THC concentrations after oral THC intake. These data were available from the general safety data provided above for oral THC ingestion.

I evaluated the safety of THC exposure from Fresh Hemp Foods, Ltd hemp products including hulled hemp seed, hemp protein powder, hemp protein concentrate and hemp oil in the breastfeeding population. Fresh Hemp Foods Ltd provided the data on total amounts of each product consumed each day. Maximum cumulative THC exposure estimates for individuals over the age of two were based on the individual using the mean and 90th percentile amounts of all products in a single day. These data were used as mean and 90th percentile amounts of all products in a single day exposures for the lactating woman.

The THC calculations are based on the new Fresh Hemp Foods, Ltd standards for ≤4 µg THC/g as verified by the Quality Department for hulled hemp seed, hemp protein powder and hemp protein concentrate. The Fresh Hemp Foods, Ltd standard for hemp oil will be

the same as the Canadian Industrial Hemp Regulations requirement of ≤10 µg THC/g product. These values were used in determining daily THC intake if the recommended dose of all products were consumed each day.

Preclinical data

Reisner et al 1983 reported that only 0.2% of a labeled THC dose to squirrel monkeys appeared in their breast milk as hydrophilic & lipophilic metabolites within 24 hours; 0.01% of the dose appeared in the squirrel monkeys' offspring's urine. In lactating ewes, milk contained less radiolabel than their feces or urine, with radiolabel being detected 4 and 96 hours after THC injection (Mourh and Rowe 2017). Endocrine and behavioral changes were noted in suckling rodents after THC exposure in breast milk. THC acted as an in vivo weak competitor of the estrogen receptor, producing a primary estrogen effect in male & female rats (Warner et al 2014). In addition, THC was shown to reduce trophoblast cell proliferation and inhibit placenta development. In some studies, THC also produced hormonal changes reducing fertility. In animal models, THC crossed the placenta resulting in fetal plasma concentrations approximately 10% of maternal plasma concentrations after acute exposure; however, significantly higher fetal concentrations were observed after repetitive exposures (American College of Obstetricians & Gynecologists' Committee on Obstetric Practice 2015). Furthermore, these clinicians noted that although animal models may be poor surrogates for the human condition, endocannabinoids played key roles in normal fetal brain development, including neurotransmitter systems, and neuronal proliferation, migration, differentiation, and survival.

Battista et al 2014 noted that the endocannabinoid-CB1 receptor system is important for milk suckling, and in growth and development early in life. It was suggested that increased endocannabinoids and/or cannabinoids in milk might have relevant effects on breastfed newborns.

Murphy et al 1998 showed that THC inhibited gonadotropin, prolactin, growth hormone and thyroid-stimulating hormone release and stimulated release of corticotropin, inhibiting the quantity and reducing the quality of breast milk. In a recent review, Mourh and Rowe 2017 demonstrated that animals exposed to THC in milk had decreased prolactin concentrations and motor, neurobehavioral, & developmental effects. Lactating rats and non-pregnant rhesus monkeys displayed lower prolactin concentrations following THC injections, with maximum reductions of 74% (in male monkeys) and 85% (in female monkeys) over the first 30-90 minutes. There was a >70% reduction in prolactin from baseline after 1.25 mg/kg THC and >90% reduction following a 4 mg/kg dose over 30-60-min. In addition, lactating rats displayed lower blood oxytocin concentrations following THC dosing. THC prevented suckling-induced oxytocin secretion by the posterior pituitary, leading to a longer delay in initial ejection of milk and between successive ejections. Additional effects seen in monkeys & rats included lethargic behavior, reduced maternal care, and anxiety.

In milk samples from buffaloes eating cannabis plants, 50% contained cannabinoids (Ahmad and Ahmad 1990). Consumers of the contaminated milk were passively exposed to THC and metabolites were detectable in at least 30% of children up to the age of 3 years. Mouse pups whose mothers consumed food containing hashish during lactation weighed significantly less (by 10– 14%) than control pups from day 11 onward. The endocannabinoids play key roles in normal fetal brain development, including neuronal proliferation, migration, differentiation, & survival (The American College of Obstetricians & Gynecologists' Committee on Obstetric Practice 2015). Suggested that this occurred due to malnutrition (which could be the result of poorer milk production in the mothers or the direct influence of THC on the pups). The degree to which we can correlate effects of THC exposure in breast milk in animals and humans, especially neurobehavioral changes, is unclear. Also, the animal doses were frequently greater than those in human studies and were usually administered intravenously, making comparison of pharmacokinetics difficult. Exposure to cannabis includes exposure to numerous other cannabinoids, terpenes and polyaromatic hydrocarbons and might have different effects than synthetic IV THC.

Clinical data & recommendations

All drugs may pass into breast milk depending upon the drug's molecular weight and size, protein binding, amount of free drug in the blood, the lipophilicity of the drug, and the drug's pKa. Berlin and Briggs describe the transport of compounds across the mammary alveolar cells as primarily due to transcellular diffusion, in which small molecules (molecular weight 100-200) pass through with the flow of water due to hydrostatic or osmotic pressure differences. Larger molecular weight compounds may enter milk through intercellular diffusion, explaining the presence in breast milk of maternal proteins such as cow milk antigen and antibodies. The 3-dimensional shape of the molecule also may be a determinant in transfer to breast milk. Ionophore diffusion facilitates charged ions transfer and carrier proteins transfer other substances. THC is a highly lipophilic compound and transfers readily into breast milk.

Perez-Reyes and Wall reported that cannabis & metabolites pass into breast milk in concentrations dependent upon the amount of drug ingested by the mother. These authors published the one and only breast milk/plasma THC ratio data (one single paired sample) as the primary source for THC concentrating in breast milk, and many recommendations to not breastfeed if the mother continues to use marijuana. Breast milk from two chronic frequent cannabis users were studied. There were no data on the amount of THC ingested by the women, thus, there are no data on maternal THC intake per event or per day. Woman #1 reported smoking cannabis once per day and woman #2 reported smoking approximately seven times per day. A single matched plasma and breast milk sample was collected from woman #2, as described as under steady state conditions. THC concentrations in the plasma were 7.2 µg/L THC, 2.5 µg/L 11-OH-THC, and 19 µg/L THCCOOH, and 60.3, 1.1, and 1.6 µg/L THC, 11-OH-THC and THCCOOH concentrations in the breast milk, respectively. These are the sole data supporting a human THC breast milk/plasma ratio of 8.4, indicating that THC is concentrated up to 8-fold in breast milk compared to maternal plasma. At these concentrations, it was

estimated that the infant's daily THC exposure was 0.01 to 0.1 mg THC/day. There were no observable side effects in the infant receiving this amount of THC (Hale 2012). Concentrations in woman #1's breast milk were 105 µg/L THC, with no detectable 11-OH-THC and THCCOOH. Marcei et al 2011 reported cannabinoid concentrations in breast milk from one lactating woman of 86 µg/L THC and 5 µg/L 11-OH-THC, but maternal plasma was not tested. Also, the duration of THC in the breast milk after cessation of use is unknown (Wang 2016). The evidence is unclear if breastfeeding benefits (nutrition, immune protective factors, sudden infant death syndrome (SIDS), bonding, etc.) outweigh potential THC breast milk exposure risks.

Most experts refer to the effects of in utero cannabis exposure as a means of evaluating potential adverse developmental outcomes; however, this is inappropriate to determine the risk of ingesting THC in breast milk. Blood THC concentrations in pregnant women who smoke or vaporize cannabis are much higher (can be as high as 200-400 µg/L immediately after inhalation, and typical abused oral THC doses range from 10-100 mg or more. Furthermore, most women who use cannabis during pregnancy continue use during breastfeeding, making it difficult to assign causation to one source of exposure.

Reported cannabis use prevalence rates in pregnancy vary from 3-34% (Metz & Stickrath 2015), with cannabis the most common illicit drug taken during gestation. Sixty percent of women who used cannabis in the year prior to pregnancy continued to use more than 10 joints per week, indicating that many women continue use throughout pregnancy. Identification of cannabis use in the mother at birth does not differentiate the amount of use and designation of occasional or chronic frequent use. The American College of Obstetricians & Gynecologists' Committee on Obstetric Practice (2015) estimate that 48–60% of cannabis users continue use during pregnancy, with many women believing that it is relatively safe to use during pregnancy and less expensive than tobacco. Colorado's largest local Tri-County health department serves >26 % of the population (Wang 2016). Their Women's Infants & Children (WIC) Program survey revealed 7.4% of mothers aged <30 years & 4% of mothers >30 years are current cannabis users. Of all cannabis users (past, ever, current), 35.8% said they used at some point during pregnancy, 41% since the baby was born & 18% while breastfeeding.

Breast milk samples (N=109) from lactating women were analyzed for cannabinoids and questionnaires were completed about their drug use during pregnancy and while breastfeeding (Mourh & Rowe 2017). Of 19 women reporting drug use, 1 had 20 µg/L THC in her breast milk, with no detectable cannabinol or cannabidiol, and her urine was positive for cannabinoids. Another woman not reporting drug use had 31 µg/L THC in her breast milk with no detectable cannabidiol. Infant THC exposure was estimated as 2 and 3.1 µg THC/100 mL breast milk. Oral THC bioavailability is estimated to be 6-12%; using the higher 12% oral THC bioavailability, infant exposure was estimated at 0.24 & 0.37 µg THC. Maternal THC dose and dosing time in relation to breast milk collection were unknown.

Astley & Little 1990 suggested that cannabis use by the breastfeeding mother during the first month of life could impair neurodevelopment. Glial and myelin formation in the infant

brain continues after birth during breastfeeding and might lead to sedation and weakness. Other disadvantages include the possibility that THC in breast milk may decrease the production, volume, composition & ejection of breastmilk, resulting in poor feeding patterns (Liston 1998).

The American Academy Pediatrics Committee on Drugs 2001 noted that there were no reported adverse effects of cannabis ingestion from breast milk in published studies.

In the WHO Breastfeeding 1997 Report, it was estimated that in one feeding the infant will ingest 0.8% of the weight-adjusted maternal intake of 1 joint (Garry et al 1990). The authors suggest that mothers who use cannabis must stop breastfeeding, or ask for medical assistance to stop cannabis use, to provide their babies with all the benefits of human milk. THC in breast milk could sedate the infant and result in growth delays.

Liston 1998 suggested that infants exposed to marijuana via breast milk show signs of sedation, reduced muscular tonus, & poor sucking. Two studies evaluated the effects of cannabis use by the lactating mother on their child's development. In the first, no significant differences were found in terms of weaning, growth, and mental or motor development with regard to age. The second study found that cannabis exposure via the mother's milk during the first month postpartum appeared to be associated with a decrease in infant motor development at one year of age. Infants exposed to cannabis for more than half of the days during the 1st trimester of gestation or 1st month of lactation had significantly lower mean Psychomotor Development. Other factors come into play like cannabis exposure during pregnancy, passive exposure to cannabis smoke in ambient air, or the quality of the mother-child relationship. There are no studies relating to the long-term effects of marijuana exposure through breast milk. There are almost no studies of lactation exposure only; the infant was usually prenatally exposed and almost all of their mothers continued use after birth (Reece-Stremtan et. al 2015).

Despite preclinical studies suggesting that THC exposure during breastfeeding can reduce the quality and quantity of breast milk, these effects have not been confirmed in humans (Sharma et al 2012). According to Warner et al 2014, the identification of side effects in the lactation-exposed infant are inconsistent and there are no long-term outcome studies. Hotham and Hotham 2015 stated that the most commonly used drugs are relatively safe for breastfed babies. Drugs contraindicated during breastfeeding include anticancer drugs, lithium, oral retinoids, iodine, amiodarone & gold salts. Estimated intake by an exclusively breastfed baby is 150 mL/kg/d.

Hale 2012 placed cannabis in highest risk category, L5 or Hazardous, stating that using cannabis during breastfeeding clearly outweighs the benefits of breastfeeding; however, many lactation experts disagree with this conclusion. Jansson et al 2015 noted the importance of active, passive (from maternal sidestream smoke) and cumulative exposures to breastfed infants must be considered. THC delivered via lactation to the infant may affect the ontogeny of various neurotransmitter systems, leading to changes in neurobiological functioning. The authors describe the recent new recommendation by the Academy of Breastfeeding Medicine as erroneous & disappointing, and question why

a recommendation would err on the side of breastfeeding with potentially toxic exposures and other risk factors that could portend short- & long-term infant harm.

Most adverse effects of drugs in breast milk occurred in newborns under 2 months and rarely in those older than 6 months (Jansson et al 2015). A follow-up study of 1-year-old breastfed infants of mothers who used cannabis found some impairment in motor development, although researchers found it difficult to determine whether in utero exposure or breastfeeding was the greater influence. Women should be encouraged to stop using cannabis & avoid exposure of the baby to second-hand smoke.

In a survey of mothers by lactation experts, 15% of women reported using cannabis during breastfeeding (Bergeria and Heil 2015). Forty-four percent of the lactation experts reported that their recommendations were based on marijuana use factors like the severity of maternal use. Another 41% reported recommending continued breastfeeding because benefits outweigh harms, and the remaining 15% recommended that a woman should stop breastfeeding if she cannot stop using marijuana. Infants whose mothers used marijuana during lactation (n = 27) had similar growth outcomes, mental & motor development, & weaning ages compared with infants of non-using mothers (n=35). In contrast in a larger study, significant deficits in motor development was found at 1 year of age among exposed infants (n = 68) versus matched controls (n = 68); however, marijuana exposure occurred during the first trimester of pregnancy & the first month of lactation, making it difficult to determine which period of exposure had a stronger influence on infant motor development.

The American College of Obstetricians & Gynecologists Committee on Obstetric Practice released new recommendations on breastfeeding and marijuana use in 2015. Obstetricians and gynecologists should be discouraged from prescribing or suggesting marijuana use for medicinal purposes during preconception, pregnancy, & lactation. There are insufficient data to evaluate effects of marijuana use on infants during lactation & breastfeeding; thus, marijuana use is discouraged. In animal models, THC crossed the placenta, producing fetal plasma levels that were approximately 10% of maternal levels after acute exposure. Significantly higher fetal concentrations were observed after repetitive exposures. Animal models demonstrate that endocannabinoids play key roles in normal fetal brain development, including in neurotransmitter systems, & neuronal proliferation, migration, differentiation, & survival. Breastfeeding women should be informed that the potential risks of exposure to marijuana metabolites are unknown & should be encouraged to discontinue marijuana use.

The strongest determinant of breast milk medication concentration is the non-protein bound maternal plasma drug concentration (Newton & Hale 2015). THC is a highly bound drug that should result in lower breast milk concentration; however, THC has a large volume of distribution (Vd) in maternal compartments, with especially rapid tissue sequestration that will reduce maternal free drug concentrations. However, THC is a highly lipid soluble drug that passes through the alveolar cells more easily and is sequestered in milk. Marijuana is an example of a highly lipid soluble drug with higher concentrations in breastmilk based on a single paired maternal plasma and breast milk

sample. THC's pKa is 10.2, leading to ion trapping in milk due to the higher ionization at lower pH. The relative infant dose (RID) is amount of the drug dose to the breastfeeding infant. The infant dose (mg/kg/d) is divided by the mother's dose (mg/kg/d). An RID <10% is considered acceptable in healthy postnatal infants. The bioavailability of the drug in the infant must be known. THC's oral bioavailability is low- estimated to be about 6-12% in adults. Premature, term or ill neonates could have higher absorption rate than adults. The ultimate measure of drug in breast milk is the infant's plasma blood concentrations but none have been published. Mothers are advised to choose drugs with a low M/P ratio and to avoid drugs with a long half-life (12-24 h).

The Academy of Breastfeeding Medicine stated that "A recommendation of abstaining from any marijuana use is warranted. At this time, although the data are not strong enough to recommend not breastfeeding with any marijuana use, we urge caution (Foeller & Lyell 2017).

We included the data for marijuana use during breastfeeding because no data are available for oral THC dosing and breastfeeding; however, maternal blood THC concentrations following maternal cannabis smoking or vaporization can be as high as 200-300 µg/L, while blood THC concentrations after oral THC from ingestion of Fresh Hemp foods is expected to be low.

Based on the studies administering known quantities of THC and blood/plasma/serum concentrations, we can estimate the blood concentrations that would result from intake of 0.0968 (mean daily mg THC from 4 Fresh Hemp Foods, Ltd products) to 0.1938 (90^{th} percentile daily mg THC from 4 Fresh Hemp Foods, Ltd. Products) mg oral THC. Stott et al 2013 administered two Sativex (2.7 THC and 2.5 CBD in each 100 µL spray) doses (total 5.4 mg THC) to adults. There are no infant THC administration data. The mean plasma Cmax was <1.2 µg/L THC and <2 µg/L 11-OH-THC. The mean daily amount (0.0968 mg) and 90^{th} percentile (0.1938) of THC exposure from ingesting all 4 Fresh Hemp Foods, Ltd. Products is 55- and 27-fold lower than this exposure, respectively. These data would estimate the plasma Cmax in the breastfeeding mother assuming a 0.0968 mg daily dose as <0.02 µg/L THC and <0.04 µg/L 11-OH-THC, and if the highly conservative 0.1938 mg THC dose is assumed, plasma Cmax in the mother of <0.04 µg/L THC and <0.07 µg/L 11-OH-THC.

Furthermore, based on the Monte Carlo simulation, the maximum THC exposure was estimated at 0.1025 mg 99.9% of the time based on ingestion of all 4 hemp food products. This amount is 53 times lower than the 5.4 mg THC Stott et al dose, estimating a maximum THC concentration of <0.02 µg/L and <0.04 µg/L.

In a single maternal plasma and breast milk pair, the THC plasma to breast milk ratio was 8.4. Based on this ratio and the mean-90% maternal plasma THC concentrations the maximum THC concentration in the breast milk would be between 0.17-0.34 µg/L. There are no data on breast milk/plasma ratios, but if one assumed a similar distribution for 11-OH-THC into breast milk, maximum 11-OH-THC concentrations in breast milk would be 0.34-0.59 µg/L.

The estimate of daily breast milk intake is 150 mL/kg/day. Our estimates of maximum THC concentration in breast milk and daily intake would suggest THC intake of 0.05 – 0.09 µg/kg/day THC. As 11-OH-THC is equipotent to THC, assuming the breast milk to plasma ratio is also 8.4, the total active cannabinoids exposure for the infant is estimated to be <0.08-0.14 µg/kg/day. Gustafson et al 2014 administered 0.39 and 0.47 mg THC per day for 5 days, resulting in non-detectable THC concentrations in human plasma. These doses are 2-4 times the dose a breastfeeding mother would consume with all 4 hemp products. This low-level exposure is not expected to produce adverse developmental outcomes in the infant whose mother consumes the maximum amount of all 4 Fresh Hemp Foods, Ltd. per day.

Estimated THC food daily intake mg	Maternal THC plasma Cmax µg/L	Maternal 11-OH-THC plasma Cmax µg/L	Breast Milk THC Cmax µg/L B/P 8.4	Breast Milk 11-OH-THC Cmax µg/L B/P 8.4	Infant THC Exposure µg/kg/day*	Infant 11-OH-THC Exposure µg/kg/day
0.0968	<0.02	<0.04	<0.17	<0.34	<0.03	<0.05
0.1938	<0.04	<0.07	<0.34	<0.59	<0.05	<0.09
0.1025	<0.02	<0.04	<0.17	<0.34	<0.03	<0.05
5.4@	<1.2	<2	<10.1	<16.8	<1.5	<2.5
0.39#	ND	ND				
0.47#	ND	ND				

@Stott et al 2013 oral mucosa THC dose; #Gustafson et al 2014 oral THC dose
*150 mL/kg/day infant breast milk dose

Furthermore, Stott et al 2013 also administered the 5.4 mg THC/day dose for 9 consecutive days and showed that THC and 11-OH-THC concentrations did not accumulate over time. This also demonstrates that daily use of the 4 Fresh Hemp Foods, Ltd doses that are much lower than the 5.4 mg Stott dose should not accumulate. At birth, a 10 lb. (4.55 kg) infant would receive about 0.14-0.23 µg/day THC and 0.23-0.41 µg/day 11-OH-THC. The total active cannabinoid dose would be approximately 0.37-0.64 µg/day. The oral bioavailability of THC and 11-OH-THC is low, estimated to be 6-12% in adults; bioavailability could be different in the infant although first pass metabolism would still reduce active cannabinoid exposure. This low concentration of active cannabinoids should not produce adverse developmental effects.

References for general safety, blood/plasma/serum THC concentrations and urine cannabinoid tests

Alt A, Reinhardt G. Positive cannabis results in urine and blood samples after consumption of hemp food products. J Anal Toxicol 1998;22:80–1.

Bosy TZ, Cole KA. Consumption and quantitation of delta-9-tetrahydrocannabinol in commercially available hemp seed oil products. J Anal Toxicol 2000;24:562–6.

Brenneisen R, Egli A, Elsohly MA, et al. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int J Clin Pharmacol Ther 1996; 34 (10): 446-52.

Callaway JC, Weeks RA, Raymon LP, Walls HC, Hearn WL. A positive THC urinalysis from hemp (Cannabis) seed oil. J Anal Toxicol 1997;21:319–20.

Cone EJ, Johnson RF, Paul BD, Mell LD, Mitchell J. Marijuana-laced brownies: Behavioral effects, physiologic effects, and urinalysis in humans following ingestion. J Anal Toxicol 1988;12:169-175.

Costantino A, Schwartz RH, Kaplan P. Hemp oil ingestion causes positive urine tests for 9-tetrahydrocanabinol carboxylic acid. J Anal Toxicol 1997;21:482–5.

Crew S. Hemp Oil Canada Inc., Ste. Agathe, MB, Canada. Development of hemp food products and processes. Report prepared for the Agricultural Research and Development Initiative (ARDI), Winnipeg, MB, Canada, 2000).

ElSohly MA, deWit H, Wachtel SR, Feng S, Murphy TP. Delta-9- tetrahydrocannabivarin as a marker for the ingestion of marijuana versus Marinol: results of a clinical study. J Anal Toxicol 2001; 25:565–71.

Fortner N, Fogerson R, Lindman D, Iversen T, Armbruster D. Marijuana-positive urine test results from consumption of hemp seeds in food products. J Anal Toxicol 1997;21:476–81.

Frytak S, Moertel CG, Rubin J. Metabolic studies of delta-9-tetrahydrocannabinol in cancer patients. Cancer Treat Rep 1984; 68 (12): 1427-31.

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

Gustafson RA, Levine B, Stout PR, Klette KL, George MP, Moolchan ET and Huestis MA. Urinary cannabinoid detection times following controlled oral administration of delta-9-tetrahydrocannabinol to humans. *Clinical Chemistry*, 2003 Jul; 49(7):1114-1124.

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.

Hollister LE, Gillespie HK, Ohlsson A, et al. Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? J Clin Pharmacol 1981; 21 (8-9 Suppl.):171S-7S.

Huestis MA, Abulseoud O, Sempio C, Andersson M, Newmeyer MN, (unpublished urine data following smoked, vaporized and oral administration of 50.6 mg THC).

Indorato F, Liberto A, Ledda C, Romano G, Barbera N. The therapeutic use of cannabinoids: Forensic aspects. Forensic Science International 2016;265:200–203.

Interpretation of listing of “tetrahydrocannabinol” in Schedule I [Interpretive Rule]. Federal Register 2001;195:51530–44.

Law B, Mason PA, Moffat AC, et al. Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin. J Pharm Pharmacol 1984; 36 (5):289-94.

Lehmann T, Sager F, Brenneisen R. Excretion of cannabinoids in urine after ingestion of cannabis seed oil. J Anal Toxicol 1997;21:373–5.

Leson G, Pless P, Grotenhermen F, Kalant H, ElSohly MA. Evaluating the impact of hemp food consumption on workplace drug tests. J Anal Toxicol 2001;25:691–8.

Mölleken and H. Husmann. Cannabinoids in seed extracts of Cannabis sativa cultivars. J. Int. Hemp Assoc. 4: 1, 76–79 (1997).

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther. 1980 Sep;28(3):409-16.

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma levels of delta 9-tetrahydrocannabinol after intravenous, oral, and smoke administration. NIDA Res Monogr. 1981 Feb;34:250-6.

Ohlsson A, Agurell S, Lindgren JE, Gillespie HK, Hollister LE. Pharmacokinetic studies of delta-1-tetrahydrocannabinol in man. In Pharmacokinetics and pharmacodynamics of psychoactive drugs. Barnett G and Chiang CN (Eds). 1985 Mosby Yearbook, Inc. Volume 4 Pages 75-92.

Perez-Reyes M, Lipton MA, Timmons MC, Wall ME, Brine DR, Davis KH. Pharmacology of orally administered delta-9-tetrahydrocannabinol. Clinical Pharmacology Therapeutics 1973;14:48-55.

Research, Health Protection Branch, Health Canada. Industrial hemp technical manual: TPP-BDS-004 – Basic method for determination of THC in hempseed oil, 1992.

Sadler BM, Wall ME, Perez-Reyes M. The pharmacokinetics of delta-9 - tetrahydrocannabinol after simultaneous intravenous and oral administration. In: Agurell S, Dewey WL, Willette RE, eds. The cannabinoids: chemical, pharmacologic, and therapeutic aspects. New York: Academic Press, 1984:227–38.

Sporkert F, Pragst F, Ploner CJ, Tschirch A, Stadelmann AM. Pharmacokinetic investigations and delta-9-tetrahydrocannabinol and its metabolites after single administration of 10 mg Marinol in attendance of a psychiatric study. The Annual Meeting of The International Association of Forensic Toxicologists, Prague, Czech Republic. 2001.

Struempler RE, Nelson G, Urry FM. A positive cannabinoids workplace drug test following the ingestion of commercially available hemp seed oil. J Anal Toxicol 1997;21:283–5.

Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray.
Eur J Clin Pharmacol. 2013 May;69(5):1135-47. doi: 10.1007/s00228-012-1441-0. Epub 2012 Nov 22.

Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. AIDS Res Hum Retroviruses 1997; 13 (4):305-15.

Wall ME, Perez-Reyes M. The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man. J Clin Pharmacol 1981; 21 (8-9 Suppl.): 178S-89S.

Wall ME, Sadler BM, Brine D, et al. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol, in men and women. Clin Pharmacol Ther 1983; 34 (3): 352-63.

References for determining infant THC exposure from breastfeeding

Ahmad GR, Ahmad N. Passive consumption of marijuana through milk: a low level chronic exposure to delta-9-tetrahydrocannabinol(THC). J Toxicol Clin Toxicol 1990;28(2):255–260.

Alaniz VI, Liss J, Metz TD, Stickrath E. Cannabinoid hyperemesis syndrome: a cause of refractory nausea and vomiting in pregnancy. Obstet Gynecol. 2015;125(6):1484-6.

American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk Pediatrics 2001;108(3):776-789.

Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. Neurotoxicol Teratol 1990;12(2):161–168.

Battista N, Sergi M, Montesano C, Napoletano S, Compagnone D, Maccarrone M. Analytical approaches for the determination of phytocannabinoids and endocannabinoids in human matrices. Drug Testing Analysis 2014;6:7–16.

Bergeria CL, Heil SH, Surveying Lactation Professionals Regarding Marijuana Use and Breastfeeding. Breastfeeding Medicine 2015;10(7):377-380.

Berlin CM, Briggs GG. Drugs and chemicals in human milk. Seminars in Fetal & Neonatal Medicine. 2005;10:149e159.

Brooks E, Gundersen DC, Flynn E, Brooks-Russell A, Bull S. The clinical implications of legalizing marijuana: Are physician and non-physician providers prepared? Addictive Behaviors 72 (2017) 1–7.

Burns L, Mattick RP, Cooke M. The use of record linkage to examine illicit drug use in pregnancy. Addiction 2006;101(6):873–882.

Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. Neurotoxicol Teratol 2011;33(1):129–136.

DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P et al. Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. Biol Psychiatry 2011;70(8):763–769.

Dotters-Katz SK, Smid MC, Manuck TA, Metz TD. Risk of neonatal and childhood morbidity among preterm infants exposed to marijuana. J Matern Fetal Neonatal Med. 2017;30(24):2933-2939.

El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatry 2009;48(12):1173–1181.

El Marroun H, Hudziak JJ, Tiemeier H, Creemers H, Steegers EA, Jaddoe VW et al. Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. Drug Alcohol Depend 2011;118(2-3):470–474.

Escuder-Vieco D, Garcia-Algar Ó, Pichini S, Pacifici R, García-Lara NR, Pallás-Alonso CR. Validation of a screening questionnaire for a human milk bank to determine the presence of illegal drugs, nicotine, and caffeine. J Pediatr. 2014;164(4):811-4.

Escuder-Vieco D, Garcia-Algar Ó, Joya X, Marchei E, Pichini S, Pacifici R, Pallás-Alonso CR. Breast Milk and Hair Testing to Detect Illegal Drugs, Nicotine, and Caffeine in Donors to a Human Milk Bank. Journal of Human Lactation 2016;32(3):542-5.

Foeller ME, Lyell DJ. Marijuana Use in Pregnancy: Concerns in an Evolving Era. J Midwifery Womens Health 2017;62:363–367.

Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 1999;21(5):513–525.

Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2003;25(4):427–436.

Garry A, Rigourd V, Amirouche A, Fauroux V, Aubry S, Serreau R. Cannabis and Breastfeeding. J Toxicol. 2009:596149.

Gleason KA, Birnbaum SG, Shukla A, Ghose S. Susceptibility of the adolescent brain to cannabinoids: long-term hippocampal effects and relevance to schizophrenia. Transl Psychiatry 2012;2:e199.

Godding V, Bonnier C, Fiasse L, Michel M, Longueville E, Lebecque P et al. Does in utero exposure to heavy maternal smoking induce nicotine withdrawal symptoms in neonates? Pediatr Res 2004;55(4):645–651.

Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. Neurotoxicol Teratol 2000;22(3):325–336.

Goldschmidt L, Richardson GA, Willford JA, Severtson SG, Day NL. School achievement in 14-year-old youths prenatally exposed to marijuana. Neurotoxicol Teratol 2012; 34(1):161–167.

Hale TW. Medications and Mother's Milk, 15th ed. Plano, TX: Hale Publishing, 2012.

Hotham N, Hotham E. Drugs in breastfeeding. Australian Prescriber. 2015;38;5:156-160.

Jansson LM, Bunik M, Bogen DL. Lactation and the Marijuana-Using Mother Breastfeeding Medicine 2015;10(6):1.

Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, Abdel-Latif ME, Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology 2014;34:417–424.

Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, Abdel-Latif ME, Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. Journal of Perinatology 2014;34(6):417-24.

Jarlenski M, Zank J, Tarr J, Chang JC. Public health messages about perinatal marijuana use in an evolving policy context. Substance Abuse. 2017;38(1):48-54.

Kacew S Adverse effects of drugs and chemicals in breast milk on the nursing infant. J Clin Pharmacol. 1993;33(3):213-21.

Khare M, Taylor AH, Konje JC, Bell SC. Delta9-tetrahydrocannabinol inhibits cytotrophoblast cell proliferation & modulates gene transcription. Mol Hum Reprod 2006;12(5):321–333.

Klonoff-Cohen H, Lam-Kruglick P. Maternal and paternal recreational drug use and sudden infant death syndrome. Arch Pediatr Adolesc Med 2001;155(7):765–770.

Liston J. Breastfeeding and the use of recreational drugs – alcohol, caffeine, nicotine and marijuana. Breastfeeding Review 1998;6(2):27-30.

Marchei E, Escuder D, Pallas CR, Garcia-Algar O, Gómez A, Friguls B, Pellegrini M, Pichini S. Simultaneous analysis of frequently used licit and illicit psychoactive drugs in breast milk by liquid chromatography tandem mass spectrometry. J Pharm Biomed Anal. 2011;55(2):309-16.

Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. Am J Obstet Gynecol. 2015;213(6):761-78.

Metz TD, Allshouse AA, Hogue CJ, Goldenberg RL, Dudley DJ, Varner MW, Conway DL, Saade GR, Silver RM. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. Am J Obstet Gynecol. 2017;217(4):478.e1-478.

Mourh J, Rowe H. Marijuana and Breastfeeding: Applicability of the Current Literature to Clinical Practice. Breastfeed Med. Epub 2017 Sep 5.

Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M et al. Metabolic effects of chronic cannabis smoking. Diabetes Care 2013;36(8):2415–2422.

Murphy LL, Munoz RM, Adrian BA, Villanu´ a MA. Function of cannabinoid receptors in the neuroendocrine regulation of hormone secretion. Neurobiol Dis 1998;5(6PtB):432–446.

Neugebauer R, Kline J, Stein Z, Shrout P, Warburton D, Susser M. Association of stressful life events with chromosomally normal spontaneous abortion. Am J Epidemiol 1996;143:588–596.

Newton ER & Hale TW. Drugs in Breast Milk. Clinical Obstetrics and Gynecology. 2015;58(4):868–884.

Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. N Engl J Med 1982; 307(13): 819–820.

Reece-Stremtan S, Marinelli KA. The Academy of Breastfeeding Medicine. ABM Clinical Protocol #21: Guidelines for Breastfeeding and Substance Use or Substance Use Disorder, Revised 2015. Breastfeeding Medicine 2015:10(3);135-141.

Reisner SH, Eisenberg NH, Stahl B, Hauser GJ. Maternal medications and breast-feeding. Dev Pharmacol Ther. 1983;6(5):285-304.

Sharma P, Murthy P, Bharath MMS. Chemistry, Metabolism, and Toxicology of Cannabis: Clinical Implications. *Iran J Psychiatry* 2012;7(4):149-156.

Sipsma A, Divney AA, Magriples U, Hansen N, Gordon D, Kershaw T. Breastfeeding Intentions Among Pregnant Adolescents and Young Adults and Their Partners. Breastfeeding Medicine 2013;8(4):374-380.

Sipsma A, Magriples U, Divney AA, Gordon D, Gabzdyl, E, Kershaw T. Breastfeeding behavior among adolescents: Initiation, duration, and exclusivity. J Adolesc Health. 2013;53(3):394–400.

Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. Neurotoxicol Teratol 2006;28(2):286–295.

Smithers LG, Lynch JW, Yang S, Dahhou M, Kramer MS. Impact of neonatal growth on IQ and behavior at early school age. Pediatrics 2013;132(1):e53–e60.

The American College of Obstetricians and Gynecologists. Committee on Obstetric Practice. Marijuana Use During Pregnancy and Lactation. 2015;126(1):234-8.

Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. In utero marijuana exposure associated with abnormal amygdala dopamine D2 gene expression in the human fetus. Biol Psychiatry 2004;56(12):909–915.

Warner TD, Roussos-Ross D, Behnke M. It’s Not Your Mother’s Marijuana: Effects on Maternal-Fetal Health and the Developing Child. *Clin Perinatol*. 2014;41(4):877–894.

Warner TD, Roussos-Ross D, Behnke. It's not your mother's marijuana: effects on maternal-fetal health and the developing child. Clin Perinatol. 2014;41(4):877-94.
Wang GS Pediatric Concerns Due to Expanded Cannabis Use: Unintended Consequences of Legalization. J. Med. Toxicol. 2017 Mar;13(1):99-105.

10 pages of Curriculum Vitae removed in accordance with the Privacy Act of 1974.