FDA ATTY

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September 14, 2018

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

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

Dr. Cournoyer,

Thank you again for your time by telephone on August 16, 2018, and subsequent e-mail on August 31, 2018. In the pages that follow are the detailed replies to your questions.

This response adds nearly 100-pages and dozens of new references to Fresh Hemp Foods GRAS notices. As described below, there is an abundance of good evidence for the consumption of hemp as described in GRN 765, 771, and 778, including the historical record, the animal studies where no lethal dose could be obtained in large mammals and where high dose testing typically produced small, transitory, toxicological effects, and in the human clinical studies.

We feel strongly that GRNs 765, 771, and 778 fully satisfies the "reasonable certainty of no harm standard" (21 C.F.R. 170.30).

Kind Regards,

Digitally signed by Marc C. Sanchez, Esq.
Date: 2018.09.14 16:29:31 -04'00'
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Responses to Additional Information Request

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1. Animal toxicology data

Traditional animal toxicological studies typically form the foundation of scientific food safety assessments. NOAEL or LOAEL values from animal studies are often used to calculate a margin of exposure, which facilitates risk management. Animal studies can also be useful for addressing specific endpoints such as developmental and reproductive toxicity. Amending your safety narrative to include a robust discussion of animal toxicology data would serve as an appropriate context for the human data discussed in the original submission. You may wish to consult EFSA's scientific opinion (2015), which includes a detailed discussion of animal studies and could serve as a useful reference for a revised safety narrative.

Response:

All preclinical studies referenced in the "EFSA Scientific Opinion on the risks for human health related to the presence of Δ9-tetrahydrocannabinol (THC) in milk and other food of animal origin", and in the ANZFA Final Assessment Report Application A360 Use of Industrial Hemp as a Novel Food were reviewed. In addition, a brief literature search was performed in PubMed for any recently published articles that could be informative.

Review of Experimental Animal Studies on THC Effects

THC Toxicity LD50

The median lethal doses of oral THC in rats and mice were 666 mg Δ9-THC/kg bw and 482 mg Δ9-THC/kg bw, respectively (Phillips et al., 1971). No deaths occurred when dogs were administered 3000 mg/kg bw oral THC and rhesus monkeys received 9000 mg/kg bw oral THC (Thompson et al., 1973a). To date, there are no human deaths attributed to oral THC self-administration; therefore, there is no established human lethal dose (Huestis review of published literature).

Effects of THC on the Endocrine Hormone System

According to the ANZFA Final Assessment Report endocrine hormone changes were the most sensitive indicator of oral THC administration in experimental animals; however, the changes were transitory and not strongly dose-related. Following intramuscular injection of 0.625 mg/kg bw or greater THC to female rats, luteinizing (LH) and follicle stimulating (FSH) hormones were reduced (Smith et al. 1978). THC also inhibited the surges of LH and FSH that are essential for ovulation by suppressing normal circulating levels of LH in female rats and monkeys (Smith et al., 1979). In addition, the normal rhythm of menstrual cycles in monkeys were disrupted. THC altered pituitary secretion of LH, FSH and prolactin when administered acutely or repeatedly to intact and ovariectomized female rats, (Steger et al., 1980, 1981). Oral THC administration of 0.5 mg/kg to rats reduced LH concentrations 60 min after dosing but not at 30 or 120 min (Murphy et. al.1990). Similarly, single oral 0.1, 1 or 10 mg/kg bw THC doses reduced plasma LH and testosterone at 60 min, but there was no dose-response effect (Steger et. al. 1990).

THC and other cannabinoids may affect the hypothalamic-pituitary-gonadal axis mainly via the interaction with CB1 receptors expressed in the hypothalamus, resulting in a depression of the reproductive hormones, prolactin, and growth hormone (EFSA Journal 2015;13(6):4141). Lower oral doses and intravenous (IV) and intraperitoneal (IP) routes of administration led to minor changes, suggesting a lack of relevance of these changes. THC increases the secretion of adrenocorticotropin (ACTH) that stimulates the synthesis of glucocorticoids in the adrenal gland. Acute 2-50 mg/kg bw THC administration elevated plasma corticosterone concentrations in both male and female rats (ANZFA Final Assessment Report). THC induced age-degenerative changes in rat brain tissue similar to those resulting from elevated corticosterone (Landfield et. al. 1988). Later, Block et. al. 1991 did not observe changes in cortisol concentrations in male frequent cannabis users, consistent with other human data from earlier studies. Also, through hormonal effects, THC can inhibit milk production and release, with possible adverse implications for postnatal growth. Other preclinical studies documented THC disruption of the hypothalamus and pituitary gland.

Acute and chronic THC administration altered pituitary gonadotropin concentrations in animals; Wenger et. al. (1992) suggested that this might be mediated through direct effects on catecholamines, such as norepinephrine.

Five or 10 mg/kg bw IP THC for 5 days produced a significantly higher incidence of abnormal sperm in mice (Zimmerman et al 1979). Early 1980's studies reported that THC decreased concentrations of male reproductive hormones and sex organ weights, but later studies did not support these findings. The authors suggested that effects observed in animals were not considered significant to human health assessment. Early human and primate studies indicated that cannabis exposure produced no effect or a transient reduction in plasma LH and testosterone concentrations (Cone et al., 1986; Smith and Asch, 1984). Similarly, early studies in male rats did not provide conclusive evidence that THC inhibits growth hormone secretion. Direct infusion of THC into the brain of adult male rats suppressed growth hormone secretion (ANZFA Final Assessment Report). Circulating thyroxine levels also were reduced following acute or chronic THC administration in male rats and rhesus monkeys. THC treatment also affected the release of oxytocin (Tyrey & Murphy, 1988).

A recent review evaluated the current literature on cannabis use and regulation of the female hypothalamic-pituitary-ovarian (HPO) axis, ovarian hormone production, the menstrual cycle, and fertility (Brents 2016). Daily 2.5 mg/kg bw IM THC dosing during the follicular phase of the menstrual cycle induced longer, anovulatory cycles in rhesus monkeys, while luteal phase length was not affected at doses up to 5.0 mg/kg bw. The authors stated that overall findings from human and animal studies suggest that acute THC suppresses the release of gonadotropin-releasing hormone (GnRH) and thyrotropin-releasing hormone (TRH) from the hypothalamus, preventing these hormones from stimulating the release of prolactin and the gonadotropins, FSH and LH, from the anterior pituitary. Thrice-weekly administration of THC (2.5 mg/kg bw) robustly suppressed serum estradiol, progesterone, LH, and prolactin, and inhibited ovulation and menses, but the monkeys developed complete tolerance after about 4 months after this high THC dose. Two studies examined cannabis effects across the menstrual cycle in humans and found no effects.

Different experimental procedures and different cannabis exposure histories can affect experimental results, but the ANZFA report concluded that there is general agreement that cannabinoids do alter reproductive hormones controlling testicular function. Although some disturbances are noted in animals after acute THC exposure, the doses were 2 mg/kg bw THC or higher, and the route of administration had greater bioavailability than oral administration being considered here. In addition, tolerance to THC effects developed with subchronic exposure.

Effects on reproduction

Decreases in testicular, seminal vesicle, prostate and ovarian weights, and increases in pituitary and adrenal weights were documented in preclinical studies following cannabinoid exposure (WHO, 1997). An elevated risk of birth complications, abnormal labor progress and/or premature births have not been confirmed in cannabis users. Fetal hypoxia is suggested to be the mechanism for observed reproductive effects, similar to the effects produced by cigarette smoking (WHO, 1997). THC in milk and other food of animal origin decreases the number of viable pups, an increase in fetal mortality and early resorptions (EFSA Journal 2015).

THC rapidly transfers across the placenta to the developing fetus (Bailey et. al., 1987). Pregnant rhesus monkeys receiving 0.3 mg/kg bw IV THC had peak plasma THC concentrations after 3 mins in maternal blood and after 15 mins in the fetus, within 3 h maternal and fetal plasma THC concentrations were equivalent. THC crosses the placenta to the vascular system of the fetus although in rats, sheep, dogs and monkeys fetal plasma concentrations were lower than maternal concentrations.

Effects on intrauterine and post-natal development

THC produced teratogenic effects in some preclinical studies, although these studies had questionable study designs (Abel, 1985), and were not consistent with other well-conducted oral THC studies (Fleischmann et al., 1975). Dose-related maternal toxicity and embryotoxicity was noted when THC was administered early in gestation, but malformations were only observed following high dose IP administration. A confounding issue in these studies is the significant THC-induced reduction of food and water intake by the pregnant rats during treatment in this and other studies at lower dose levels (15 mg/kg bw, Hutchings et al. 1987). This may partially account for the poor fetal

development. The only consistent finding was a decrease in birthweight (Abel, 1985). Hernandez et al (1997) administered 5 mg/kg bw THC daily to pregnant rats, much lower THC doses than those used previously in fetal toxicity studies, and showed doubling of tyrosine hydroxylase activity in specific fetal brain cells. These data documented that THC could produce physiological effects at lower doses, albeit at doses almost a thousand-fold higher than those from ingesting maximal doses of hemp foods. There were no behavioral alterations in the offspring of dams exposed to 50 mg/kg bw THC (Abel et. al., 1984). Long-term effects of developmental THC exposure were noted in adult animals, suggesting that the brain is more sensitive during development than in adult animals (Downer et al., 2007). In addition, THC doses that did not have detrimental effects alone potentiated effects of additional chemical insults (Hansen et al., 2008).

Effects on the immune system

IP doses of 15 - 50 mg/kg bw THC to mice resulted in resistance to bacterial or viral infections (ANZFA Final Assessment Report). Although multiple studies established that THC is an immunomodulator, this occurred only at relatively high doses. A single 10 mg/kg bw THC dose inhibited functional and/or biochemical immune parameters following THC exposure and in mice, following repeated dosing up to 14 days (EFSA 2015). Apoptosis in bone marrow-derived dendritic cells from mice and in macrophages isolated from the peritoneal cavity in mice were demonstrated following THC. Inflammatory myeloid cells and macrophages/monocytes were the most sensitive to THC. Perinatal exposure of mice to THC caused fetal thymic atrophy and T cell dysfunction postnatally.

THC in high doses of 10 to 50 mg/kg bw caused immune disturbances.

Genotoxicity and carcinogenicity

THC is not mutagenic in the Ames test (Zimmerman et. al., 1978), although cannabis smoke was sometimes mutagenic. THC interfered with the normal cell cycle (Zimmerman & McClean, 1973) and also decreased DNA, RNA and protein synthesis (Blevins & Regan, 1976). THC also disrupted microtubule formation (Tahir & Zimmerman, 1992). There was no increase in sister-chromatid exchanges (SCE) in cannabis users' lymphocytes compared to tobacco smokers (Joergensen et. al., 1991).

The US National Toxicology Program evaluated THC's carcinogenicity at high 125, 250 and 500 mg/kg/day doses in rats and mice (NTP, 1996). Thyroid hyperplasia was observed in male and female mice at all doses. Zebrafish embryos had defects following exposure to 2 ppm THC in solution for greater than 24h (Thomas et al., 1975). No evidence of teratogenicity following exposure to THC in rodent studies was observed (EFSA Journal 2015). Epidemiological studies in human pregnant cannabis users do not support an increase in congenital malformations (Knight et al., 1994; Astley, 1992; Witter & Niebyl, 1990).

Neurotoxicity

Following long term exposure to THC in rats, morphological changes in synapses and hippocampal neuronal loss were observed (Sidney et al. 1997). Mice received up to 100 mg THC/kg bw IP to control seizures (Rosenberg et al., 2017). Activity was reduced in some mice, and no adverse effects were reported. Gerbils were dosed with 50 mg THC/kg bw IP to control seizures without adverse effects (Ten Ham et al., 1975). In addition, chronic administration of cannabis for one year to rhesus monkeys impaired their ability to perform operant tasks, but performance returned to normal three weeks after treatment (Slikker et. al., 1992). THC effects in experimental animal models include alterations in locomotor activity and decreased responsiveness to amphetamine, reduced social interactions and impaired learning (EFSA Journal 2015). Effects occurred only immediately following acute or chronic THC dosing in adult animals exposed to THC during development. While activity effects had a biphasic dose-dependence curve, impairment of learning and memory were consistent across most studies (exception: Silva et al., 2012), and were long lasting even after single administration of low THC doses.

Well-controlled preclinical studies provided data only in response to high THC doses that have important methodological problems related to depression of maternal food and water consumption (Abel, 1985). When pregnant rats received daily oral 15 or 50 mg/kg bw THC, dose-related decreases in birth weight and weight gain in the offspring were reported; however, decrease in birth weight was most likely due to poor maternal nutrition and

dehydration in the THC treated group, rather than from any direct toxic effects (Hutchings, 1985). Such studies are unlikely relevant to low-dose human exposure.

The effect on reproductive hormone concentrations was the most sensitive parameter for cannabinoid toxicity in animals. In rats, LH and FSH changes were observed at 0.1 mg/kg bw oral THC, although there was no apparent dose-response relationship. Exposure at 0.1 mg/kg much higher than cumulative daily exposure to all hemp products described in this application. Furthermore, the significance of much of the preclinical data to humans is unclear since high THC concentrations were employed, dose-response relationships were generally not demonstrated, and frequently the route of administration was IP or IV rather than oral.

Based on the data included in the ANZFN review, it was not possible to establish a level at which no effects were observed; however, the lowest-observed-effect level (LOEL) was 5 mg/person, equivalent to a dose of 60 µg/kg bw. Effects at this dose were minimal and reversible. There were no psychotropic effects observed at this dose. In order to take account of the possible variability in response in the human population, an uncertainty factor of 10 should be applied to the LOEL to derive an overall tolerable daily intake of 6 µg/kg bw.

Total THC exposures in µg/kg bw following ingestion of all three Fresh Hemp Foods Ltd. hemp products (Hulled Hemp Seed, Hemp Protein Powder and Hemp Seed Oil) according to body weight are shown in Table 1. Refer to response to Question 4 and referenced Tables and Figures for values. The data are presented in three different ways. In column B, the data are based on consuming the maximum amount recommended for each product and total THC at the highest permissible concentration- if Hulled Hemp Seed contained 4 µg/g THC (maximal permitted limit by Fresh Hemp Foods Ltd), Hemp Protein Powder (maximal 4 µg/g) and Hemp Seed Oil (maximal 10 µg/g). Body weights for each age level and suggested meal amounts for each age are contained in other attached tables. Average µg/g bw THC exposures are 2.2 and 2.5 for males and females 2 years and older, respectively, which is below the acceptable daily intake established by the German, Swiss, Australian and New Zealand regulatory standards. This concentration is approximately double that recommended by the EFSA and Austrian regulatory standards. Column C addresses total THC exposures from all three hemp products based on the actual total THC concentrations in Fresh Hemp Foods Ltd. products. Based on these more precise total THC concentrations, average µg/g bw THC exposures are 0.7 and 0.8 for males and females 2 years and older, respectively, which is below the acceptable daily intake established by all regulatory standards, including the EFSA standard. Column D addresses total THC exposure based on the Monte Carlo predicted exposure at the 99.9% certainty level. The Monte Carlo predictions were based on the more precise Total THC concentrations (limit of quantification [LOQ] of 0.2 µg/g for analyses of total THC in Hulled Hemp Seed, Hemp Protein Powder and Hemp Seed Oil). Average µg/g bw THC exposures are 1.3 and 1.5 for males and females 2 years and older, respectively, which is below the acceptable daily intake established by all regulatory standards except for the EFSA standard in milk products of 1 µg/kg bw. The Monte Carlo data assume ingestion of the maximal amount of all three hemp food products at the highest certainty level and this yields concentrations only slightly above the EFSA recommendations and below all the other international regulatory bodies.

However, these low total THC exposures are 100 to 1000 fold lower than the total THC exposures described above in the animal toxicology data. Furthermore, many of the animal studies utilized IV or IP routes of administration with higher THC bioavailability than through the oral consumption of hemp food products. THC exposure from hemp foods in infants and toddlers is addressed in the response to Question 9.

2. Assurance of conformity to Health Canada industrial hemp regulations

Yang et al. (2017) report that samples of hempseed purchased from grocery stores in Canada exceeded Health Canada's THC limit of 10 µg/g, sometimes by more than 10-fold. Please discuss this finding in light of your assurance that THC levels in your hempseed are below 4 µg/g.

Yang, Y., Lewis, M.M., Bello, A.M., Wasilewski, E., Clarke, H.A., and Kotra, L.P. (2017). Cannabis sativa (Hemp) Seeds, Δ (9)-Tetrahydrocannabinol, and Potential Overdose. Cannabis Cannabinoid Res 2: 274-281.

Response:

Yang et al (2017) did not report the identity or country of origin for any of the samples included in their article. This lack of information makes it difficult to confirm what controls or testing was applied by the manufacturers to assure their products comply with the Canadian Regulations.

Fresh Hemp Foods Ltd. assures that its products comply with Health Canada's THC limit of ≤10 µg/g. All Fresh Hemp Foods Ltd. hempseed products are produced in accordance with Health Canada's *Industrial Hemp Regulations* and Fresh Hemp Foods Ltd. specifications and quality management systems.

Mandatory requirements per *Industrial Hemp Regulations*

- Only Health Canada approved low THC cultivars may be grown for seed production. Refer to 2018 cultivar list to see current authorized varieties (accessible at https://www.canada.ca/en/health-canada/services/health-concerns/controlled-substances-precursor-chemicals/industrial-hemp/commercial-licence/list-approved-cultivars-cannabis-sativa.html)
- All hemp crops intended for seed production in Canada must be grown by licensed growers using pedigreed seed
- Growers are not allowed to save seed from year to year for planting
- Industrial hemp crops must be tested for conformance with the limit of ≤0.3% THC before their seeds are allowed to be harvested for food production. Testing must be done by accredited laboratories using the gas chromatography (GC) methodology cited in Health Canada's Industrial Hemp Technical Manual (HECS-OCS-001, Basic Analytical Procedure for the Determination Of Delta-9-tetrahydrocannabinol (THC) in Industrial Hemp)
- Hempseed derivatives must be tested to confirm compliance with the limit of ≤10 µg/g THC by accredited laboratories using the GC-MS methodology cited in Health Canada's Industrial Hemp Technical Manual (HECS-OCS-004, Basic Method for Determination of THC in Hempseed Oil)

Fresh Hemp Foods Ltd. Specification and Quality Management Systems

- Only seed produced from Health Canada approved low THC cultivars are processed into food ingredients by Fresh Hemp Foods Ltd.
- All whole hemp seed processed by Fresh Hemp Foods Ltd. must be thoroughly cleaned to stringent Fresh Hemp Foods Ltd. specifications by a licensed seed cleaner to remove plant debris (the source of THC and THCA contamination on the seed surface) and other contaminants
- All hemp seed derivatives must be tested for conformance with the Fresh Hemp Foods Ltd. Total THC specification prior to sale; specifically, ≤10 µg/g for Oil and ≤4 µg/g for Protein Powder and Hulled Hemp Seed. Testing must be done by accredited laboratories using the HECS-OCS-004 GC-MS method. Which is required to have a minimum 4 µg/g LOQ.

Delta-9-tetrahydrocannabinolcarboxylic acid (THCA) is known to rapidly decarboxylate to THC when exposed to heat and slowly convert during ambient temperature storage (Citti et al. 2018, Escrivá et al. 17). EFSA's Scientific Opinion (2015) and Lachenmeier and Walch (2005) report that studies examining analytical techniques for

quantification of THC confirmed that GC quantifies Total THC (free THC and THCA) because of the high temperature to which the sample is exposed during injection Health Canada (2013).

Fresh Hemp Foods Ltd. commissioned tests to verify THC content of its Hulled Hemp Seed, Protein Powder and Hemp Oil. These tests were performed by accredited labs that are quantifying Total THC using method HECS-OCS-004.. Refer to response for Question 4 for a summary of these historical data. The historical data confirm that the Fresh Hemp Foods Ltd. products comply with the maximum THC limits required by the *Industrial Hemp Regulations* and/or the tighter limits self-imposed by Fresh Hemp Foods Ltd.

Consultation with Dr. Art McElroy, a plant breeder with a back ground in genetics and almost 20 years experience working with industrial hemp confirms that any THCA or THC that is detected in a hemp seed derivative resulted from cross contamination of the shell exterior with the essential oil produced by the trichomes. However, the levels of THC in the flower parts (bracts) is very low in industrial hemp, so any resin that could stick to the seed is expected to contain low levels of cannabinoids. Molecular genetic research performed over the last few years elucidated the THC transcriptome and confirmed that there is no evidence that the alleles for THC are expressed in anything other than the trichomes on Cannabis plants. It is the common belief of plant breeders that there is no evidence of production THC within the seed (McElroy 2018). This supports the interpretation that the inhomogeneous THC content identified by Yang et al. (2017) during their analysis of commercial hulled hemp seeds is due to inadequate cleaning of the intact raw seed by the manufacturer prior to dehulling, because no significant THC is found when hempseeds are cleaned properly (Hemphill, Turner and Mahlberg 1980, Ross et al. 2000, Karimi and Hayatghaibi 2006). This is also consistent with the work of Citti et al. 2018 who report that the concentration of cannabinoids in hemp seed oil depends on the cleaning process of the seed and is highly variable amongst different varieties. In support, they reference low THC European cultivars authorized for seed production which are regulated to a maximum limit of 0.2% THC resulting in THC contamination in hemp seed oil which is generally low and only exceptionally exceeds the German limit of 5 mg/kg.

The European approach of controlling THC in the cultivar is in place to reduce exposure of the seed to high levels of THC in the resin. Health Canada utilizes a similar approach and requires authorized low THC cultivars with a maximum 0.3% THC to be used for seed production. Health Canada reinforces this approach by disallowing growers to retain seed from year to year for planting, thereby preventing the possibility of a variety reverting to producing high THCA and Δ-9-THC. Fresh Hemp Foods Ltd. only processes seeds grown from Health Canada authorized low THC cultivars, so it can be expected that the resulting seed derivatives were exposed to less cannabinoids than seeds produced from non-authorized cultivars.

Plant breeders are using molecular markers to eliminate THC production from new hemp varieties. The intent of their work is to produce varieties which have non-detectable amounts of THC even in the bracts, so there will be absolutely none on the seed McElroy (2018). This is highly relevant to the continued safety of industrial hemp since these new varieties will eventually be available to produce seed for human food.

3. Fresh Hemp's specification for THC limits and testing methodology

The analytical methodology cited in your notices as part of the specification limit for THC is Health Canada's Industrial Hemp Technical Manual. The methods described in this manual are intended for the analysis of dried leaf powder or seed oil and the applicability of the methods to analysis of seeds is not discussed. Yang et al. (2017), for example, reported significant variation in the detectable level of cannabinoids among batches of hempseed and notes that this inconsistency might be attributable to variations among the hempseeds themselves as well as to variability in the extraction process. Yang et al. suggest that THC may partition into seed material due to its higher oil content compared to the rest of the plant and the hydrophobicity of THC, and that analysis of seed material may result in an underestimation of THC content. Considering this information, please discuss the analytical method you use to assure your hempseed products conform with specifications, and why you think this method is appropriate for ensuring actual THC levels in seed remain below your specification of 4 µg/g.

Response:

Sample preparation is the most important step to achieve accurate and precise results in almost any analytical protocol. Sample preparation is typically achieved in four or five steps, including matrix homogenization, analyte extraction, clean-up to eliminate interfering materials, and preconcentration of the extract into a small volume.

The Industrial Hemp Technical Manual also outlines sample preparation procedures for the saponification and preconcentration of the extract for analysis GC-MS. While this method does not explicitly outline the extraction methods for plant tissues and foodstuffs, the author of the reference for the method highlighted the importance of the preparation of plant and foodstuff samples. The author's suggested and preferred method is through grinding, suggesting the use of a Retsch mill (of the type used in the generation of the data used in this submission) to reduce particle size prior to solvent extraction (Giroud, C., 2002). Consultation with the accredited laboratories confirms that the hemp samples (hulled hemp seed, hemp protein powder, hemp meal powder, hemp hearts) are milled to a homogeneous fine powder to make the material compositionally uniform and to maximize sample surface area to ensure complete saponification and extraction of the cannabinoid analytes.

One validated method had a sample preparation step of grinding using a mortar and pestle prior to THC analysis (Meng et al.), a method that would arguably provide more variation than grinding using a mechanical mill but still provided adequate particle size reduction.

Liquid-liquid microextraction (LLE) is the most widely used method for extraction of analytes from complex matrices (Ridgeway et al., 2007). Coupled with saponification, this method ensures the full recovery of cannabinoids. Because cannabinoids are strongly lipophilic, cannabinoid–lipid binding is viewed as a potential reason why cannabinoid values may be under-reported in THC quantification (Wei et al, 2016). Saponification is commonly used as a separation method. The saponification of oils from oilseeds will allow for the separation of fats from unsaponifiable hydrophobic compounds such as alkylphenols, a compound class that includes cannabinoids (Fontanel, 2013). Wei et al., 2016 speculated that formation of esters between cannabinoids and fatty acids could result in low recovery and observed "remarkable improvement in preparation efficiency" following saponification. Wei suggested that two major mechanisms underlie the improvement in sensitivity and efficiency. First is the conversion of triacylglycerols (TAG) into water-soluble materials. Conversion of TAG during saponification would reduce any triacylglycerol–cannabinoid binding. The second suggested mechanism is the liberation of cannabinoids from fatty acids during saponification.

After saponification, the THC is extracted using 3 successive portions of 3 mL petroleum ether/diethyl ether (1:1, v/v). The organic solutions are then combined and evaporated under nitrogen. After the sample is preconcentrated, the sample is derivatized and injected into the gas chromatography-mass spectrometry (GC-MS). GC-MS historically has been the favorite choice for cannabinoids analysis in both biological matrices and hemp products due to its versatility and feasibility (Lachenmeier and Walch, 2005, Pelligrini et al, 2004). Georgi et al followed a similar method for quantifying THC in a variety of food products using hexane extraction saponification, and GC-MS analysis, and demonstrated a LOQ of 12.9-17.3 µg/kg foodstuff.

4. THC values for Monte Carlo modeling

In your notices, you provide an exposure assessment model that uses THC concentration data obtained from 'historical third-party analytical testing.' Please discuss the data used in more detail, for example: the number of samples, their source, whether they are representative of the cultivars used, the analytical methodology used, limits of detection (LOD) or quantification, and how results below the LOD were handled.

Response:

Refer to Table 2 for summary detailing the Fresh Hemp Foods Ltd. historical data.

The historical data used in the original GRN765, 771, 778 notices was reassessed. Reports providing Total THC results were included. Analysis was performed using the Health Canada GC-MS method described in question 3. Health Canada approved low THC cultivars were used to produce the seed which was processed into the derivatives that were tested. Results were analysed to determine mean, minimum, maximum and standard deviation (Table 2).

Hulled Hemp Seed was tested 20 times with an LOQ of 0.2 µg/g. The mean is 0.3 µg/g, minimum is 0.1 µg/g (1/2 of LOQ concentration) and the maximum is 1.5 µg/g. Hemp Oil was tested 106 times with a 0.2 µg/g limit. The mean value is 6.0 µg/g, minimum is 0.1 µg/g and the maximum is 9.9 µg/g. Hemp Protein Powder was tested 6 times with an LOQ of 0.2 µg/g. The mean is 0.6 µg/g, minimum is 0.1 µg/g and maximum is 1.2 µg/g. Hundreds of other tests are routinely performed at an LOQ of 4 µg/g which is more cost effective and meets routine quality control criteria than the lower LOQ of 0.2 µg/g. The higher LOQ did not provide the level of sensitivity needed for the determinations made in these GRNs. Based on the intake and exposure levels discussed in the notices, use of the lower LOQ does not provide any additional benefit to justify the cost or adoption into the quality program.

The mean, minimum and maximum values obtained from this recent assessment of the historical data resulted in slightly different values compared to the evaluation performed during the original assessment. Accordingly, Fresh Hemp Foods Ltd. recalculated the THC exposure estimates using the mean historical THC concentrations and also recreated the THC exposure estimates using the crystal ball (Monte Carlo) probability model with a very high level of uncertainty. These updated data are provided to amend the relevant portions of the original notices and to determine µg/kg bw exposure estimates.

As described above in response to Question 1, the mean historical total THC values were used to determine how much Total THC would be consumed from food consumed at the 90% percentile and which contains maximum level of hemp ingredients (Tables 1, 16, 21). The mean, minimum and maximum total THC concentrations from the historical hemp testing were inputted as the key assumptions (refer to Table 2 and Figures 5, 6, 7) and the estimated total THC exposure based on body weight resulting from maximum consumption of each hemp material (Table 21) was inputted into the crystal ball probability model. The model ran the trial 10,000 times, each time selecting a different combination of THC µg/kg bw values from the individual ingredients, and then combining all results to produce the histograms shown in Figures 8 to 75. Refer to Table 1 for a summary of the predicted Total THC exposure based on body weight at a 99.99% certainty level for each of the age groups.

Children age 6 to 11 months were predicted to be exposed to 2.5 and 2.7 µg/kg bw for males and females respectively. Males age 11 to 23 months were predicted to be exposed to 6.4 µg/kg bw and females were predicted to be exposed to 5.9 µg/kg bw. Male and female children age 2 to 5 years and 6 to 11 years were predicted to be exposed to 5.1, 5.0. 3.5 and 3.7 µg/kg/bw respectively. Males age 2 years and older were predicted to be exposed to 1.3 µg/kg bw and females were predicted at 1.5 µg/kg bw.

Table 1 reflects the current information from the notices as well as this response. The exposure in µg/kg bw is estimated using three scenarios; specifically, THC based on maximum Fresh Hemp Foods Ltd. specifications (column A), THC based on mean historical testing levels (column B) and THC based on predicted values from probability modelling (column C). Each scenario uses the same level of cumulative hemp consumption in their calculations. The differences in values relates to how the quantity of Total THC provided by the hemp has been estimated. Multiple upper bound factors were used in the estimates of Total THC consumption for each age group:

1. Maximum level of the hemp seed derivatives defined in GRN765 Hulled Hemp Seed, 771 Hemp Protein Powder and 778 Hemp Oil being included into foods
2. 90th percentile consumption of all foods that may contain hemp
3. Cumulative consumption of Hulled Hemp Seed, Hemp Protein Powder and Hemp Oil at maximum inclusion and 90th percentile
4. Lowest body weight for children age 11 to 23 and 6 to 11 months based on anthropometric reference data for children, Fryar et al. (2016)
5. 100% replacement of fluid milk by hemp based beverage in children age 6 to 11 months and use of cumulative hemp consumption levels for 2 to 5 years old to estimate consumption by children age 11 to 23 months

The most conservative estimate of exposure relates to the consumption of hemp which contains maximum levels of Total THC as permitted by the Fresh Hemp Foods specifications.

The least conservative estimate based relates to the consumption of hemp which contains the mean Total THC level using historical data obtained by Fresh Hemp Foods Ltd. between 2011 and 2018 (Table 2).

The most representative estimate of exposure is determined from the forecasted values generated by the Monte Carlo model. Exposure was calculated using the Total THC based on body weight predicted at the 99.99% certainty level instead of the mean to add another conservative upper bound factor to the calculations.

5. Potential conversion of THCA to THC

You state that THC and THCA are present in the plant at ratio of approximately 1 to 9, that THCA is non-psychotropic, and that THCA converts to THC with heat and with time. Citti et al. (2018) report that conversion of THCA to THC can occur at room temperature with a half-life of approximately 49 days, and the reaction is further accelerated by sunlight and heat. Further, Escrivá et al. (2017) note that conversion of THCA to THC begins immediately after harvest.

Throughout processing, cooking, and storage, significant conversion of THCA to THC appears possible. It was not clear whether this was accounted for in your exposure estimate. Please discuss whether the analytical methods for measuring THC also measure THCA and whether your specification of 4 µg/g is a combined limit for both THC and THCA.

Citti C, Pacchetti B, Vandelli MA, Forni F, Cannazza G. J. (2018) Pharm Biomed Anal. 149: 532-540.

Escrivá Ú, Jesús Andrés-Costa M, Andreu V, Picó Y. (2018) Food Chem. 254: 391

Response:

Refer to responses for Question 2 and 4. Fresh Hemp Foods Ltd. uses accredited labs who are quantifying Total THC (THC and THCA).

In fresh, unprocessed hemp plants, THC mostly occurs in the form of its inactive carboxylic acid precursor: i.e. Δ9-tetrahydrocannabinol-carboxylic acid or THCA). THCA is present at a rate of about 90% of the total THC and is devoid of psychotropic effects (Dewey, 1986). However, THCA can be decarboxylated, i.e. converted into its active form, usually with heat, to provide its biologically active product THC. Decarboxylation occurs primarily as a function of time, pressure, temperature and long exposure to light, for instance in food processing or when combusted. Thus, largely unprocessed foods, such as cold-pressed oils, usually contain large fractions of the pharmacologically inactive THCA. THC can naturally accumulate even if THCA-containing material is not heated, with a half-life of between 35 and 91 days (depending on storage conditions and type of material this half-life can even be considerably longer), whereas THC degrades to cannabinol (CBN) at a half-life rate of only 24 to 26 months (Lindholst, 2010).

THC exposure estimates in GRN765, 771, 778 were conservatively estimated based on the cumulative consumption of Hulled Hemp Seed, Hemp Oil and Hemp Protein powder containing the maximum levels of Total THC per Fresh Hemp Foods Ltd. specifications. Results obtained with the GC method outlined in Health Canada's Industrial Hemp Technical Manual (HECS-OCS-004), quantifies the "total THC content" which includes not only THC, but the precursor THCA, since it is decarboxylated by the heat in the inlet of the GC (Health Canada, 2013). While THCA has no psychoactive effect, the useful and logical reason for its co-quantification is the possibility of increased THC content in hemp food products based on the age of the material (Escrivá et al., 2017) through heat applied during processing into value added products, or over shelf-life due to heat or exposure to light (Citti et al., 2018). Consequently, the 'total THC content' is also determined in the 'Community method for the quantitative determination of Δ-9-tetrahydrocannabinol' enforced at the EU level (Regulation (EC) No 796/2004, Annex I)18, and the 'Gas chromatographic determination of tetrahydrocannabinol in cannabis' enforced in Canada (Bureau of Drug Research, Health Protection Branch, 1992). The THC and THCA in hemp plant materials are extracted simultaneously from the plant matrix by a non-polar solvent and the extract is analysed by GC. THCA is decarboxylated quantitatively to THC during the saponification process (heating at 70°C for 2 hours) and in the injector (>200 °C) of the gas chromatograph and detected/quantified as THC. THC can degrade to cannabinol (CBN), with about 10% of THC's psychoactivity. Trofin et al. (2012) demonstrated the degradation kinetics of THC to CBN under ambient temperatures and exposure to light.

6. Other cannabinoids

Huestis (2007) states that "Cannabis sativa contains over 421 chemical compounds, including over 60 cannabinoids ..." Please discuss the typical levels and any associated limits for other cannabinoids, such as THCA (if not already accounted for in limits for THC), CBD, and CBDA. Briefly describe why levels of cannabinoids other than THC or any other chemicals that may be present in hemp seed products are safe.

Huestis, M.A. (2007). Human cannabinoid pharmacokinetics. Chem Biodivers 4, 1770-1804.

Response:

The firm is unaware of any other regulatory body or organization monitoring or regulating all 421 chemical compounds or 60 cannabinoids, all of which are naturally occurring in hemp. Currently only THC, which often includes THCA, and CBD levels are studied or regulated. As Huestis (2007) stated, "Cannabinoid pharmacokinetics research is challenging due to low analyte concentrations, rapid and extensive metabolism, and physico-chemical characteristics hindering the separation of drugs of interest from biological matrices and from each other." The body of scientific research reflects this with very limited research conducted on these compounds and cannabinoids. In particular, for terpenes which are rarely studied. These compounds and cannabinoids occur at low levels and the safety can be inferred from historical consumption, animal studies and human studies. In the historical data, humankind has cooked and pressed hemp plants for thousands of years, which would include exposure to these compounds and cannabinoids. In human studies, for example, 800mg CBD oral administration has produced no adverse effects. Exposure levels of CBD have exploded recently with the popularity of CBD supplementation. The levels proposed in the GRNs is considerably lower than any CBD supplement. Even at worse case intake levels, these compounds and cannabinoids would only be present in extremely low levels that are not only unreasonable to isolate and remove but very likely impossible to do so.

Based on a limited analysis the firm found the following.

Fresh hemp Foods Ltd. tested Hulled Hemp Seed, Hemp Oil and Hemp Protein Powder for 9 cannabinoids including THC, THCA, Δ-8-Tetrahydrocannabinol (Δ-8-THC), Cannabidiol (CBD), Cannabidiolic acid (CBDA), CBN, Δ-9-Tetrahydrocannabivarin (THCV), Cannabigerol (CBG) and Cannabichromene (CBC). The data on the other cannabinoids is largely based on analysis of Hulled Hemp Seed and Hemp Oil that was produced in 2018.

One lot of Hemp Protein Powder was tested for CBD (refer to Table 3). The lot contained 20 µg/g CBDA. The other cannabinoids were not tested.

Twelve lots of Hemp Oil were tested for some or all of the above 9 cannabinoids (refer to Table 3). All lots contained CBDA with the highest amount of 150 µg/g. None of the lots tested for THCV and Δ-8-THC had detectable concentrations. CBC was identified in two lots, CBD in three, CBG in two lots, one lot had THC and one lot had THCA

Eleven lots of Hulled Hemp Seed were tested for some or all of the above 9 cannabinoids (refer to Table 5). Δ-8-THC, THC, THCA and THCV were not identified in any lot. CBC, CBD, CBG were not detected in nine lots and eight lots contained no CBN. Nine lots contained CBDA, with the highest concentration 120 µg/g. One lot had 30 µg/g CBC, 20 µg/g CBD, 20 µg/g CBG and 10 µg/g CBN (lot NADI147FC), Only one other lot contained measurable CBN (lot TEAB15NCJ).

Refer to Tables 6 and 7 for estimate of exposure levels to other cannabinoids at upper bound consumption levels of all hemp ingredients. The historical data available to estimate other cannabinoids are relatively small. The highest tested concentration of each cannabinoid was used to estimate the concentration in the other hemp materials. For instance, the highest CBDA concentration was 150 µg/g in one lot of Hemp Oil so this concentration was used to calculate the upper bound estimates for Hulled Hemp Seed and Hemp Protein Powder. All estimates were calculated at the 90th percentile for consumption of hemp in food based on the NHANES data as detailed in the notices (Table 36 of GRN765)) except for the estimated exposure for children under the age of 24 months. The NHANES data used in the notices did not include data for children under the age of 24 months; therefore, 2 to 5 year

old children's intake was used to conservatively estimate exposure for children 12 to 23 months. Exposure of Infants 11 months and younger was estimated by substituting hemp-based beverage in place of fluid milk into a typical daily meal plan as recommended by the United States Department of Agriculture Infant Meal Pattern, USDA 2016.

Industrial hemp varieties show THC/CBD ratios ranging from 0.06:1 to 0.5:1. Thus, CBD is by far the dominant cannabinoid in industrial hemp varieties (de Meijer et al. 1992). This ratio is an intentional effect of specialized plant breeding intended to lower the psychoactive THC content. CBG, CBC and CBD are also found in industrial hemp. Using the upper bound cumulative estimated cannabinoid exposure, it can be conservatively estimated that males and females age 2 years and older would be exposed to 5420 µg/g CBDA, 723 µg/g CBD and 361 µg/g CBN per day from the cumulative consumption of all hemp materials in the notices. Male and female children age 2 to 5 years would be exposed to 4332 µg/g CBDA, 578 µg/g CBD and 289 µg/g CBN per day and 3800 µg/g CBDA, 507 µg/g CBD and 253 µg/g CBN per day respectively. Male and female children age 6 to 11 years would be exposed to 4548 µg/g CBDA, 606 µg/g CBD and 303 µg/g CBN per day and 4664 µg/g CBDA, 622 µg/g CBD and 311 µg/g CBN per day respectively. Infants from birth to 5 months are not expected to consumer hemp products directly so no estimate on other cannabinoid exposure is provided for this age range. Male and female infants age 6 to 11 months are anticipated to consume some hemp containing foods resulting in an estimated exposure of 2130 µg/g CBDA, 284 µg/g CBD and 142 µg/g CBN. Male and female children age 12 to 23 months would be exposed to 4332 µg/g CBDA, 578 µg/g CBD and 289 µg/g CBN per day and 3800 µg/g CBDA, 507 µg/g CBD and 253 µg/g CBN per day respectively. The levels of CBD estimated for all age groups, even when considering CBDA contribution is significantly lower than the levels that have been evaluated in human clinical studies.

Bergamaschi et al. (2011) assessed CBD's safety and side effects in a comprehensive review of 132 published in-vitro and in-vivo studies. The authors report that several studies suggest that CBD is non-toxic in non-transformed cells and does not induce changes in food intake or catalepsy, does not affect physiological parameters (heart rate, blood pressure and body temperature) or gastrointestinal transit and does not alter psychomotor or psychological functions. They also reported that chronic use and high doses up to 1,500 mg/day CBD are reportedly well tolerated in humans. However, they also report that in vitro and in vivo studies showed potential drug metabolism interactions, cytotoxicity, and decreased receptor activity and these data therefore highlight the need for careful monitoring of CBD use in humans, especially when CBD is used in clinical practice, such as in the treatment of psychiatric disorders or as an option for drug abuse treatment. CBD concentrations for pharmacotherapy are many times higher than the level conservatively estimated from the upper bound exposure detailed in Tables 6 and 7 for all age groups. The European Industrial Hemp Association reviewed clinical data on CBD and determined that doses ranging from 20 to 200 mg CBD per day exert physiological effects, but substantial pharmacological activity is not observed under approx. 200 mg oral CBD per day for an average adult EIHA (2017).

Karniol et al. (1975) evaluated an oral 50 mg/day CBD dose and determined that it did not cause any measurable effect on pain threshold, skin sensitivity, heart rate, electrocardiogram, blood pressure and body temperature but appeared to slightly increase the effect of THC on some physiological and psychological processes. The highest estimated exposure level of CBN at 361 µg/g from the cumulative daily consumption of all hemp ingredients was found in all individuals age 2 years and older. This level is over 100 times lower than the level evaluated by Karniol et al.

Animal studies suggest that CBN is as effective as THC in influencing gonadotropin and testosterone secretion. The LOAEL for this effect was 0.1 mg oral CBN (the same as for THC) in a study by Steger et al. (1990) with male rats. However, much higher THC doses had no effect on testosterone concentrations in humans (Dax et al.1989; Mendelson et al. 1978).

Health Canada published an information document intended for use by health care professionals in medical treatment of patients with cannabis or cannabinoids. Their review is a summary of peer-reviewed literature and international reviews concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. It is intended to complement other reliable sources of information. Health Canada reports that drug type cannabis contains a large number of compounds spanning many chemical classes including cannabinoids, nitrogenous compounds, amino acids, proteins, enzymes, glycoproteins, hydrocarbons, simple alcohols, aldehydes, ketones and

acids, fatty acids, simple esters and lactones, steroids, terpenes, non-cannabinoid phenols, flavonoids, vitamins, and pigments. It can be anticipated that low THC industrial hemp contain the same compounds. Health Canada further elaborates that relatively little is known about the pharmacological actions of the various other compounds found within cannabis (e.g. terpenes, flavonoids), but that it is believed that some of these compounds (e.g. terpenes) may have a broad spectrum of action (e.g. anti-oxidant, anti-anxiety, anti-inflammatory, anti-bacterial, anti-neoplastic, anti-malarial), although this this information comes from a few in vitro and in vivo studies and no clinical trials exist to support these claims. Terpenes vary widely among cannabis varieties, and the theory that they may somehow modify or enhance the physiological effects of the cannabinoids, for the moment, is hypothetical as there is little, if any, pre-clinical evidence to support this hypothesis and there are no clinical trials on this subject (Health Canada, 2013).

Cannabinol (CBN) is a product of Δ-9-THC oxidation and has 10% of the activity of Δ-9-THC. Its effects are not well studied but it appeared to have some possible immunosuppressive properties in a small number of in vitro studies. Cannabigerol (CBG) is a partial CB1/2 receptor agonist and a small number of in vitro studies suggest it may have some anti-inflammatory and analgesic properties and that it may also block 5-HT1A receptors and act as an α2-adrenoceptor agonist (Health Canada, 2013).

Health Canada reviewed clinical data and reported that two types of mechanisms could govern possible interactions between CBD and THC: those of a pharmacokinetic origin, and those of a pharmacodynamic origin. CBD lacks detectable psychoactivity and does not appear to bind to either CB1 or CB2 receptors at physiologically meaningful concentrations, but it affects the activity of a significant number of other targets including ion channels, receptors, and enzymes. Despite the limited and complex nature of the available information, it generally appears that CBD pre-administration may potentiate some THC effects (through a pharmacokinetic mechanism), whereas simultaneous co-administration of CBD and THC may result in attenuation of THC effects (through a pharmacodynamic mechanism). However, Karschner et al found no pharmacokinetic or pharmacodynamic interaction in humans between CBD and THC when they were in a 1:1 ratio in the cannabis plant extract (Sativex). The ratio between the two phytocannabinoids also plays a role in determining whether the overall effect will be potentiating or antagonistic. CBD-mediated attenuation of THC-induced effects may be observed when the ratio of CBD to THC is at least 8 : 1 (±11.1), whereas CBD appears to potentiate some of the effects associated with THC when the CBD to THC ratio is around 2 : 1 (±1.4). Potentiation of THC effects by CBD may be caused by inhibition of THC metabolism in the liver, resulting in higher plasma levels of THC. This contrasts with the review performed by Huestis (2017) which identified Hunt et al. (1981) as reporting that the pharmacokinetics of THC were not affected by CBD, except for a slight slowing of the metabolism of 11-OH-THC to THCCOOH. The Huestis review also identified data indicating that co-administration of CBD did not significantly affect the total clearance, volume of distribution, and terminal elimination half-lives of THC metabolites. Concentration vs. time curves, and ratios of the maximum average concentration and AUC values for 11-OH-THC/THC, THCCOOH/THC, and THCCOOH/11-OH-THC showed that CBD only partially inhibited the hydroxylation of THC to 11-OH-THC catalyzed by CYP 2C, when data were compared after oral administration of THC alone, as compared to a THC and CBD preparation (Nadulski et al., 2005). Like THC, CBD concentrations are high in the liver following oral administration due to a significant first-pass effect; however, unlike THC, a large proportion of the CBD dose is excreted unchanged in the feces (Wall et al., 1976). The effect of CBD on hydroxylation of THC was small in comparison to overall variability. There is virtually no information in the peer-reviewed scientific or medical literature concerning the effects of varying CBD to THC ratios in the treatment of different medical disorders (Health Canada, 2013).

Tetrahydrocannabivarin (THCV) acts as a CB1 receptor antagonist and CB2 receptor partial agonist in vitro and in vivo and pre-clinical studies suggest it may have anti-epileptiform/anti-convulsant properties. Much of what is known about the beneficial properties of the non-psychotropic cannabinoids (e.g. CBD, THCV) is derived from in vitro and animal studies and a few clinical studies. However, the current available data suggest potential therapeutic indications for psychosis, epilepsy, anxiety, sleep disturbances, neurodegeneration, cerebral and myocardial ischemia, inflammation, pain and immune responses, emesis, food intake, type-1 diabetes, liver disease, osteogenesis, and cancer properties (Health Canada, 2013).

THC, CBD, and CBN are known to inhibit CYP isozymes such as CYP1A1, 1A2, and 1B1 (Yamaori et al. (2010). Cannabis may therefore increase the bioavailability of drugs metabolized by these enzymes. Such drugs include amitryptiline, phenacetin, theophylline, granisetron, dacarbazine, and flutamide. THC, THCCOOH, CBD, and CBN all stimulate, and in some cases even inhibit, the activity of the drug transporter P-glycoprotein in vitro (Zhu et al. 2006). This suggests a potential additional role for these cannabinoids in affecting the therapeutic drug efficacy and toxicity of co-administered drugs. Health Canada therefore advises in their review that clinicians should be aware of other medications that the patient is taking and carefully monitor patients using other drugs along with cannabis or cannabinoids.

The cannabis terpenoids are limonene, myrcene, a-pinene, linalool, b-caryophyllene, caryophyllene oxide, nerolidol and phytol. They share a precursor with the phytocannabinoids and are synthesized in the secretory cells inside glandular trichomes. Terpenoids may represent up to 10% of the trichome content (Russo, 2011), and should also be present in the resin that adheres to hemp seed during harvesting. The cannabis terpenoids are all flavour and fragrance components that have been designated Generally Recognized as Safe by the US Food and Drug Administration and other regulatory agencies (Russo, 2011). They are common to the human diet and are present in other foods at varying levels, specifically, lemon (limonene), hops (myrcene), pine (a-pinene), lavender (linalool), pepper (b-caryophyllene), lemon balm (caryophyllene oxide), orange (nerolidol) and green tea (phytol). In-vitro studies demonstrate their pharmacological activity and they appear to be synergistic with the phytocannabinoids (Russo, 2011).

7. Heavy metals and aflatoxins

Although Angelova et al. (2004) state that concentrations of heavy metals are highest in roots and lowest in seeds, we note that the data from the study show that only Pb clearly fits this pattern, whereas Cu, Zn, and Cd do not. Since you state that hemp is known to uptake metals, please explain why you consider the risk of presence of heavy metals to be low. You state that because risk is low, testing is not needed per lot, but instead on an as-needed basis determined by risk. Please describe the risk conditions that would warrant testing for heavy metals. Also, please describe the risk conditions that warrant testing for aflatoxins.

Angelova V, Ivanova R, Delibaltova V, Ivanov K. (2004) Industrial Crops and Products. 19: 197–205.

Response:

Aflatoxin

Mycotoxins are produced by molds and can have a negative impact on human and animal health. Aflatoxins are a mycotoxin that can be found in oilseeds, such as hemp. Aflatoxin production is more likely to occur when the oilseeds moisture content is 20-25% (Manitoba Agriculture, Mycotoxins, accessed August 29, 2018).

Fresh Hemp Foods Ltd. contracts hemp seed growers to immediately dry harvested hemp seed. Contracted specifications require moisture to be $\leq 9.5\%$. Samples are submitted to our laboratory after harvest and regularly throughout storage for laboratory testing with results communicated to the farmer suppliers. As we manage the risk of aflatoxin by maintaining low moisture, aflatoxins are not tested in every seed lot but rather at a lower frequency on final product based on risk.

Refer to Tables 8 to 10 for historical 3rd party laboratory aflatoxin testing results confirming that Hulled Hemp Seed, Hemp Oil and Hemp Protein Powders were tested below the limit of detection (<5 ng/g) at a 3rd party accredited laboratory.

Heavy Metals

Proposition 65, officially known as the Safe Drinking Water and Toxic Enforcement Act of 1986, was enacted in November 1986. The proposition protects the state's drinking water sources from being contaminated with chemicals known to cause cancer, birth defects or other reproductive harm, and requires businesses to inform Californians about exposures to such chemicals.

Certain listed chemicals, such as lead, are naturally distributed through the environment in air, soil, and water. As a result, crops grown in western Canada often contain varying levels of heavy metals. These heavy metals are considered naturally occurring. During manufacture of our products, we do not add heavy metals.

Fresh Hemp Foods Ltd. tests raw hemp seed and the hemp seed derivatives described in GRN765, 771, 778 for the most common heavy metals; arsenic, cadmium, mercury, and lead. We conducted continuous validation studies to verify heavy metals level in our products. Refer to Figures 1 to 4 and Tables 11 to 13 for historical 3rd Party Laboratory Heavy Metal Testing Results and trending data. Historic testing results confirm that while these heavy metals are naturally occurring, our processing does not increase levels of these heavy metals beyond limits as set by Proposition 65. Typical heavy metal levels tested in our products are Arsenic < 0.16 µg/g, Cadmium < 0.14 µg/g, Mercury < 0.10 µg/g and Lead < 0.18 µg/g. Therefore, heavy metals are not tested in every seed lot but rather at a lower frequency on final product or upon customer request.

8. Anti-nutritional factors

You state that, "there are no known anti-nutritional properties," without citing evidence. According to Galasso et al. (2016), high variability of antinutritional compounds, including phytic acid, were found in hempseed from various cultivars. The authors state that, "the high phytate content found ... will greatly limit the use of this protein source in novel food or feed formulations." Please discuss antinutritional factors in hempseed, addressing information in the literature showing their presence.

Galasso, I., Russo, R., Mapelli, S., Ponzoni, E., Brambilla, I.M., Battelli, G., and Reggiani, R. (2016). Variability in Seed Traits in a Collection of Cannabis sativa L. Genotypes. Front Plant Sci 7, 688.

Response:

In hemp, antinutrients including trypsin inhibitors, phytic acid, glucosinolates, and condensed tannins were identified in the cotyledon fractions. Of these, the concentration of phytic acid is generally viewed as being considerable in all varieties, while the content of cyanogenic glycosides, condensed tannins, trypsin inhibitors and saponins are typically at acceptable levels in hemp seed meals, and in fact, may be inversely correlated with phytic acid content (Russo and Reggiani, 2013). Other researchers found the non-nutritive compounds in seeds varied among genotypes, and phytic acid was the most abundant (Galasso et al., 2016).

Phytate, the salt form of phytic acid, is the primary phosphorus storage compound of cereal grains, oil seeds, and tree nuts. Across these types of materials, phytate may account for 1-7% of the kernel dry weight and upwards of 75% of the total kernel phosphorus (Raboy, 2003). Phytate is historically considered an anti-nutrient because it will chelate minerals such as calcium, magnesium, iron, and zinc. More recently, the ability of phytic acid to chelate minerals was reported to have some protective effects. In animal studies, phytic acid was shown to decrease iron-mediated colon cancer risk and lower serum cholesterol and triglycerides (Zhou and Erdman, 1995). Phytic acid is also a contributor to the total antioxidant capacity of foods and may have potential functions of reducing lipid peroxidation in foods (Schlemmer et al. 2009). These beneficial effects were summarized:

"In industrialised countries where various civilisation diseases are prevalent, the beneficial properties of phytic acid, such as its anticancer, antioxidative and anti-calcification activities, are of great importance. Due to the enormous problems of civilisation diseases, any contribution to prevent these diseases is highly significant. If phytate really does show these beneficial properties in humans, then phytate will be no longer considered an antinutrient." "Terms for phytate such as 'antinutrient' or , 'bad food compound'
should belong to the past."

Human intake of phytate is well documented, as is the higher level of phytate associated with vegetarian diets (Schlemmer et al., 2009). The greatest phytate intake ever reported in humans was 5770 mg for a lacto-ovo vegetarian community. A study in American students and university faculty staff members (19–35 years) showed

ranges from 198 to 3098 mg (Held et al., 1988), with a high mean daily phytate intake of 1293 mg. In another study measuring phytate in the western diets of omnivorous females and males, the phytate intake was found to be 631 mg (590–734 mg) and 746 mg (714–762 mg) and in female and male vegetarians (1250 ±450 and 1550 ±550 mg, respectively (Ellis et al., 1987). Comparatively, diets that do not follow "typical" western patterns exhibit higher phytate intake. Adult Asian immigrants to Canada consuming a lacto-ovo vegetarian diet showed a daily phytate intake of 1487 ±791 mg (Bindra et al., 1986). Mexican infants aged 18–30 months showed a daily phytate intake of 1666 ±650 mg and youth (7–9 years) 3380 ±1070 mg (Murphy et al., 1992). Females in Guatemala also demonstrate a high daily phytate consumption of 2254 mg for females (15–37 years) (Fitzgerald et al., 1993).

Refer to Table 14. For Canadian grown seed, 3 consecutive lots of hulled hemp seed averaged 32 mg/g phytic acid. Coarse hemp flour, which is the ground press cake from hemp oil production, averaged 22.4 mg/g phytic acid for 3 consecutive lots. In comparison, hemp protein concentrates of 50% and 70% protein content (three consecutive lots each) averaged 36.3 mg/g, and 13.6 mg/g respectively.

Although the phytic acid levels in hemp are higher than some cereals, some common foods such as Peanuts, Almonds, Walnuts, Cashews, and Pecans have higher reported phytic acid levels above that of hemp (Schlemmer et al., 2009). When comparing the cumulative total exposure of phytate through hemp ingredients (hemp hearts and protein), one observes that the total phytate contributed to the diet from the conservative estimate of hemp material consumed per day falls well within the range of phytate ingested when consuming one reference amount of common foods including wheat bran (RACC of 15g), and many types of nuts (RACC of 30g). Refer to Table 15 for summary of phytate levels in common foods.

9. Exposure in infants/toddlers

Your safety narrative discusses exposure to THC in children 2-11 years old and the breastfed population. However, you do not discuss exposure and safety in infants and toddlers who directly consume foods derived from hempseed. Also, your narrative did not include a published report of a toddler with mild cannabinoid poisoning upon 3-week ingestion of hemp seed oil at what was considered a low dose (Chinello et al., 2017). Please discuss this sub-population in an amended safety narrative.

Chinello, M., Scommegna, S., Shardlow, A., Mazzoli, F., De Giovanni, N., Fucci, N., Borgiani, P., Ciccacci, C., Locasciulli, A., and Calvani, M. (2017). Cannabinoid Poisoning by Hemp Seed Oil in a Child. Pediatr Emerg Care 33, 344-345.

Response:

Huestis Review of Chinello et al., 2017 article

At the time of the review of effects of THC in children, this article was not found, and may not have been available through online searches. This 2017 case report described a 2-yr-7-month-old child prescribed 2 teaspoons of hemp oil per day to improve his immune system (Chinello M, et al., Pediatr Emer Care 2017;33: 344–345). After 21 days of dosing, the child was brought to an emergency department presenting with symptoms of decreased alertness, refusal to walk, and no verbal response in the last 2 hours. Examination reported paleness, stupor, low reactivity to stimulation, fixed gaze with pupils of medium size and normal reaction to light, and conjunctival hyperemia. The child had a positive urine test for cannabinoids (>50 µg/L) that was also positive after 19 h in the emergency department. The hemp oil was later determined by GCMS to contain 0.06% THC. Using standard conversion measures and assuming the oil had a density of 1 g/mL, the child had ingested approximately 6 mg THC per day for 21 days. The average weight of a child 2-5 years old is 14.2 kg, yielding a daily THC intake in this child of 423 µg/kg bw. The hospital conducted basic genetic tests and did not find any indications of unusual metabolism in this child. After discharge the parents reported irritability that disappeared after a few days and at a 6-month follow-up the child was healthy.

This is a case of a child ingesting hemp oil for multiple days for medicinal purposes and presenting with symptoms consistent with ingestion of an effective THC dose. The hemp oil described had a THC content higher than for most currently marketed hemp oils that lowered THC content over time and in 2008 contained less than 0.012% THC (Holler et al., 2008). Our estimates show that daily intake of our product at the 90th percentile level for a child is estimated to be 10.2 µg/kg total THC from the most conservative estimate of maximal ingested Hulled Hemp Seed, Protein Powder and Hemp Oil in one day, only 2.8 µg/kg total THC based on historical data and 5.0 µg/kg bw based on the conservative Monte Carlo data with certainty of 99.99%. Our estimates are 41 to 151 times lower than this child received on a daily basis. The illness of the child in this case report was clearly due to receiving a high daily 6 mg/day dose of THC in hemp oil.

Huestis For the purposes of this response, we divided infants into newborn to 2 months, 2 to 5 months, 6 to 11 months, and toddlers as 12 to 24 months old. Data in the original submission were supplied for children 2 to 5 years and 6 to 11 years old.

Although we provided maximal total THC exposure data for children 2-5 years old following ingestion of all three hemp food products consumed in a single day, and information on infants being breastfed by women consuming the maximum of all three hemp foods in a single day, we did not address exposure of infants and toddlers who were not exclusively breast fed, and who might be fed hemp food products by caregivers. We now provide data on total THC exposure in µg/kg bw of infants and toddlers, meals throughout the day, the type of food consumed based on reference data, the potential addition of hemp products to the foods, and infant and toddler weights. All data were retrieved from cited references and calculated data are found in Tables 1, 16 and 21). We assumed that non-breastfed infants up to 6 months old only receive formula that is prepared with the addition of water to powdered milk, yielding no THC exposure. Infants 6 to 11 months old could have supplementation of hemp food products into infant cereal at breakfast, lunch, dinner and two daily snacks providing a maximal total THC exposure of 6.7 (males) and 7.1 (females) µg/kg bw based on Table 1 Column B THC exposure based on consumption of all products at the Fresh Hemp Foods maximal limits of 4 µg/g for Hulled Hemp Seeds and Hemp Protein Powder and 10 µg/g for Hemp Oil. Total THC exposure based on historical THC analysis of Hemp Food products would be 0.6 µg/kg bw for this aged males and females, and based on the Monte Carlo predictions 2.5 and 2.7 µg/kg males and females, respectively.

Toddlers (12 to 24 months old) receive a larger amount of food than infants; however, no normative data were available on the amounts, so a conservative approach was to use the data for 2-5 year olds. Assuming addition of hemp food products at every meal and snack, and the maximal THC concentrations allowable in Fresh Hemp Foods Ltd. products the total THC exposure would be 12.7 µg/kg bw for male and 11.5 µg/kg bw for female toddlers. This may be an overestimation based on using food intake amounts for 2 to 5 year olds. Using the historical THC data, total exposure in the toddlers would be 3.5 and 3.3 µg/kg bw and according to the Monte Carlo predictions 6.4 and 5.9 µg/kg bw. These exposure levels are close to the µg/kg bw limits set by German, Swiss, Australian and New Zealand authorities, but exceed the limits set by the EFSA and Austrian governments. These data assume that toddlers receive maximal hemp food supplementation at every meal and snack during the day. In addition, the EFSA applied uncertainty factors of 30 for setting their exposure limit, while the Australian authorities employed an uncertainty factor of 10 for determining their limits. It is unlikely that infants and toddlers would receive this degree of hemp food supplementation, and drug metabolism in this age group is more rapid than in adults, perhaps leading to lower active THC analytes and more inactive metabolites. Based on the historical THC data from Fresh Hemp Food products and the Monte Carlo predictions, total THC exposures are less than 6.4 µg/kg bw; only the data based on the maximal allowable THC concentrations are about double the recommended µg/kg bw levels set by multiple regulatory bodies around the world.

Refer to GRN765 (Hulled Hemp Seed) Section 3.4 Dietary Exposure to Hemp Protein and to GRN778 Section 3.4 Dietary Exposure to Hemp Derived Oil. These sections discuss the safety of protein and oil derived from hemp seed and should be read concurrently with the response to Question 9. Cumulative protein exposure is about 13.3 g/day and 11.4 g/day for males and females 11 to 23 months based on hemp consumption being estimated at same level as 2 to 5 year old children (Tables 30 and 31, GRN765). Protein intake for 6 to 11 month old children is estimated at 5.4 g/day based on the protein content of Hulled Hemp Seed (Table 3 GRN765). Cumulative oil exposure is about 4.8 g/day and 4.6 g/day for males and females 11 to 23 months based on hemp consumption being estimated at same

level as 2 to 5 year old children (Tables 30 and 31, GRN778). Oil intake for 6 to 11 month old children is estimated at 7.7 g/day based on the oil content of Hulled Hemp Seed (Table 3 GRN765). The levels of protein and oil are well within the Institute of Medicine (2005) Recommended Dietary Allowance (RDA) of 13 g for children age 1 to 3 years and Adequate Intake (AI) for omega-3 at 0.7 g and 0.9 g for males and females age 1 to 3 years.

10. Health Canada's evaluation

The notices discuss the Health Canada Non-Prescription and Natural Health Products Directorate Workout Supplements Monograph. Although the notices present the monograph as a safety evaluation of hempseed protein, the monograph is not specific to hempseed protein and states that it "is not intended to be a comprehensive review of the medicinal ingredients described within." Please acknowledge that the Workout Supplements Monograph does not reflect a comprehensive safety evaluation of hempseed protein by Health Canada and is not necessarily directly applicable to general use in food.

Response:

The following statement is intended to be reviewed concurrently with the following Sections of the notices:

GRN765 (Hulled Hemp Seed) and GRN771 (Hemp Protein Powder) - Sections 3.4 Dietary Exposure to Hemp Protein and Section 5.9 Nutritional Benefits of Hemp as Food

Fresh Hemp Foods Ltd. acknowledges that the Non-Prescription and Natural Health Products Directorate Workout Supplements Monograph does not reflect a comprehensive safety evaluation of hempseed protein by Health Canada and is not necessarily directly applicable to general use in food.

GRN778 (Hemp Oil) - Section 5.9 Nutritional Benefits of Hemp as Food

Fresh Hemp Foods Ltd. acknowledges that the Non-Prescription and Natural Health Products Directorate Workout Supplements Monograph does not reflect a comprehensive safety evaluation of hempseed protein by Health Canada and is not necessarily directly applicable to general use in food.

11. Additional Requests:

11a. Allergenicity Statement

Response:

The following statement is intended to be reviewed concurrently with Section 5.8 Allergenicity of GRN765 (Hulled Hemp Seed), 771 (Hemp Protein Powder) and 778 (Hemp Oil).

A review of published literature indicates that consumption of derivatives of Cannabis sativa L seed, including those described by GRN765, 771, 778 has the potential to cause an allergic reaction in some sensitive individuals. The current prevalence rate of this allergy is low and is not anticipated to be a concern to the general population.

The Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004 is enforced by FDA to help Americans avoid the health risks posed by food allergens. There are over 160 foods that can cause allergic reactions in people with food allergies FDA (2018). US law identifies the eight most common allergenic foods which account for 90 percent of food allergic reactions and are the food sources from which many other ingredients are derived. The eight foods identified by the law are:

1. Milk
2. Eggs

3. Fish (e.g., bass, flounder, cod)
4. Crustacean shellfish (e.g., crab, lobster, shrimp)
5. Tree nuts (e.g., almonds, walnuts, pecans)
6. Peanuts
7. Wheat
8. Soybeans

These eight foods, and any ingredient that contains protein derived from one or more of them, are designated as "major food allergens" by FALCPA (FDA 2018). Hemp seed derivatives are not considered a major US food allergen.

11b. Time Frame Covered by Literature Search

Response:

No specific cut-off date was used during the literature searches performed during preparation of the notices. General search terms to identify information to assess risk from THC included but are not limited to the following: oral administration, THC, cannabis, cannabinoids, dronabinol, urine, drug test, toxicity etc.

11c. Historical Consumption of Hemp

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 hemp seed's safety and utility as a nutritive food.

A summary of the history of consumption is provided below to further support the safety of consuming hemp.

There are three notable aspects to bear in mind when reviewing the historical consumption of hemp. First, historical consumption, which extends thousands of years, clearly pre-dates the development of modern industrial, low-THC hemp cultivars. Therefore, the historical evidence supports hemp consumption at higher levels of THC, CBD, and other Cannabinoids. Second, authors researching and writing on THC and hemp make a distinction between food use, medicinal or therapeutic use, and ritual use. Much of the summary below comes from textbooks with specific chapters on the consumption of hemp as food. Finally, the history is extensive and global. There is no way to fully summarize the entire history of hemp cultivation and use as food. It has been eaten around the world by men, women, and children for thousands of years. A timeline from *Cannabis: Evolution and Ethnobotany*, was adapted and is included on page 121.

This summary will cover:

A. History of Hemp Generally
B. Ancient Use in Asia
C. Ancient Use in the Middle East
D. Ancient Use in Europe
E. Historical Use with Children

A. History of Hemp Consumption Generally

The Cannabis sativa plant is a botanical product with origins tracing back to the mists of time. Since early humans gathered "a broad diversity of edible plant material much further back in time than has been generally accepted by scholars of prehistory" it is likely Cannabis seeds were consumed as far back as the Paleolithic era.[1] The seed of Cannabis sativa L. has been an important source of nutrition for thousands of years.[2] There is historical evidence of use in Japan[3] dating back 10,000 years ago and in modern Moldova, Ukraine and Romania[4] 6,000 years ago. Similar dates are found around the world and are briefly discussed below.

Ancient Use in Asia

Hemp seeds have an ancient history of use in China. It was regarded as an important crop in the Neolithic era with archaeo-botanical evidence found at several sites.[5] Written records from1600 to 771 BCE, show hemp listed as one of five major grains. Those included foxtail millet (chi), broomcorn millet (shu), rice (tao), barley or wheat (mai), and hemp (ma).[6] Other written records include poems and songs about growing and eating hemp. Other archeological evidence from ancient northern China found hemp among nine important grains including millets, rice, wheat, barley, soybeans, lesser beans, and hemp seed.[7] The archeological record contains much more evidence as discussed in *Cannabis Evolution and Ethnobotany*.

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[1] *See e.g.*, Flannery, K. V. 1969. "Origins and ecological effects of early Domes- tication in Iran and the near east." In The *Domestication and Exploitation of Plants and Animals*, edited by P. J. Ucko and G. W. Dimbleby, 73–100. London: Duckworth; Weiss, e., W. Wetterstrom, D. Nadel, and O. Bar-Yosef. 2004. "The Broad spectrum Revisted: evidence from Plant Remains." *Proceedings of the National Academy Science* 101 (26): 9551–55; Dolukhanov, P.M. 2004. "Prehistoric environment, Human Migrations and Origin of Pastoralism in northern eurasia." In Impact of the Environment on Human Migration in Eurasia: Proceeding of the Nato Advanced Research Workshop, Held in St. Petersburg, 15–18 November 2003, edited by e. M. Scott, A. Y. Alekseev, and G. Zaitseva, 225–42. Dordrecht, The Netherlands: Kluwer Academic.

[2] *See, e.g.,* J.C. Callaway, Hempseed as a nutritional resource: An overview, Euphytica January 2004, Volume 140, Issue 1–2, pp 65–72)("*Cannabis sativa* L. has been an important source of food, fiber and medicine for thousands of years in the Old World."

[3] Okazaki. H., M. Kobayashi, A. Momohara, S. Eguchi, T. Okamoto, S. Yanagisawa, S. Okubo, and J. Kiyonaga. 2011. "Early Holocene coastal environment change Inferred from Deposits at Okinoshima Archeological site, Boso Peninsula, central Japan." *Quaternary International* 230:87–94; and Kudo, Y., M. Kobayashi, A. Momohara, T. Nakamura, S. Okitsu, S. Yanagisawa, and T. Okamoto. 2009. "Radiocarbon Dating of the fossil Hemp fruits in the earliest Jomon Period from the Okinoshima site, chiba, Japan." [In Japanese with English abstract.] *Japanese Journal of Historical Botany* 17, 27–32.

[4] Yanushevich, Z. V. 1989 "Agricultural evolution north of the Black sea from the Neolithic to the Iron Age." In *Foraging and Farming— The Evolution of Plant Exploitation*, edited by D. R. Harris and G. c. Hillman, 607–19. London: Unwin Hyman.

[5] (Chang, K.C. 1979. Food in Chinese Culture: Anthropological and Historical Perspectives. new Haven, cT: Yale University ; Huang, H. T. 2000. Science and Civilization in China. Volume 6: Biology and Biological Technology. Part V: Fermentations and Food Science. Cambridge: Cambridge University). (Zhimin, A. 1989 "Prehistoric Agriculture in China." In *Foraging and Farming—The Evolution of Plant Exploitation.*, edited by D. R. Harris and G. C. Hillman, 641–49.London: Unwin Hyman). (Chang, K.C. 4th ed. *The Archeology of Ancient China.* Revised, Lon- don: Yale University; Crawford, G. W., and H. Takamiya. 1990. "The Origins and Implications of Late Prehistoric Plant Husbandry in Northern Japan." *Antiquity* 64 (245): 889–911).

[6] *Id.* Huang (2000)

[7] L u, X., and R. C. Clarke. 1995. "The cultivation and Use of Hemp (*Cannabis Sativa* L.) in Ancient china." *Journal of the International Hemp Association* 2 (1): 26–30.

It's suggested based on linguistic evidence that hemp seeds were the first crop processed for oil (the Mandarin Chinese character for seed or grain mill (*mò*) is 磨, which combines 麻 (*má*) or "hemp" and 石 (*shí*) or "stone").[8] Hemp oil production became common in the sixth century which developed commercial factories that pressed oil seeds.[9] The evidence is clear this was used for cooking.

Hemps seeds continue to be pressed for their oil, and in some "areas the fruits of large-seeded varieties are quite commonly eaten raw or roasted as snacks."[10] In China, subsistence farmers living in remote mountainous regions of south-western China "still make porridge with hemp seeds" while in Tibet hemp seeds are "commonly parched, milled, and mixed into buttered tea."[11]

There is also evidence of early hemp consumption across Asia. Hemp seeds were introduced into Korea by China and remain a staple in impoverished North Korea.[12] Hemp seeds appear very early on in the archeological record of Japan, some recently discovered dating back about 10,000 years. For centuries, people living in the northwestern Himalayan foothills of India and Nepal have "roasted and eaten the [hemp] seeds.[13] Hemp is still part of Indian cuisine, a dish called *bosa* consists of the seeds of goose grass (*Eleusine indica*) and hemp, and another, referred to as *mura*, is made with parched wheat, amaranth or rice, and hemp seed.[14] The use of hemp seeds in Indian cuisine is described as making all vegetables more palatable and complete foods.[15]

Ancient Use in the Middle East

In Pakistan, Iran, and Turkey, baked hemp seeds are sold by street vendors and are very popular among children as nuts.[16] In ancient Persia (Iran), hemp seeds were consumed as a food and oil since at least the Middle Persianor Pahlavi period (about the tenth century CE).[17] Historical written records also refers to the economic value of hemp oil.

Many contemporary authors also point to the German-Hungarian scholar Immanuel Löw 's 2,600 page book titled *Die Flora der Juden* or "Flora of the Jews" for evidence of hemp seed use in the Middle East. Löw describes a sixth-century edible preparation in Persia contained hemp seeds and was called *sahdanag*, the "royal grain" or "king's grain." Löw tells us the Jewish people referred to hemp as *q'aneh-bosm*, the "root name" for *Cannabis*, and learned to make *sahdanag* from the Persians. A meal of roasted hemp seeds migrated with Jewish merchants and was well liked in the medieval period of Europe.

Ancient Use in the Europe

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[8] *Id.* Huang (2000)
[9] *Id.*
[10] Clarke and Merlin, Cannabis Evolution and Ethnobotany, Chapter Title: Food, Feed, and Oil Uses of Hemp (Univ. of California Press, 2013).
[11] Hong, s., and R. C. Clarke. 1996. "Taxonomic studies of *Cannabis* in china." *Journal of the International Hemp Association* 3 (2): 55–60.
[12] *Id.* at 9.
[13] Watt, G. 1908. *Commercial Products of India*. Calcutta, India: E. P. Dutton.
[14] Robinson, R. 1996. *The Great Book of Hemp*. Rochester, VT: Park street.
[15] *Id.* Robinson (1996).
[16] Hayatghaibi, H., and I. Karimi. 2007. "Hypercholesterolemic effect of Drug-Type *Cannabis Sativa* L. seed (Marijuana seed) in Guinea Pig." Pakistan Journal of Nutrition 6 (1): 59–62.
[17] *Id.* at 9.

There are many examples of hemp eaten as food in Europe. For example, one author referred to the cooking and consumption of hemp seed by peoples of Eastern Europe: "Russians and Poles, even of the higher class, bruise or roast the seeds, mix them with salt, and eat them on bread."[18] There are in fact many Baltic and Eastern European references to people preparing and eating hemp seeds. The history is well documented in the Baltic and Eastern Europe. In Poland hemp seeds are stewed or made into porridge, which is common across the region.[19] In Latvia and Lithuania hemp became a staple in the Eighteenth Century and is commonly eaten as a soup or boiled with potatoes.[20] In Estonia hemp is wildly prepared as butter, milk or porridge.[21] It is also eaten in Northern Europe. In Finland hemp seeds have a history of being ground into a cereal meal and mixed with barley, buckwheat and salt.[22] This is called hempen meal. Oil derived from pressed hemp seeds was an important part of traditional societies in Finland, Russia, Poland, and other Eastern European countries.

The first literary evidence that ancient Greeks consuming hemp seed cakes appeared around the middle of the fourth century BCE. Among the foods served at a symposium were "*kannabides*," which translates as "a confection of *Cannabis* seeds and honey."[23]

Eastern European settlers in Canada, carried hemp seeds with them when they immigrated into the prairie regions, including Canada. There they grew Cannabis and utilized the seeds "for fresh oil, baking and traditional dishes," while Canadians of Chinese ancestry "have also long eaten hemp seeds for medicinal and dietary reasons."[24]

Ancient Use in the Middle East

The use of hemp has links to the Iron Age and continued through to the Romans, medieval Europe to the present day. A tomb found in 1896 in Germany dating back to the iron age contained a vase with plant remains, including hemp.[25]

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[18] Porcher, F. P. 1863. Resources of the Southern Fields and Forests. Medical, Economical and Agricultural: Being also a Medical Botany of the Southern States. Charleston, NC: Walker, Evans & Cogswell; or Dembinska, M. 1999. Food and Drink in Medieval Poland. Translated by M. Thomas with revision by W. W. Weaver. Philadelphia: University of Pennsylvania. First published 1963 in Polish by the Polish Academy of Sciences; *See also*, Zajaczkowa, J. 2002. "Hemp and nettle: Two food/fiber/Medical Plants in Use in eastern Europe." *Slovo, the Newsletter of the Slavic Interest Group.* http//www.gallowglass.org/jadwiga/scA/ hempnettle.html.

[19] *Id.*

[20] Ambrazevicius, R., ed. 1996. "Lithuanian Roots: An Overview of Lithuanian Traditional culture." *Lithuanian Folk Culture Center*. http://thelithuanians.com/booklithuanianroots node55.html. *American Heritage Dictionary: Dictionary of the English Language*. 2000. 4th ed. Boston: Houghton Mifflin.

[21] Kokassaar, U. 2003. "Kanepiseemnetest tehti vanasti jurssi, piima ja putru" [Hemp seeds were used for making hemp butter, milk and porridge]. [In estonian.] *Eesti Looduse* 10. http:/www .loodusajakiri.ee/eesti_loodus/index.php?artikkel=485. Kokugakuin University. 1997. *Basic Terms of Shinto*. Tokyo: Kokugakuin University, Institute for Japanese culture and classics. http://www2.kokugakuin.ac.jp/ijcc/wp/bts/bts_j .html#jingu_taima.

[22] Ahokas, H. 2002. "Cultivation of *Brassica* Species and *Cannabis* by Ancient Finnic Peoples, Traced by Linguistic, Historical and Eth- nologicala Data; Revision of *Brassica Napus* as *B. Radice-Rapi*." *Acta Botanica Fennica* 172:1–32.

[23] Butrica, J. L. 2006. "The Medicinal Use of *Cannabis* among the Greeks and Romans." In *Handbook of Cannabis Therapeutics: From Bench to Bedside*, edited by Russo, Ethan B. and Franjo Grotenhermen, 23–42. New York: Haworth.

[24] CHTA/Accc. 2004. "canadian Hemp: A Plant With Opportunity." *Canadian Hemp Trade Alliance*. http://www.hemptrade.ca

[25] *Id.* Hayatghaibi (2007)

Historical Use with Children

Historical examples of children eating hemp are plentiful. In South Africa, Suto tribal women "grind up [hemp] seeds with bread or mealie pap [porridge] and give it to children when they are being weaned."[26]. As noted above, in Pakistan, Iran, and Turkey, baked hemp seeds are very popular among children as nuts.[27]

Conclusion

This summary while only touching on a deep history, shows hemp baked, boiled, roasted, milled and pressed to make a wide variety of foods. This history over thousands of years joins the evidence submitted in other parts of the submission to provide a reasonable assurance of safety.

12. Conclusion:

The standard for eligibility classification as GRAS is a, "reasonable certainty that the substance is not harmful under the conditions of its intended use" (21 C.F.R. 170.30). The original notices outlined a basis for consensus on this conclusion and this supplement underscores that conclusion. Together the GRNs establish a body of evidence and information that any expert could review and reasonably, if not comfortably, find certainty on the consumption of hemp as described. We employed an expert on cannabis and THC to contribute two summaries as part of this review – both unquestionably support the safety of consumption of hemp. In the latest report, animal studies using exceptionally high mg/kg oral THC on dogs and monkeys report little toxicity and at levels that are far above intake levels proposed in the GRNs. Animal studies examining the endocrine hormone system, immune system, intrauterine and post-natal development, genotoxicity and carcinogenicity, neurotoxicity, all concluded the risks, if any, were nominal. The lowest-observed-effect level (LOEL) was 5 mg/person, equivalent to a dose of 60 µg/kg bw. Effects at this dose, which are above the levels proposed, were minimal and reversible. The consensus of safety found in the animal studies is not surprising when considering the history of human consumption. That history shows hemp baked, boiled, roasted, milled and pressed to make a wide variety of foods enjoyed and nutritiously eaten by every age group. This history over thousands of years joins the evidence submitted in other parts of the submission to provide a reasonable assurance of safety. There is an added element of the psychoactive effects of THC, which is unique to these notices. This is shown in the animal and human studies not to be a safety concern. While other regulatory bodies, like EFSA or FSANZ, have set intake levels for hemp they have done so following their own procedures and adhering to the policies of their respective governments, in particular to authorizing the consumption of materials with minute levels of THC.

[26] Ames, f. 1958. "A clinical and Metabolic study of Acute Intoxication with *Cannabis Sativa*." *Journal of Mental Science* 104:972– 99.
[27] *Id.* Hayatghaibi (2007)

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Table 1 Upper Bound Estimate of Total THC Exposure Based on Body Weight

Age & Body Weight	A - TOTAL THC EXPOSURE AT MAXIMUM SPECIFICATION LEVELS (µg/kg Body Weight)[1,2,3,4] 90% Percentile Cumulative Consumption	B - TOTAL THC EXPOSURE USING MEAN VALUES CACULATED FROM HISTORICAL DATA (µg/kg Body Weight)[1,2,3,5] 90% Percentile Cumulative Consumption	TOTAL THC EXPOSURE BASED USING MONTE CARLO PREDICTED DAILY EXPOSURE (µg/kg Body Weight)[1,2,3] 99.99% Certainty 90% Percentile Cumulative Consumption	LEVELS RECOGNIZED BY OTHER REGULATORY AUTHORITIES (µg/kg Body Weight)					
				Germany Acceptable Daily Intake	Switzerland Provisional Daily Intake	Australia and New Zealand Tolerable Daily Intake	EFSA Acute Reference Dose	Canada	Austria
Newborn - 2 months Males - 5.4 kg	0.0	0.0	0.0						
Newborn - 2 months Females - 4.8 kg	0.0	0.0	0.0						
2 - 5 months Males - 7.3 kg	0.0	0.0	0.0						
2 - 5 months Females - 6.8 kg	0.0	0.0	0.0						
6 - 11 months Males - 8.5 to 9.7 kg	6.7	0.6	2.5						
6 - 11 months Females - 8.0 to 9.3 kg	7.1	0.6	2.7						
11 to 23 months Males - 11.4 to 14.2 kg	12.7	3.5	6.4						
11 to 23 months Females - 11.2 to 13.3 kg	11.5	3.3	5.9	**5**	**7**	**6**	**1**	**Not Set**	**1-2**
2 to 5 years Males - 14.2 kg	10.2 (Table 42, GRN778)	2.8	5.1						
2 to 5 years Females - 13.3 kg	9.7 (Table 43, GRN778)	2.8	5.0						
6 to 11 years Males - 23.9 kg	6.6 (Table 44, GRN778)	2.0	3.5						
6 to 11 years Females - 23.8 kg	6.9 (Table 45, GRN778)	2.1	3.7						
2 years & older Males - 88.8 kg	2.2 (Table 41, GRN778)	0.7	1.3						
2 years & older Females - 75.48 kg	2.5 (Table 41, GRN778)	0.8	1.5						

[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]Estimated that infants age birth to 5 months would consume no hemp and infants age 6 to 11 months could consume hemp beverage in place of fluid milk (Table 16). Estimated hemp consumption for children age 11 to 23 months based on consumption levels for 2 to 5 year old children per NHANES (Tables 17 and 18)

[3]Exposure based on body weight for infants 6 to 11 months calculated using hemp estimates from Tables 17 and 18. Other ages calculated using cumulative daily consumption of all hemp ingredients at 90% percentile taken from GRN778: 36.12 g all individuals 2 years and older (Table 14), 28.88 g boys age 2 to 5 years (Table 15), 25.33 g girls age 2 to 5 years (Table 16), 30.32 g boys age 6 to 11 years (Table17) and 31.1 g girls age 6 to 11 years (Table 17). Used lowest weight when range of body weights was cited in reference.

[4]Specification limits (µg/g THC): Hulled Hemp Seed = NMT 4, Hemp Protein Powder = NMT 4, Hemp Oil = NMT 10.

[5]Mean THC levels (µg/g): Hulled Hemp Seed = 0.3, Hemp Protein Powder = 0.6, Hemp Oil = 6.

[6]Calculated µg/kg body weight for children age 11 to 23 months using typical body weights and THC data from Tables 16 and 21.

Table 2 Summary of Historical Total THC Testing

	Hemp Oil GRN778											Hulled Hemp Seed GRN765				Hemp Protein Powder GRN771				
	Cumulative (All Years)	Cumulative (All Years Continued)	Cumulative (All Years Continued)	2011	2012	2013	2014	2015	2016	2017	2018	Cumulative (all years)	2013	2014	2016	Cumulative (all years)	2012	2013	2014	2016
Historical Data using GC-MS LOD of 0.2 µg/g	4.0	7.7	5.6	4.0	9.6	6.6	5.8	4.7	0.6	4.2	8.6	0.3	0.3	0.5	1.5	1.2	1.2	0.3	0.7	0.2
	6.0	4.3	4.5	6.0	6.7	4.4	8.0	4.9	4.7	6.9	5.4	0.3	0.3	0.3	0.2	0.3				0.5
	6.0	4.9	6.7	6.0	4.2	4.9	4.4	4.1	5.4	6.0	6.4	0.3	0.3	0.3		0.7				0.7
	9.6	4.7	5.3		8.5	4.4	7.7	7.6	8.7		6.7	0.4	0.4	0.2		0.2				
	6.7	4.9	5.2		4.0	4.3	5.2	5.6	6.0		5.6	0.4	0.4	0.2		0.5				
	4.2	4.1	6.4		8.6	5.8	4.6	6.1	0.6		6.9	0.2	0.2			0.7				
	8.5	7.6	8.0		4.2	4.5	6.9	6.6	4.9		5.8	0.2	0.2							
	4.0	5.6	9.8			5.2	4.3	4.5	6.0		8.5	0.2	0.2							
	8.6	6.1	8.9			4.3	6.1	4.0	3.1		4.3	0.2	0.2							
	4.2	6.6	9.1			4.7	4.9	4.6	8.0		5.8	0.2	0.2							
	6.6	4.5	5.9			5.8	6.5		5.7		6.6	0.2	0.2							
	4.4	4.0	8.5			9.5	5.1		5.0		5.6	0.3	0.3							
	4.9	4.6	6.9				4.0				4.5	0.3	0.3							
	4.4	0.6	6.9				7.1				6.7	0.5								
	4.3	4.7	8.0				5.2				5.3	0.3								
	5.8	5.4	5.9				6.6				5.2	0.3								
	4.5	8.7	4.7				2.6				6.4	0.2								
	5.2	6.0	4.8				7.7				8.0	0.2								
	4.3	0.6	6.9				4.3				9.8	1.5								
	4.7	4.9	5.7				4.9				8.9	0.2								
	5.8	6.0	9.1								9.1									
	9.5	3.1	6.7								5.9									
	5.8	8.0	6.7								8.5									
	8.0	5.7	8.9								6.9									
	4.4	5.0	9.9								6.9									
	7.7	4.2	8.7								8.0									
	5.2	6.9	7.5								5.9									
	4.6	6.0	6.7								4.7									
	6.9	8.6									4.8									
	4.3	5.4									6.9									
	6.1	6.4									5.7									
	4.9	6.7									9.1									
	6.5	5.6									6.7									
	5.1	6.9									6.7									
	4.0	5.8									8.9									
	7.1	8.5									9.9									
	5.2	4.3									8.7									
	6.6	5.8									7.5									
	2.6	6.6									6.7									
MEAN	**6.0**			**5.3**	**6.5**	**5.4**	**5.6**	**5.3**	**4.9**	**5.7**	**6.9**	**0.3**	**0.3**	**0.3**	**0.9**	**0.6**	**1.2**	**0.3**	**0.7**	**0.5**
MAX	**9.9**			**6.0**	**9.6**	**9.5**	**8.0**	**7.6**	**8.7**	**6.9**	**9.9**	**1.5**	**0.4**	**0.5**	**1.5**	**1.2**	**1.2**	**0.3**	**0.7**	**0.7**
MIN	**0.6**			**4.0**	**4.0**	**4.3**	**2.6**	**4.0**	**0.6**	**4.2**	**4.3**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**1.2**	**0.3**	**0.7**	**0.2**
STD DEV	**1.8**			**1.2**	**2.4**	**1.5**	**1.4**	**1.2**	**2.5**	**1.4**	**1.5**	**0.3**	**0.1**	**0.1**	**0.9**	**0.4**	**n/a**	**n/a**	**n/a**	**0.2**
COUNT	**106.0**			**3.0**	**7.0**	**12.0**	**20.0**	**10.0**	**12.0**	**3.0**	**39.0**	**20.0**	**13.0**	**5.0**	**2.0**	**6.0**	**1.0**	**1.0**	**1.0**	**3.0**

Table 3 Cannabinoid Testing – Hemp Protein Powder

Date	Lot Code	CBC (Cannabichromene)	CBD (Cannabidiol)	CBDA (Cannabidioloc Acid)	CBG (Cannabigerol)	CBN (Cannabinol)	THCV (Tetrahydrocannabivarin)	D8-THC	D9-THC	D9-THCA	Method	LOQ (µg/g)
15-Jun-18	LYQU17FC	<10	<10	20	<10	<10	<10	<10	<10	<10	HPLC-UV	10

Table 4 Cannabinoid Testing – Hemp Oil

Date	Lot Code	CBC (Cannabichromene)	CBD (Cannabidiol)	CBDA (Cannabidioloc Acid)	CBG (Cannabigerol)	CBN (Cannabinol)	THCV (Tetrahydrocannabivarin)	D8-THC	D9-THC	D9-THCA	Method	LOQ (µg/g)
23-Dec-15	KRFA15SO	n/a	n/a	30.4	n/a	n/a	n/a	n/a	n/a	n/a	GC/FID	1
12-Mar-17	BRSK13FO	n/a	n/a	20.3	n/a	n/a	n/a	n/a	n/a	n/a	GC/MS	1
18-Jul-17	ROSH15FC	n/a	n/a	30	n/a	n/a	n/a	n/a	n/a	n/a	HPLC-UV	1
23-Jan-18	KRFA17FOA	<1	10	50	<1	<1	<1	<1	<1	10	HPLC-UV	1
23-Jan-18	COGR27FOA	10	<1	60	10	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	ESKL17FOA	<1	<1	40	<1	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	GEWI85SCB	10	<1	20	10	<1	<1	<1	<1	<1	HPLC-UV	1
30-May-18	ROSH15FC	n/a	<1	30	n/a	n/a	n/a	n/a	n/a	n/a	HPLC-UV	1
30-May-18	ROSE67FO	n/a	20	60	n/a	n/a	n/a	n/a	n/a	n/a	HPLC-UV	1
30-May-18	LYQU17FC	n/a	10	150	n/a	n/a	n/a	n/a	n/a	n/a	HPLC-UV	1

Table 5 Cannabinoid Testing -Hulled Hemp Seed

Date	Lot Code	CBC (Cannabichromene)	CBD (Cannabidiol)	CBDA (Cannabidioloc Acid)	CBG (Cannabigerol)	CBN (Cannabinol)	THCV (Tetrahydrocannabivarin)	D8-THC	D9-THC	D9-THCA	Method	LOQ (µg/g)
12-Mar-14	BRCO93FC	n/a	n/a	1	n/a	n/a	n/a	n/a	0.51	n/a	GC/MS	1
23-Jan-18	TEAB15NCJ	<1	<1	10	<1	10	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	KRFA16SOE	<1	<1	10	<1	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	LAWA15FCI	<1	<1	20	<1	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	ARFR15XCI	<1	<1	10	<1	<1	<1	<1	<1	<1	HPLC-UV	1
23-Jan-18	BRMU16FOT	<1	<1	20	<1	<1	<1	<1	<1	<1	HPLC-UV	1
24-Feb-18	180208B	<1	<1	<1	<1	<1	<1	<1	<1	<1	HPLC-UV	1
24-Feb-18	180214B	<1	<1	<1	<1	<1	<1	<1	<1	<1	HPLC-UV	1
15-Jun-18	WAPA17FC	<10	<10	120	<10	<10	<10	<10	<10	<10	HPLC-UV	10
15-Jun-18	180527BB-BJ	<10	<10	10	<10	<10	<10	<10	<10	<10	HPLC-UV	10
15-Jun-18	180510BC	<10	<10	10	<10	<10	<10	<10	<10	<10	HPLC-UV	10
08-Aug-18	NADI147FC	30	20	<10	20	10	<10	<10	<10	<10	HPLC-UV	10

Table 6 Upper Bound Exposure Estimate To Other Cannabinoids - All Individuals Age 2 Years and Older, 2 to 5 Year Old Children and 6 to 11 Year Old Children

ESTIMATED EXPOSURE TO OTHER CANNABINOIDS AT UPPER BOUND HEMP CONSUMPTION LEVELS																																		
	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) 90% Percentile Consumption Level (NHANES 2013-2014)[1]					CBDA EXPOSURE (µg/Day) Based on 150 µg/g value determined in historical testing[2]					CBD EXPOSURE (µg/Day) Based on 20 µg/g value determined in historical testing[2]					CBG EXPOSURE (µg/Day) Based on 20 µg/g value determined in historical testing[2]					CBC EXPOSURE (µg/Day) Based on 30 µg/g value determined in historical testing[2]					CBN EXPOSURE (µg/Day) Based on 10 µg/g value determined in historical testing[2]					CUMMULATIVE EXPOSURE (µg/Day) CBDA, CBD, CBG, CBC, CBN				
	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		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		2 Years & Older	2 to 5 Years		6 to 11 Years	
	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F
HULLED HEMP SEED	14.1	11.7	10.2	12.1	12.1	2111	1757	1530	1818	1821	281.4	234	204	242	243	281.4	234	204	242	243	422.1	351	306	364	364	140.7	117	102	121	121	3236	2705	2356	2800	2804
HEMP PROTEIN POWDER	13.8	12.4	10.6	12.1	12.5	2076	1854	1583	1821	1871	276.8	247	211	243	249	276.8	247	211	243	249	415.2	371	317	364	374	138.4	124	106	121	125	3183	2855	2437	2804	2881
HEMP OIL	8.2	4.8	4.6	6.1	6.5	1233	722	687	909	972	164.4	96	92	121	130	164.4	96	92	121	130	246.6	144	137	182	194	82.2	48	46	61	65	1891	1111	1058	1400	1497
CUMMULATIVE	**36.1**	**28.9**	**25.3**	**30.3**	**31.1**	**5420**	**4332**	**3800**	**4548**	**4664**	**722.6**	**578**	**507**	**606**	**622**	**722.6**	**578**	**507**	**606**	**622**	**1084**	**866**	**760**	**910**	**933**	**361.3**	**289**	**253**	**303**	**311**	**8310**	**6671**	**5851**	**7004**	**7182**

M - Males, F – Females

[1]Refer to Tables 14 to 18 in GRN765 for summary of hemp consumption per age group.

[2]Refer to Tables 3 to 5 for cannabinoid test results.

Table 7 Upper Bound Exposure Estimate To Other Cannabinoids - Infants and Children Age 12 to 23 Months

ESTIMATED EXPOSURE TO OTHER CANNABINOIDS AT UPPER BOUND HEMP CONSUMPTION LEVELS																																	
	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) Highest Level of Inclusion per Food Category and 90% Percentile Consumption Level (NHANES 2013-2014)[1]					CBDA EXPOSURE (cgg/Day) Based on 150 µg/g value determined in historical testing[2]					CBD EXPOSURE (µg/Day) Based on 20 µg/g value determined in historical testing[2]					CBG EXPOSURE (µg/Day) Based on 20 µg/g value determined in historical testing[2]					CBC EXPOSURE (µg/Day) Based on 30 µg/g value determined in historical testing[1]					CBN EXPOSURE (µg/Day) Based on 10 µg/g value determined in historical testing[1]					CUMMULATIVE EXPOSURE (µg/Day) CBDA, CBD, CBG, CBC, CBN				
	Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months		Birth to 6 Months	6 to 11 Months		12 to 23 Months	
	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F	M & F	M	F	M	F
HULLED HEMP SEED	0	14	14	11.7	10.2	0	2130	2130	1757	1530	0	284	284	234	204	0	284	284	234	204	0	426	426	351	306	0	142	142	117	102	0	3266	3266	2693	2346
HEMP PROTEIN	0	0	0	12.4	10.6	0	0	0	1854	1583	0	0	0	247	211	0	0	0	247	211	0	0	0	371	317	0	0	0	124	106	0	0	0	2843	2427
HEMP OIL	0	0	0	4.8	4.6	0	0	0	722	687	0	0	0	96	92	0	0	0	96	92	0	0	0	144	137	0	0	0	48	46	0	0	0	1106	1053
CUMMULATIVE	0	14	14	28.9	25.3	0	2130	2130	4332	3800	0	284	284	578	507	0	284	284	578	507	0	426	426	866	760	0	142	142	289	253	0	3266	3266	6642	5826

M - Males, F - Females

[1]Refer to Table 16 for estimated hemp consumption for infants age 6 to 11 month. Hemp consumption for 11 to 23 old children was estimated using the NHANES data for children age 2 to 5 years (Tables 15 and 16 GRN765). No hemp expected to be added to infant formula since preparation instructions specify use of water. Manufacturing of foods specific to infants such as formula and infant cereal is outside the scope of GRN765, 778, 771.

[2]Refer to Tables 3 to 5 for cannabinoid test results.

Table 8 Historical Aflatoxin 3rd Party Laboratory Testing Results – Hemp Protein Powder

Aflatoxin Testing Results Summary		
Date	Lot Code	Result LOQ (5 ng/g)
29-Feb-16	LAWA14FC	< 5 ng/g
03-Aug-16	JOSE13FC	< 5 ng/g
31-Jan-17	NEKE16FO	< 5 ng/g
31-Jan-17	161114HC	< 5 ng/g
01-Mar-17	170104HB	< 5 ng/g
01-Mar-17	SHCH36NO	< 5 ng/g
09-Jun-17	ASBS16SO	< 5 ng/g
18-Sep-17	SEYO76FOT	< 5 ng/g
19-Dec-17	ROBR66FOE	< 5 ng/g
19-Dec-17	WIGE85SCB	< 5 ng/g
19-Apr-18	DAMA45XCE	< 5 ng/g
09-May-16	TOBY34XC	< 5 ng/g
17-Jan-17	ANBE15NC	< 5 ng/g
17-Feb-17	QUVE55FC	< 5 ng/g
01-Jun-17	ROSE26FO	< 5 ng/g
05-Apr-18	DAMA45XCM	< 5 ng/g
42405	NEVA14FC	< 5 ng/g
16-May-16	DABR54FO	< 5 ng/g
03-Aug-16	ROGL14XC	< 5 ng/g
31-Jan-17	NEKE16FO	< 5 ng/g
09-Jun-17	WIGE15SC	< 5 ng/g
18-Sep-17	WIGE45SCK	< 5 ng/g
19-Apr-18	ADSI37FOG	< 5 ng/g
01-Mar-17	161216XX	< 5 ng/g
19-Dec-17	170911XY	< 5 ng/g

Table 9 Historical Aflatoxin 3rd Party Laboratory Testing Results – Hemp Oil

Aflatoxin Testing Results Summary		
Date	Lot Code	Result LOQ (5 ng/g)
16-May-16	DABR24FO	< 5 ng/g
31-Jan-17	ANBE15NC	< 5 ng/g
01-Mar-17	SHCH26NO	< 5 ng/g
09-Jun-17	DAMA15XC	< 5 ng/g
18-Sep-17	MAEN75XCH	< 5 ng/g
19-Dec-17	DABR16FOJ	< 5 ng/g
19-Apr-18	KRFA27SOI	< 5 ng/g

Table 10 Historical Aflatoxin 3rd Party Laboratory Testing Results – Hulled Hemp Seed

Aflatoxin Testing Results Summary		
Date	Lot Code	Result LOQ (5 ng/g)
05-Feb-16	QUVE64FC	< 5 ng/g
16-May-16	RACO24FC	< 5 ng/g
31-Jan-17	161115AB	< 5 ng/g
31-Jan-17	PAGR15NC	< 5 ng/g
31-Jan-17	ROLO25FC	< 5 ng/g
01-Mar-17	JUDU25FC	< 5 ng/g
09-Jun-17	15B0113XA11C	< 5 ng/g
09-Jun-17	KEWI16NO	< 5 ng/g
18-Sep-17	170831BF	< 5 ng/g
18-Sep-17	ROBR26FO	< 5 ng/g
19-Dec-17	171127BA	< 5 ng/g
19-Dec-17	ROBR76FOP	< 5 ng/g
19-Apr-18	180328AA	< 5 ng/g
19-Apr-18	NIBO17NOH	< 5 ng/g

Table 11 Historical Heavy Metals 3rd Party Laboratory Testing Results – Hemp Protein Powders

Date	Lot Code	Result				Method
		Arsenic LOQ (0.05 µg/g)	Cadmium LOQ (0.01 µg/g)	Mercury LOQ (0.05 µg/g)	Lead LOQ (0.01 µg/g)	
41697.00	LANE62XC	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
41697.00	ROSY64FO	< 0.05	0.06	< 0.05	0.03	ICP-MS
41719.00	N/A	< 0.1	0.05	0.01	< 0.03	ICP-MS
41758.00	N/A	< 0.1	0.05	0.01	< 0.03	ICP-MS
42389.00	ROMA84FO	< 0.05	0.04	< 0.05	< 0.01	ICP-MS
42410.00	LAWA14FC	< 0.05	0.03	< 0.05	0.05	ICP-MS
42440.00	ROSE94FO	< 0.05	0.06	< 0.05	0.06	ICP-MS
42585.00	JOSE13FC	< 0.05	0.04	< 0.05	< 0.01	ICP-MS
42751.00	SCBE16GO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42765.00	SAMC16NO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42787.00	SHCH26NO	< 0.05	0.01	< 0.05	< 0.01	ICP-MS
42814.00	POGR46SO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42864.00	ASBS16SO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42865.00	BRSK36NO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42900.00	ROSE56FO	< 0.05	0.07	< 0.05	< 0.01	ICP-MS
42913.00	ROBA36FO	0.05	0.03	< 0.05	< 0.01	ICP-MS
42996.00	ROBR36FO	< 0.05	0.04	< 0.05	< 0.01	ICP-MS
43031.00	ROBR66FO	< 0.05	0.03	< 0.05	0.04	ICP-MS
41697.00	LANE62XC	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
42283.00	ROSE44FO	< 0.05	0.05	< 0.05	< 0.01	ICP-MS
42517.00	DABR64FO	< 0.05	0.03	< 0.05	0.01	ICP-MS
42517.00	ROSE94FO	< 0.05	0.06	< 0.05	0.06	ICP-MS
42585.00	DAW184FC	< 0.05	0.05	< 0.05	< 0.01	ICP-MS
41697.00	BROS83FO	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
41719.00	N/A	< 0.1	0.03	0.01	< 0.03	ICP-MS
41767.00	N/A	< 0.1	0.01	0.01	< 0.03	ICP-MS
42009.00	ROBR54FO	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
42017.00	ROBR74FO	< 0.05	0.07	< 0.05	0.11	ICP-MS
42065.00	ROBR84FO	< 0.05	0.07	< 0.05	0.01	ICP-MS
42068.00	ROBR94FO	< 0.05	0.08	< 0.05	0.01	ICP-MS
42124.00	ROYB64FO	< 0.05	0.08	< 0.05	0.01	ICP-MS
42131.00	ROYB44FO	< 0.05	0.08	< 0.05	0.03	ICP-MS
42263.00	DAFA14FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42275.00	LAMA54FO	0.05	0.05	< 0.05	< 0.01	ICP-MS
42275.00	ROSE44FO	0.06	0.08	< 0.05	0.02	ICP-MS
42283.00	NESC53FC	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42297.00	ROSE54FO	< 0.05	0.08	< 0.05	0.03	ICP-MS
42304.00	KRFA25SO	< 0.05	0.03	< 0.05	0.02	ICP-MS
42304.00	ROSE64FO	< 0.05	0.07	< 0.05	0.02	ICP-MS
42313.00	KRFA15SO	0.08	0.01	< 0.05	< 0.01	ICP-MS
42389.00	NEVA14FC	0.08	0.03	< 0.05	0.11	ICP-MS
42410.00	ROMA84FO	< 0.05	0.06	< 0.05	0.03	ICP-MS
42440.00	ROSE94FO	< 0.05	0.06	< 0.05	0.06	ICP-MS
42451.00	DABR14FO	< 0.05	0.05	< 0.05	0.07	ICP-MS
42479.00	DABR24FO	< 0.05	0.05	< 0.05	0.05	ICP-MS
42485.00	DABR34FO	< 0.05	0.06	< 0.05	< 0.01	ICP-MS
42508.00	DABR54FO	< 0.05	0.05	< 0.05	0.03	ICP-MS
42515.00	DABR64FO	< 0.05	0.04	< 0.05	< 0.01	ICP-MS
42522.00	DAGL14XC	< 0.05	0.04	< 0.05	0.02	ICP-MS
42535.00	HEBA15FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42538.00	KRFA35FO	0.05	0.02	< 0.05	0.07	ICP-MS
42580.00	LAMA45FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42585.00	ROGL14XC	< 0.05	0.01	< 0.05	< 0.01	ICP-MS
42633.00	MALA55FO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42670.00	LAMA65FO	< 0.05	0.02	< 0.05	0.06	ICP-MS
42698.00	POGR16CO	0.14	0.03	< 0.05	0.03	ICP-MS
42719.00	NEKE16FO	0.06	0.03	< 0.05	0.02	ICP-MS
42751.00	LAMA16FO	< 0.05	0.03	< 0.05	0.08	ICP-MS
42774.00	SHCH16NO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42780.00	CHSH16NO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42781.00	BRSK16NO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42788.00	SHCH26NO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42795.00	HSIC16XO	< 0.05	0.01	< 0.05	< 0.01	ICP-MS
42808.00	PGTM16SO	0.06	0.02	< 0.05	< 0.01	ICP-MS
42815.00	POGR46SO	0.09	0.03	< 0.05	0.01	ICP-MS
42822.00	PGAM16NO	0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42864.00	ASBS16SO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42873.00	BRSK36NO	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42886.00	ROSE26FO	< 0.05	0.07	< 0.05	0.05	ICP-MS
43013.00	BRAN16FO	< 0.05	0.03	< 0.05	0.01	ICP-MS

Table 12 Historical Heavy Metals 3rd Party Laboratory Testing Results – Hemp Oil

Date	Lot Code	Result (µg/g)				Method
		Arsenic LOQ (0.05 µg/g)	Cadmium LOQ (0.01 µg/g)	Mercury LOQ (0.05 µg/g)	Lead LOQ (0.01 µg/g)	
41697.00	BRSK13FO	< 0.05	0.07	< 0.05	< 0.01	ICP-MS
42087.00	MAGR33FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42087.00	ROBR84FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42087.00	ROBR94FO	0.12	< 0.01	< 0.05	< 0.01	ICP-MS
42087.00	ROYB14FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42131.00	QUVE43FC	0.08	< 0.01	< 0.05	0.01	ICP-MS
42131.00	ROYB64FO	< 0.05	< 0.01	< 0.05	0.01	ICP-MS
42144.00	ROYB74FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42171.00	DAVA43FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42171.00	ROYB94FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42177.00	BEWI14XO	< 0.05	< 0.01	< 0.05	0.02	ICP-MS
42226.00	DAVA53FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42234.00	LAMA54FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42234.00	MAGR53FC	< 0.05	< 0.01	< 0.05	0.02	ICP-MS
42255.00	NESC53FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42261.00	DAFA14FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42261.00	ROSE44FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42283.00	DAVA63FC	< 0.05	< 0.01	< 0.05	0.16	ICP-MS
42292.00	ROSE54FO	< 0.05	< 0.01	< 0.05	0.07	ICP-MS
42311.00	ROSE64FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42311.00	KRFA25SO	< 0.05	< 0.01	< 0.05	0.03	ICP-MS
42313.00	KRFA15SO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42339.00	MAHA35	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42376.00	LAWA44FC	< 0.05	< 0.01	< 0.05	0.06	ICP-MS
42376.00	NEVA14FC	< 0.05	< 0.01	< 0.05	0.12	ICP-MS
42389.00	ROMA84FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42433.00	RRMH14FO	< 0.05	< 0.01	< 0.05	0.02	ICP-MS
42451.00	DABR14FO	< 0.05	< 0.01	< 0.05	0.09	ICP-MS
42507.00	DABR54FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42515.00	DABR64FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42519.00	DABR44FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42522.00	DAGL14XC	< 0.05	< 0.01	< 0.05	0.04	ICP-MS
42535.00	TOBY34XC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42564.00	DABR74FO	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42565.00	HEBA15FO	< 0.05	< 0.01	0.06	< 0.01	ICP-MS
42580.00	LAMA45FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42585.00	WIVA74FC	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42629.00	MHRB45FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42633.00	MALA55FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42669.00	MHRS75FO	< 0.05	< 0.01	< 0.05	0.08	ICP-MS
42670.00	LAMA65FO	< 0.05	< 0.01	< 0.05	0.08	ICP-MS
42698.00	POGR16CO	< 0.05	< 0.01	< 0.05	0.02	ICP-MS
42713.00	NEKE16FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42726.00	KELE16FO	< 0.05	< 0.01	< 0.05	0.08	ICP-MS
42745.00	SCBE16GO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42751.00	LAMA16FO	0.06	< 0.01	< 0.05	< 0.01	ICP-MS
42766.00	SAMC16NO	0.07	< 0.01	< 0.05	< 0.01	ICP-MS
42774.00	SHCH16NO	0.06	< 0.01	0.08	< 0.01	ICP-MS
42780.00	CHSH16NO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42788.00	SHCH26NO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42795.00	HSIC16XO	0.07	< 0.01	< 0.05	0.10	ICP-MS
42808.00	PGTM16SO	< 0.05	< 0.01	< 0.05	0.07	ICP-MS
42815.00	POGR46SO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42822.00	PGAM16NO	0.08	< 0.01	< 0.05	0.02	ICP-MS
42864.00	ASBS16SO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42873.00	BRSK36NO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42886.00	ROSE26FO	< 0.05	< 0.01	0.08	0.08	ICP-MS
42900.00	ROSE56FO	<0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42913.00	ROBA36FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42927.00	ROSE66FO	< 0.05	< 0.01	< 0.05	0.01	ICP-MS
43004.00	GRRS16FO	< 0.05	< 0.01	0.05	0.01	ICP-MS
43013.00	BRAN16FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
43021.00	NABR16FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
43054.00	DABR16FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
43174.00	RORD47SO	< 0.05	< 0.01	< 0.05	0.09	ICP-MS

Table 13 Historical Heavy Metals 3rd Party Laboratory Testing Results – Hulled Hemp Seed

Date	Lot Code	Result (µg/g)				Method
		Arsenic LOQ (0.05 µg/g)	Cadmium LOQ (0.01 µg/g)	Mercury LOQ (0.05 µg/g)	Lead LOQ (0.01 µg/g)	
41697.00	BRCO73FC	< 0.05	0.07	< 0.05	< 0.01	ICP-MS
41747.00	N/A	< 0.1	<0.01	< 0.005	< 0.03	ICP-MS
41777.00	N/A	< 0.1	0.01	0.01	0.03	ICP-MS
41802.00	N/A	< 0.1	0.03	< 0.005	< 0.03	ICP-MS
41802.00	N/A	< 0.1	0.01	< 0.005	< 0.03	ICP-MS
41802.00	N/A	< 0.1	< 0.01	< 0.005	< 0.03	ICP-MS
41802.00	N/A	< 0.1	0.04	< 0.005	0.03	ICP-MS
41933.00	DAWI64FC	< 0.05	0.01	< 0.05	< 0.01	ICP-MS
42047.00	IACU14XO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42125.00	TOBY14FC	< 0.05	0.02	< 0.05	0.02	ICP-MS
42283.00	LAWA24FC	< 0.05	0.03	< 0.05	< 0.01	ICP-MS
42410.00	JOKL24FC	0.06	0.02	< 0.05	0.03	ICP-MS
42410.00	QUVE44FC	< 0.05	0.02	< 0.05	< 0.01	ICP-MS
42522.00	GABA24FC	< 0.05	0.04	< 0.05	0.05	ICP-MS
42585.00	LACK15FO	< 0.05	< 0.01	< 0.05	< 0.01	ICP-MS
42599.00	160519.00	< 0.1	0.02	< 0.005	< 0.03	ICP-MS
42975.00	ROBR16FO	< 0.05	0.04	0.06	0.03	ICP-MS

Table 14 Phytate Exposure from Hemp Material

ESTIMATED EXPOSURE TO OTHER CANNABINOIDS AT UPPER BOUND HEMP CONSUMPTION LEVELS		
	CONSERVATIVE ESTIMATE OF HEMP MATERIAL CONSUMED (g/Day) 90% Percentile Consumption Level (NHANES 2013-2014)[1]	**PHYTATE EXPOSURE FROM HEMP MATERIAL CONSUMED AT CONSERVATIVE ESTIMATE (mg/Day)**
	2 Years & Older Males & Females	**2 Years & Older Males & Females**
HULLED HEMP SEED	14.1	450.7
HEMP PROTEIN POWDER	13.8	505.1
CUMMULATIVE	**27.9**	955.8

Table 15 Phytates Found in Other Common Foods

Food	Reported Phytate Content (g/100g) Schlemmer et al. 2009		Range of Phytate Content (mg/Reference Amount Customarily Consumed)	
	Low	High	Low	High
Almonds	0.4	9.4	105	2826
Peanuts	0.2	4.5	51	1341
Walnuts	0.2	6.7	60	2007
cashews	0.2	5	57	1494
Pecans	0.2	4.5	54	1356
Wheat Bran	2.1	7.3	315	1095

Table 16 Estimated Hemp Consumption and THC Exposure Levels - Infant Birth to 11 Months

Age	# Meals per Day[1]	Type of Food per Meal[1]	Quantity of food per Meal	Estimated Quantity of Hemp per Food Based on Levels of Usage[2]	Total ?-9-THC Exposure (µg/Day)6 *At NMT 4 µg/g ?-9-THC limit in hulled hemp seed per FHF specifications
Newborn - 2 months	5 - 6 (all meals)	Formula	28.35 g - 85.05 g (1 - 3 oz)	0[3,7]	0.0
				TOTAL ?-9-THC Exposure - Newborn to 2 months	**0.0**
2 - 5 months	5 - 6 (all meals)	Formula	85.05 g - 170.1 g (3 - 6 oz)	0[3,7]	0.0
				TOTAL ?-9-THC Exposure - 2 to 5 months	**0.0**
6 - 11 months	1 (breakfast)	Formula	170.1 g - 226.8 g (6 - 8 oz)	0[3,7]	0.0
		Infant Cereal	56.8 g (4 tbsp)	2.84 g hulled hemp seed from 2 tbsp hemp based milk alternative[5,7]	11.4
		Meat/Meat Alternative (egg, cheese, meat, beans etc.)	56.7 g (2 oz)	0[4]	0.0
	1 (lunch)	Formula	170.1 g - 226.8 g (6 - 8 oz)	0[3,7]	0.0
		Infant Cereal	56.8 g (4 tbsp)	2.84 g hulled hemp seed from 2 tbsp hemp based milk alternative[5,7]	11.4
		Meat/Meat Alternative (egg, cheese, meat, beans etc.)	56.7 g (2 oz)	0[4]	0.0
	1 (dinner)	Formula	170.1 g - 226.8 g (6 - 8 oz)	0[3,7]	0.0
		Meat/Meat Alternative (egg, cheese, meat, beans etc.)	56.7 g (2 oz)	0[4]	0.0
		Infant Cereal	56.8 g (4 tbsp)	2.84 g hulled hemp seed from 2 tbsp hemp based milk alternative[5,7]	11.4
	2 (snacks)	Formula	56.7 g - 113.4 g (2 - 4 oz)	0[3,7]	0.0
		Infant Cereal	56.8 g (4 tbsp)	5.68 g hulled hemp seed from 2 tbsp hemp based milk alternative[5,7]	22.7
				TOTAL ?-9-THC Exposure - 6 to 11 months	**56.8**

[1]Number of meals per day and meal composition selected from choices recommended by United States Department of Agriculture Infant Meal Pattern, 11/29/2016. Accessed 09/04/2018.
https://fns-prod.azureedge.net/sites/default/files/cacfp/CACFP_infantmealpattern.pdf
[2]Refer to Table 1 Usage Levels per Food Category in GRN765 (Hulled Hemp Seed). Maximum level used. to estimate hemp content.
[3]No hemp expected to be added to formula since preparation instructions specify use of water. [4]No hemp expected to be added

to cheese, meat, eggs or beans due to physical form of the food.
[5]Estimated that infant cereal could be prepared with a milk substitute comprised of up to 10% by weight hulled hemp seed.
[6]Upper bound exposure to Δ-9-THC estimated using FHF specification Limits. No difference based on gender is anticipated.
[7]Manufacturing of foods specific to infants such as formula and infant cereal is outside the scope of GRN 765, 778, 771.

Table 17 Daily Intake of Hemp - Males 11-23 Months based on NHANES for Males 2-5 Years

Hemp Ingredient	Minimum Daily intake (g/person)[1] Males 11 to 23 Months		Mid-Point Daily intake (g/person)[1] Males 11 to 23 Months		Maximum Daily intake (g/person)[1] Males 11 to 23 Months	
	Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	0.4	0.9	2.7	5.4	5.9	**11.7**
Protein Powders (inc. concentrate)	0.3	0.6	3.0	5.9	6.2	**12.4**
Oil	0.2	0.3	1.1	2.2	2.4	**4.8**
TOTAL	**0.9**	**1.7**	**6.8**	**13.6**	**14.4**	**28.9**

[1]Highly conservative - estimates hemp consumption at same levels as a child 2 to 5 years old (refer to Table 15 GRN765).

Table 18 Daily Intake of Hemp - Females 11-23 Months based on NHANES for Females 2-5 Years

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	0.4	0.7	2.4	4.7	5.1	10.2
Protein Powders (inc. concentrate)	0.2	0.5	2.5	5.0	5.3	10.5
Oil	0.2	0.3	1.1	2.1	2.3	4.6
TOTAL	**0.8**	**1.5**	**6.0**	**11.9**	**12.7**	**25.3**

[1]Highly conservative - estimates hemp consumption at same levels as a child 2 to 5 years old (refer to Table 16 GRN765).

Table 19 Daily Intake of THC - Males 11-23 Months based on NHANES for Males 2-5 Years (using Specification THC Limits)

Hemp Ingredient	Quality Specification THC µg/g	Minimum Daily Intake delta-9-THC[1] (µg/person)		Mid-Point Daily Intake delta-9-THC[1] (µg/person)		Maximum Daily Intake delta-9-THC[1] (µg/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hulled Hemp Seeds	4.0	1.7	3.4	10.9	21.7	23.4	46.8
Protein Powders (inc. concentrate)	4.0	1.1	2.2	11.8	23.6	24.7	49.4
Oil	10.0	1.6	3.2	11.2	22.4	24.0	48.1
TOTAL		**4.4**	**8.8**	**33.9**	**67.8**	**72.2**	**144.4**

[1]Highly conservative - estimates hemp consumption at same levels as a child 2 to 5 years old

Table 20 Daily Intake of THC - Females 11-23 Months based on NHANES for Females 2-5 Years (using Specification THC Limits)

Hemp Ingredient	Quality Specification THC µg/g	Minimum Daily Intake delta-9-THC[1] (µg/person)		Mid-Point Daily Intake delta-9-THC[1] (µg/person)		Maximum Daily Intake delta-9-THC[1] (µg/person)	
		Mean	90th %	Mean	90th %	Mean	90th %
Hemp Hearts	4.0	1.5	3.0	9.4	18.9	20.4	40.8
Protein Powders (inc. concentrate)	4.0	0.9	1.8	10.1	20.2	21.1	42.2
Oil	10.0	1.5	3.1	10.7	21.4	22.9	45.8
TOTAL		**3.9**	**7.9**	**30.2**	**60.5**	**64.4**	**128.8**

[1]Highly conservative - estimates hemp consumption at same levels as a child 2 to 5 years old

Table 21 Exposure to THC at Maximum Hemp Consumption Levels Using Historical Mean Total THC Data

Age and Body Weight	Hulled Hemp Seed (g/Day)[1]	Total THC from Hulled Hemp Seed (µg)[2]	Exposure based on Body Weight (µg/kg bw)[3]	Hemp Protein Powder (g/Day)[1]	Total THC from Hemp Protein Powder (µg)[2]	Exposure based on Body Weight (µg/kg bw)[3]	Hemp Oil (g/Day)[1]	Total THC from Hemp Oil (µg/Day)[2]	Exposure based on Body Weight (µg/kg bw)[3]	Cumulative Hemp (g/Day)[1]	Cumulative Total THC (µg)	Cumulative Total THC Exposure from Hemp based on Body Weight (µg/kg bw)[3]
6 - 11 months Males - 8.5 to 9.7 kg	14.2	4.3	0.5	n/a	n/a	n/a	n/a	n/a	n/a	14.2	4.3	0.5
6 - 11 months Females - 8.0 to 9.3 kg	14.2	4.3	0.5	n/a	n/a	n/a	n/a	n/a	n/a	14.2	4.3	0.5
11 to 23 months Males - 11.4 to 14.2 kg	11.7	4.0	0.3	12.4	7.4	0.7	4.8	28.8	2.5	28.9	40.2	3.5
11 to 23 months Females - 11.2 to 13.3 kg	10.2	3.5	0.3	10.6	6.3	0.6	4.6	27.4	2.4	25.3	37.2	3.3
2 to 5 years Males - 14.2 kg	11.7	4.0	0.3	12.4	7.4	0.5	4.8	28.8	2.0	28.9	40.2	2.8
2 to 5 years Females - 13.3 kg	10.2	3.5	0.3	10.6	6.3	0.5	4.6	27.4	2.1	25.3	37.2	2.8
6 to 11 years Males - 23.9 kg	12.2	4.1	0.2	12.1	7.3	0.3	6.1	36.3	1.5	30.3	47.7	2.0
6 to 11 years Females - 23.8 kg	12.1	4.1	0.2	12.5	7.5	0.3	6.5	38.8	1.6	31.1	50.4	2.6
2 years & older Males - 88.8 kg	14.1	4.8	0.1	13.8	8.3	0.1	8.2	49.2	0.6	36.1	62.3	0.7
2 years & older Females - 75.5 kg	14.1	4.8	0.1	13.8	8.3	0.1	8.2	49.2	0.7	36.1	62.3	0.8

[1]Upper bound estimates of hemp consumption taken from GRN778 Tables 14 to 18. Used consumption levels for 2 to 5 years to conservatively estimate exposure for 11 to 23 month children. Refer to Table 16 for estimated hemp consumption by infants age 6 to 11 months.

[2]Mean Total THC levels based on historical data: Hulled Hemp Seed 0.3 µg/g, Hemp Protein Powder 0.6 µg/g, Hemp Oil 6 µg/g (Table 2).

[3]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. Used lower body weight when a range is provided.

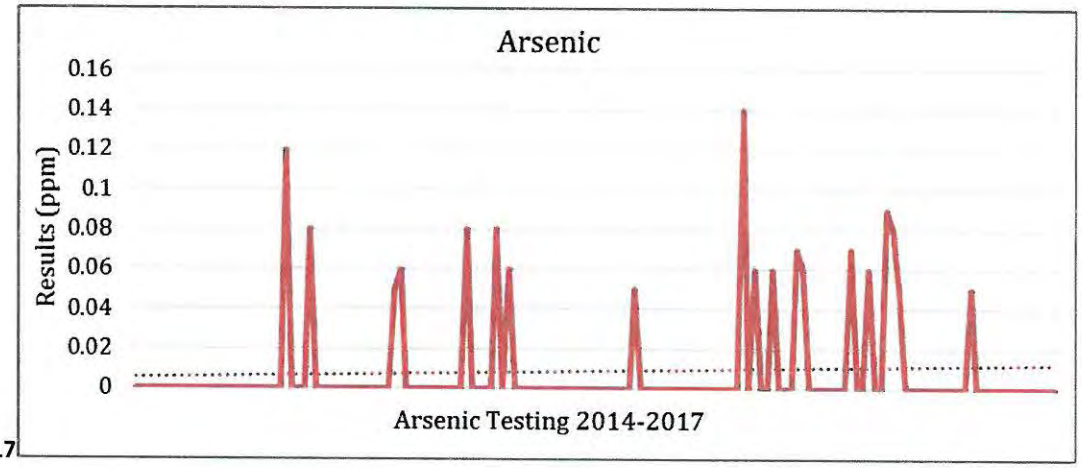


Figure 1 Arsenic Testing Results Trend 2014-2017

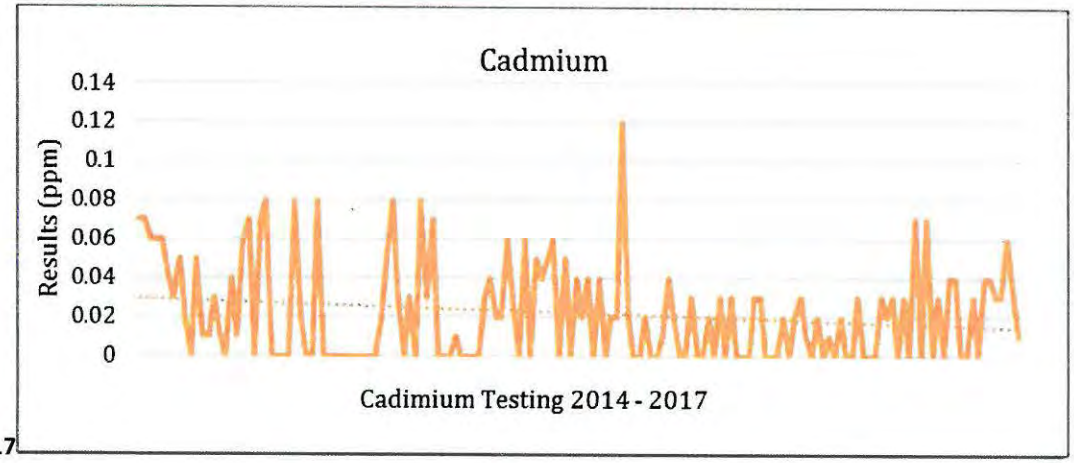


Figure 2 Cadmium Testing Results Trend 2014-2017

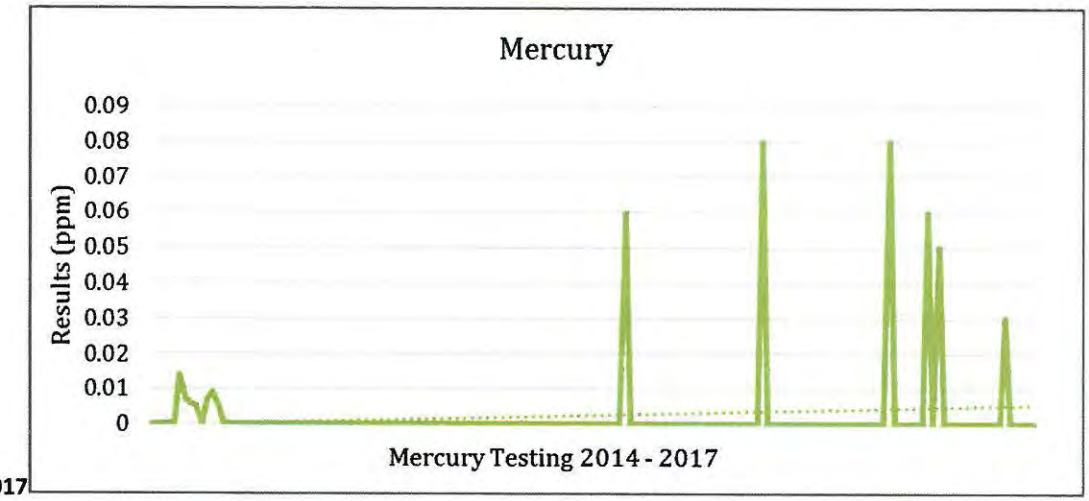


Figure 3 Mercury Testing Results Trend 2014-2017

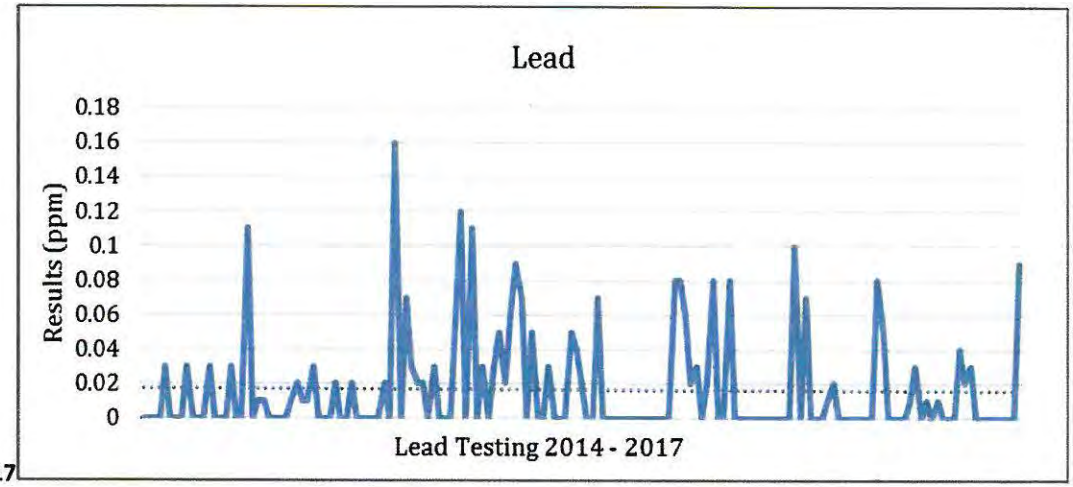


Figure 4 Lead Testing Results Trend 2014-2017

Figure 5 Crystal Ball Key Assumptions for Hulled Hemp Seed

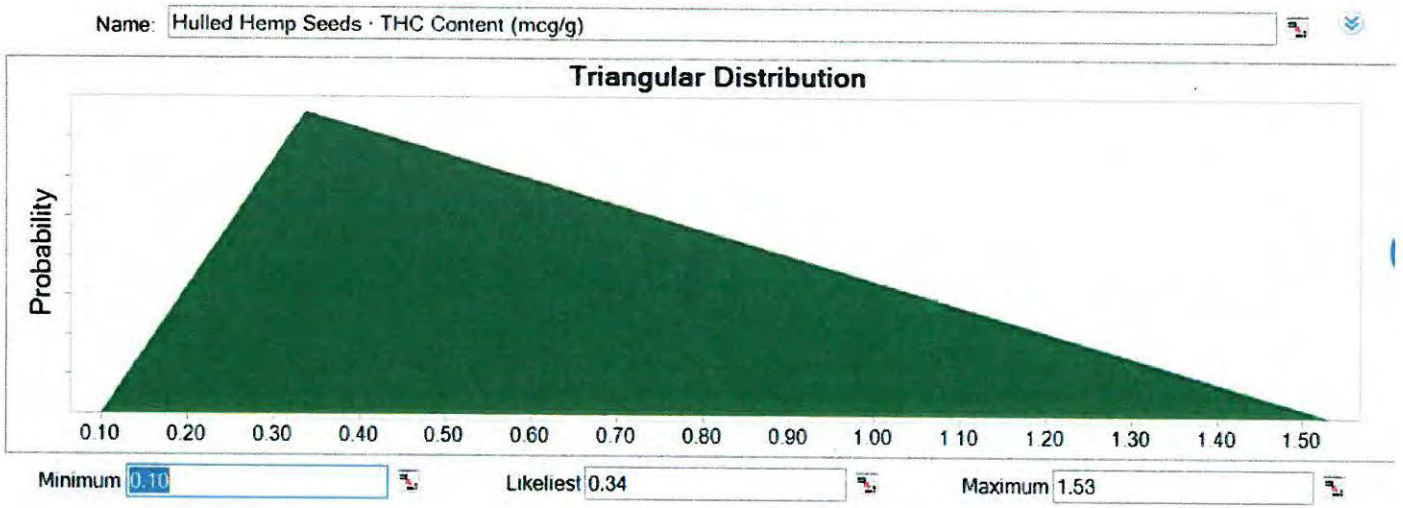


Figure 6 Crystal Ball Key Assumptions for Hemp Protein Powder

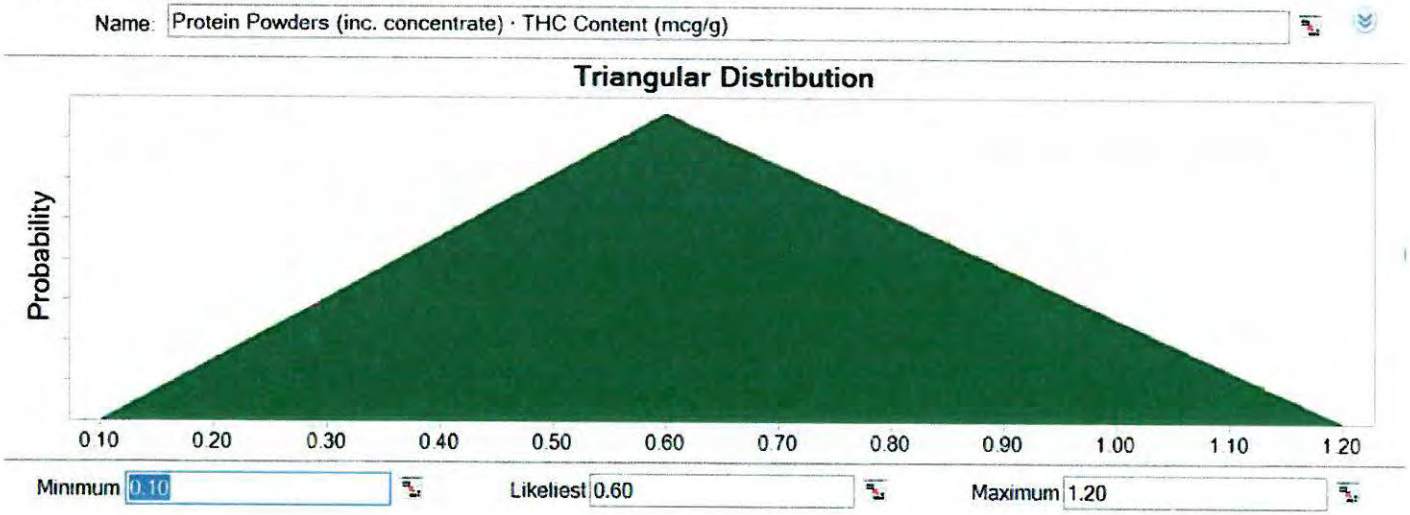


Figure 7 Crystal Ball Key Assumptions for Hemp Oil

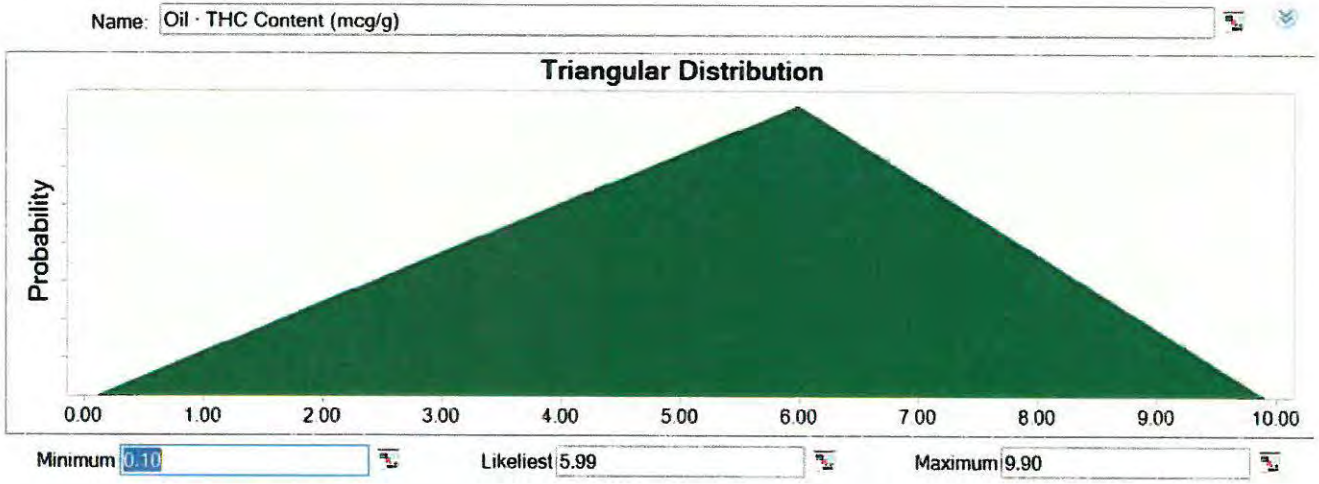
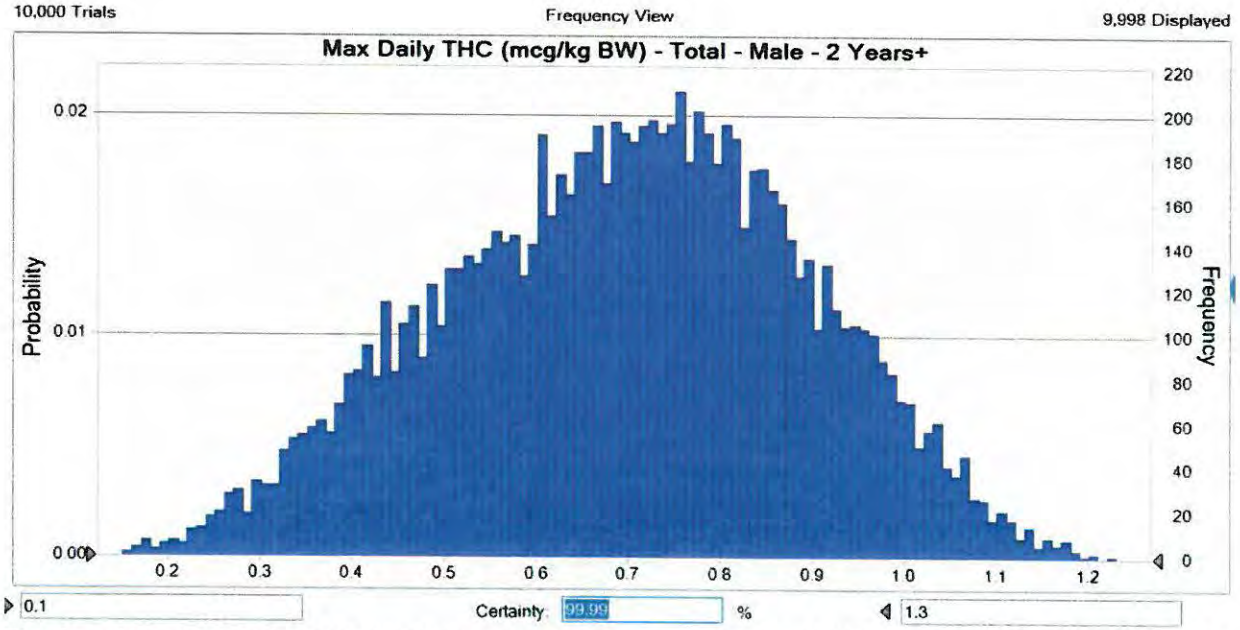


Figure 8 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Males Age 2 Years and Older

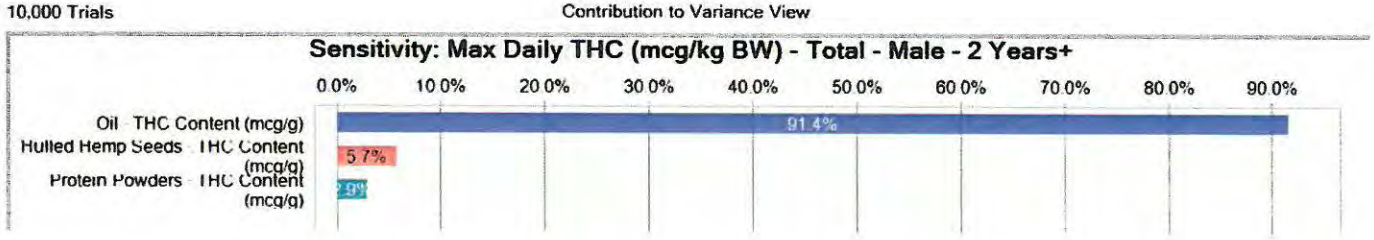


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 1.3µg/kg for males ages 2 years+.

Figure 9 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 Years and Older

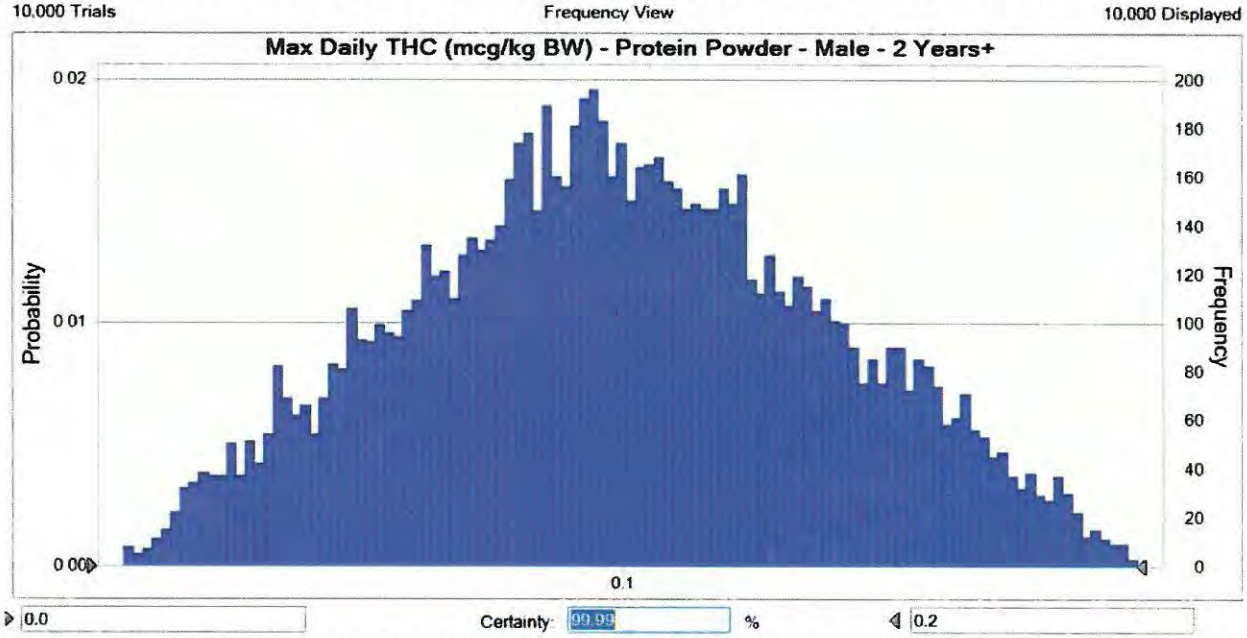
Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	0.7
Median	0.7
Mode	0.5
Standard Deviation	0.2
Variance	0.0
Skewness	-0.1329
Kurtosis	2.50
Coeff. of Variation	0.2795
Minimum	0.1
Maximum	1.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.4
20%	0.5
30%	0.6
40%	0.7
50%	0.7
60%	0.8
70%	0.8
80%	0.9
90%	0.9
100%	1.3



Variability in THC within Hemp Oil makes up 91% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 6% and Protein Powders make up 3%

Figure 10 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Males Age 2 Years and Older



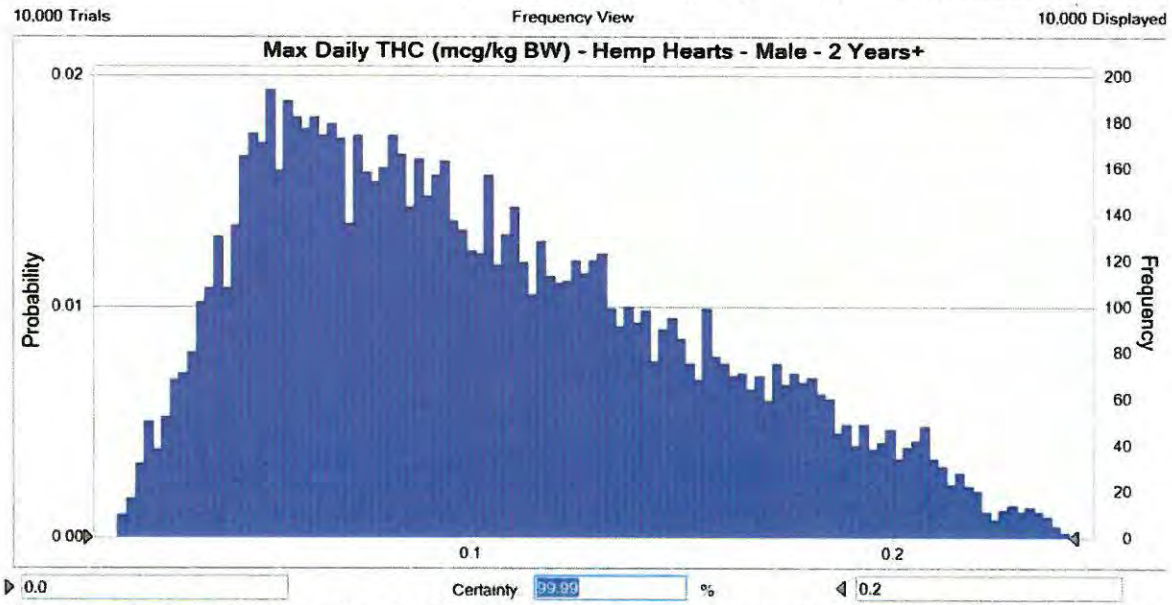
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.2µg/kg for males ages 2 years+.

Figure 11 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.0567
Kurtosis	2.42
Coeff. of Variation	0.3506
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.1
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.1
100%	0.2

Figure 12 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 2 Years and Older



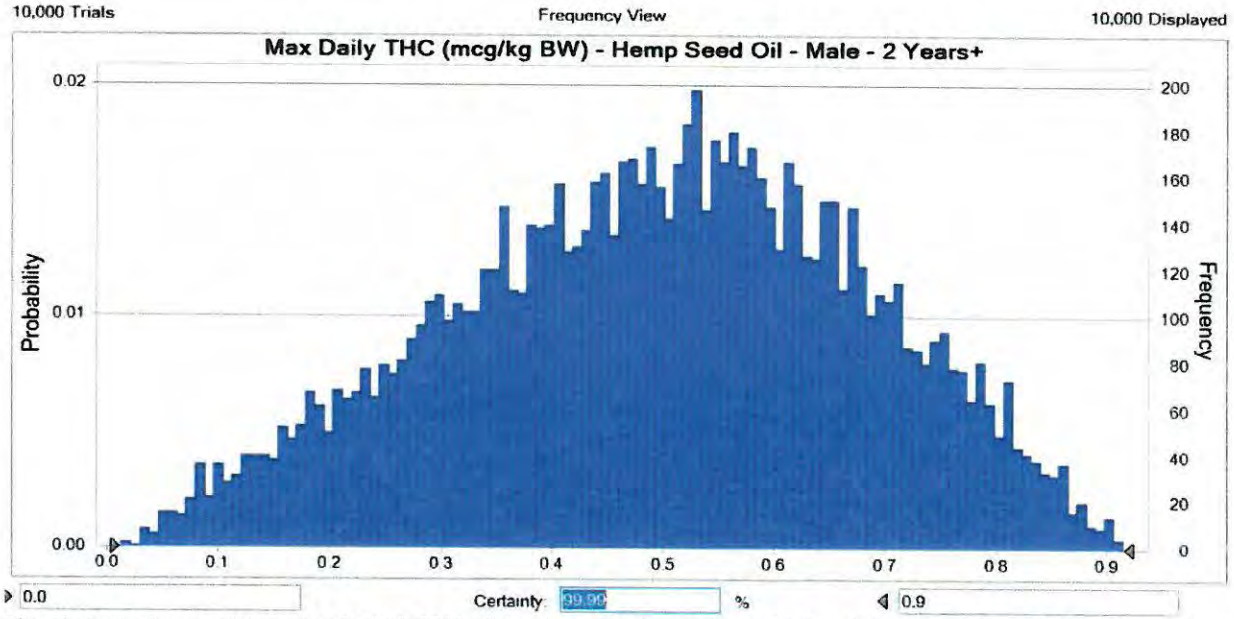
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.2µg/kg for males ages 2 years+.

Figure 13 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.5315
Kurtosis	2.43
Coeff. of Variation	0.4787
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.0
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.2
100%	0.2

Figure 14 Monte Carlo Model – Hemp Oil - THC Exposure Based on Body Weight – Males Age 2 Years and Older



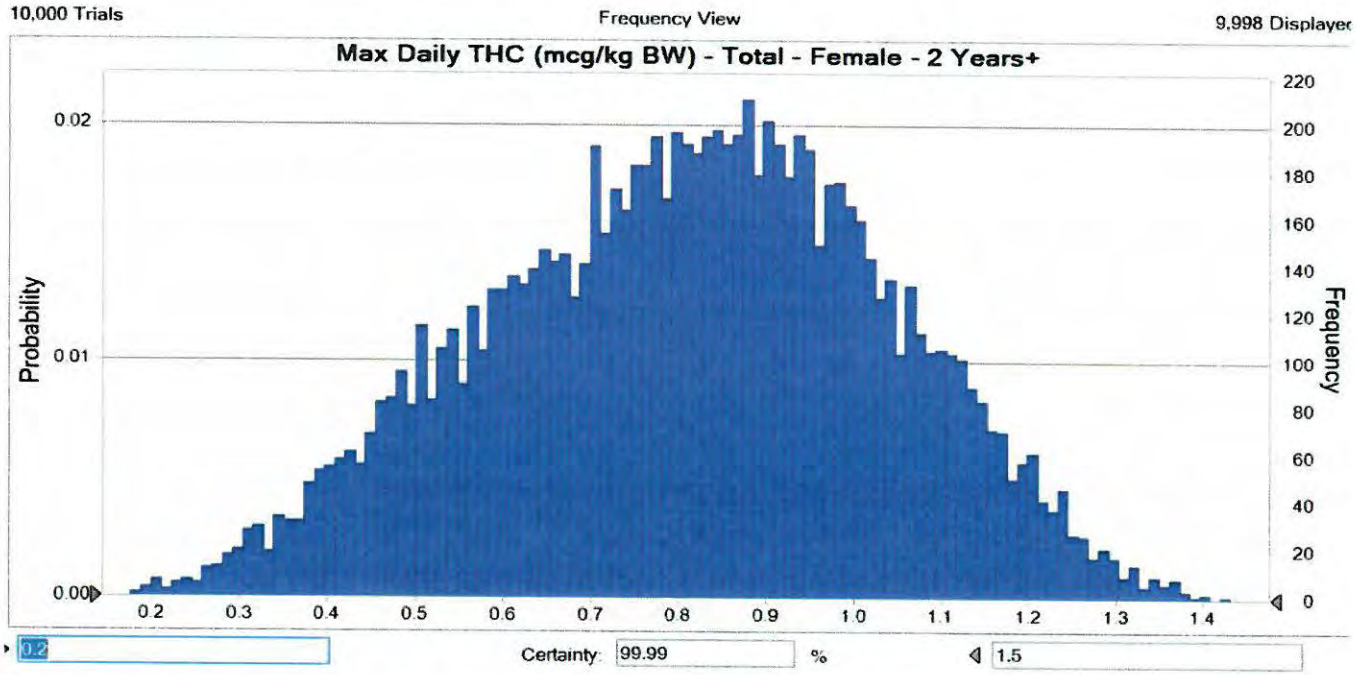
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.9µg/kg for males ages 2 years+.

Figure 15 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.5
Mean	0.5
Median	0.5
Mode	0.3
Standard Deviation	0.2
Variance	0.0
Skewness	-0.1647
Kurtosis	2.40
Coeff. of Variation	0.3752
Minimum	0.0
Maximum	0.9
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.2
20%	0.3
30%	0.4
40%	0.5
50%	0.5
60%	0.6
70%	0.6
80%	0.7
90%	0.7
100%	0.9

Figure 16 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Females 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 1.5µg/kg for females 2 years +.

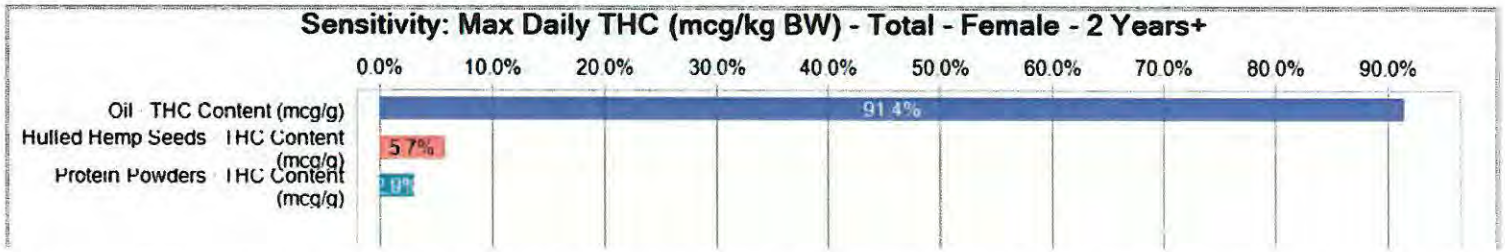
Figure 17 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	0.8
Median	0.8
Mode	0.6
Standard Deviation	0.2
Variance	0.1
Skewness	-0.1329
Kurtosis	2.50
Coeff. of Variation	0.2795
Minimum	0.2
Maximum	1.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.2
10%	0.5
20%	0.6
30%	0.7
40%	0.8
50%	0.8
60%	0.9
70%	0.9
80%	1.0
90%	1.1
100%	1.5

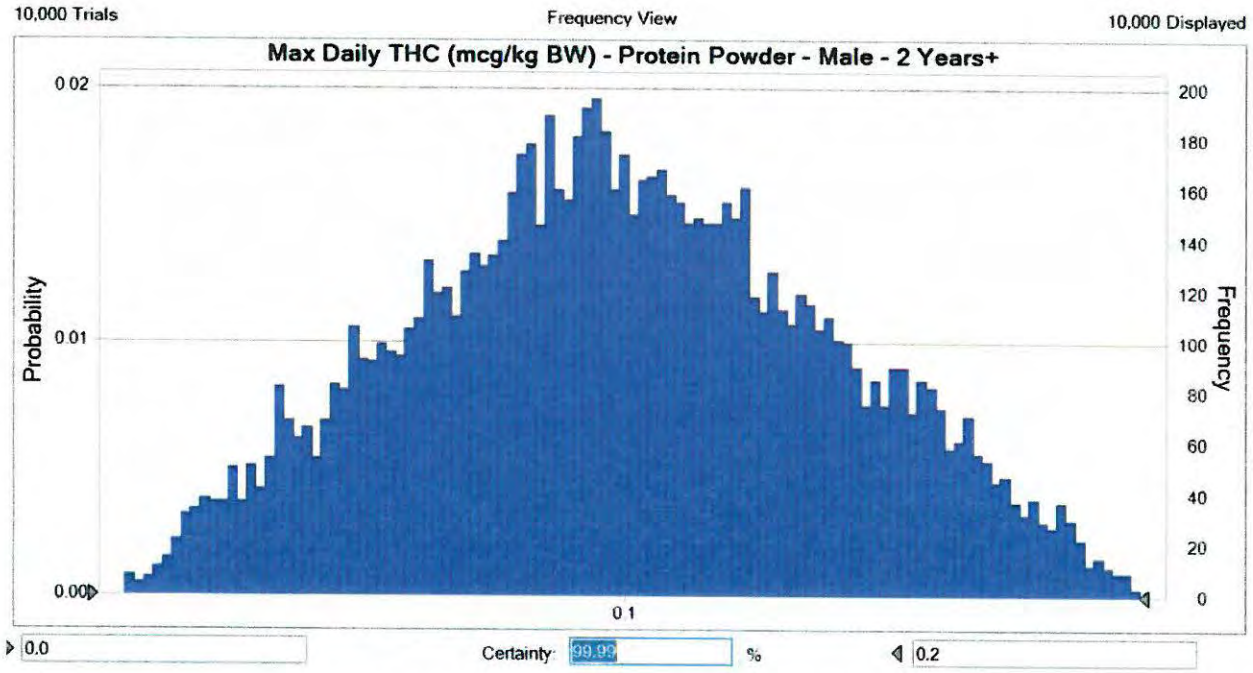
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 91% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 6% and Protein Powders make up 3%

Figure 18 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Females Age 2 Years and Older



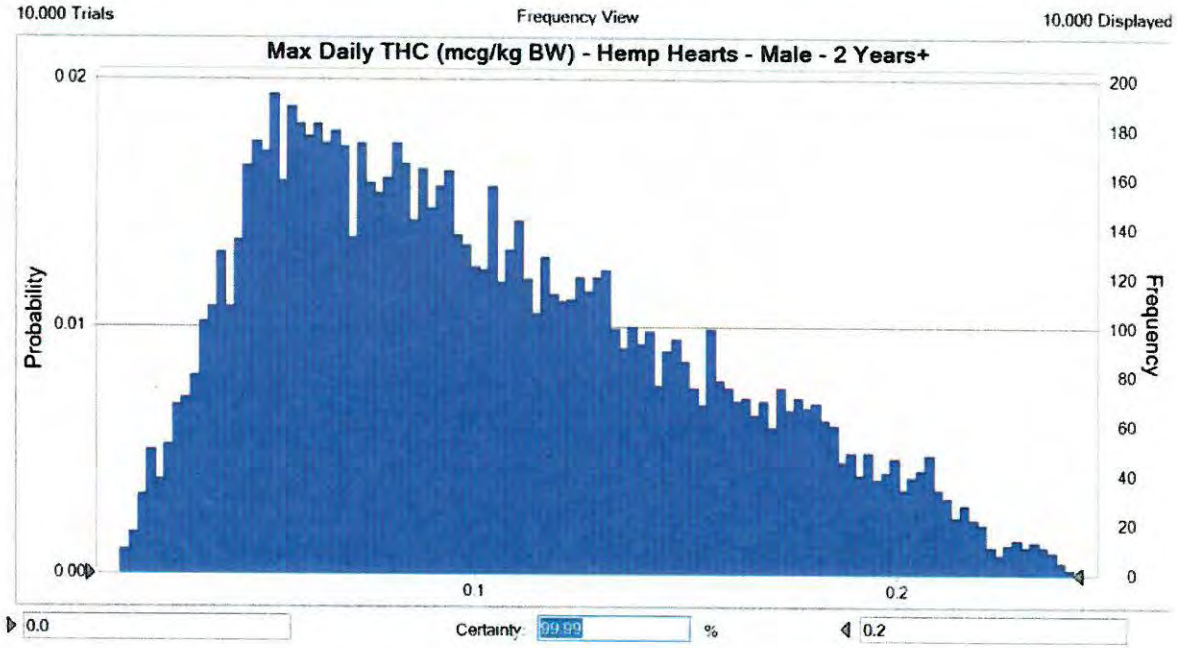
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (all hemp ingredients) of THC at a 90th percentile intake level will see no more than 1.3µg/kg for males ages 2 years+.

Figure 19 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.0567
Kurtosis	2.42
Coeff. of Variation	0.3506
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.1
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.1
100%	0.2

Figure 20 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 2 Years and Older



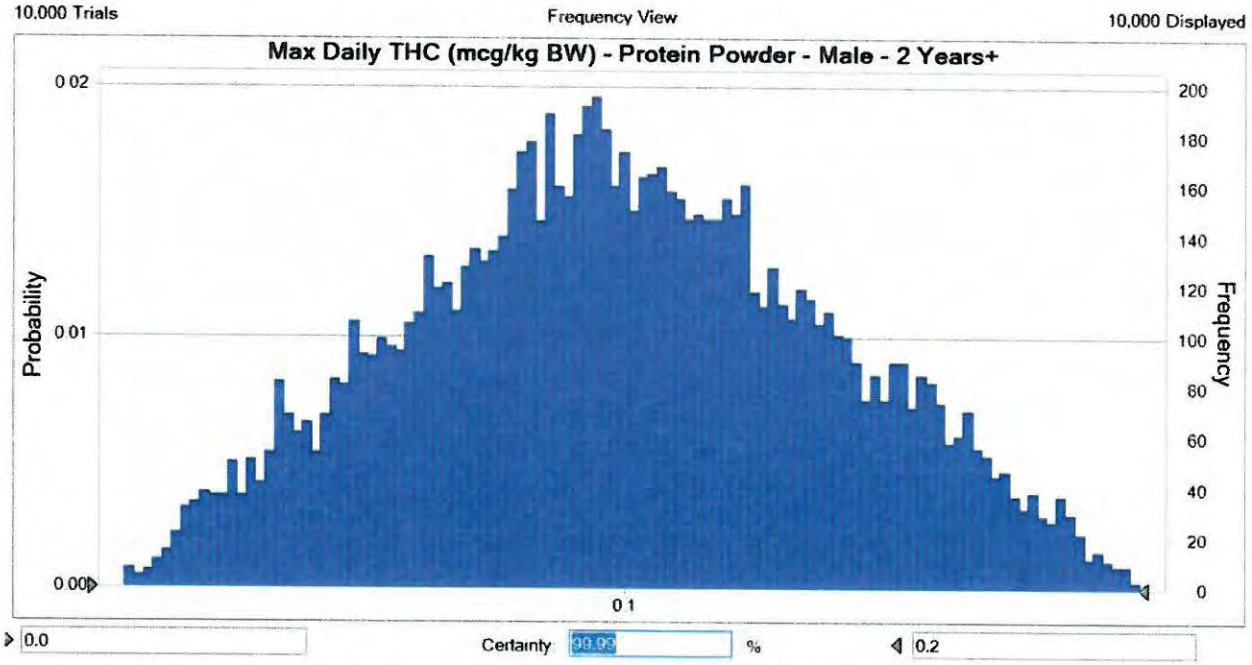
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.2µg/kg for males ages 2 years+.

Figure 21 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 Years and Older

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.5315
Kurtosis	2.43
Coeff. of Variation	0.4787
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.0
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.2
100%	0.2

Figure 22 Monte Carlo Model – Hemp Oil - THC Exposure Based on Body Weight – Females Age 2 Years and Older



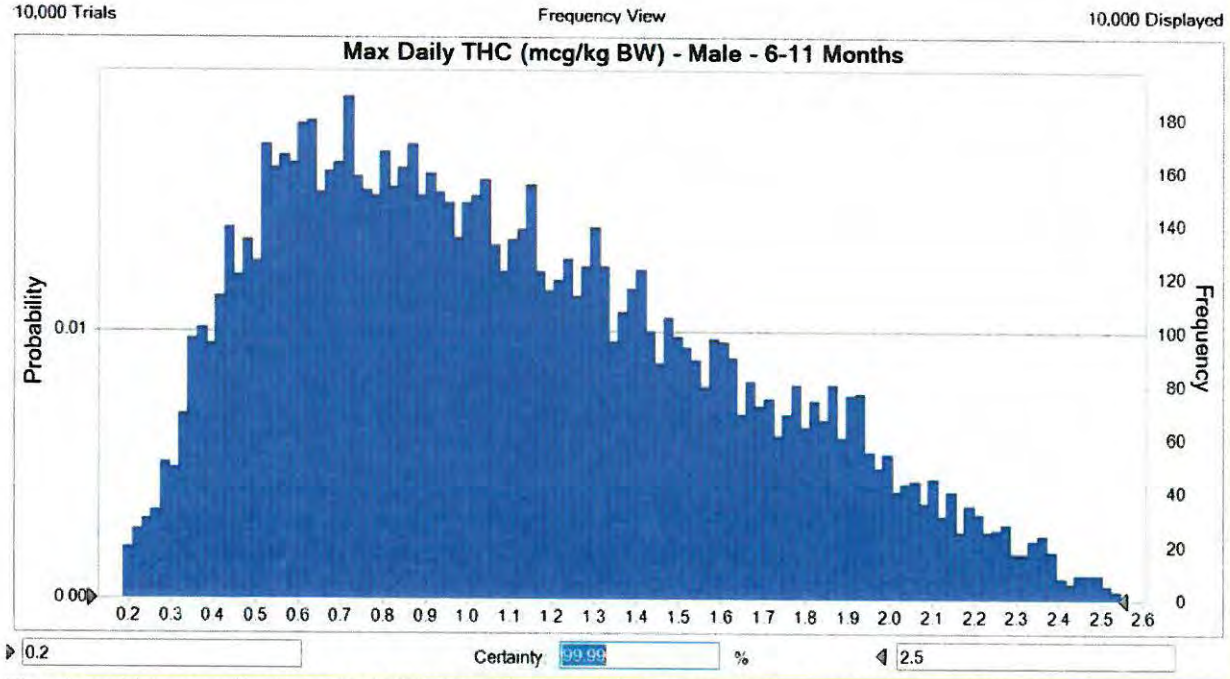
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 0.9µg/kg for males ages 2 years+.

Statistic	Forecast values
Trials	10,000
Base Case	0.0
Mean	0.1
Median	0.1
Mode	0.1
Standard Deviation	0.0
Variance	0.0
Skewness	0.0567
Kurtosis	2.42
Coeff. of Variation	0.3506
Minimum	0.0
Maximum	0.2
Mean Std. Error	0.0

Figure 23 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 Years and Older

Percentile	Forecast values
0%	0.0
10%	0.1
20%	0.1
30%	0.1
40%	0.1
50%	0.1
60%	0.1
70%	0.1
80%	0.1
90%	0.1
100%	0.2

Figure 24 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 6 to 11 Months



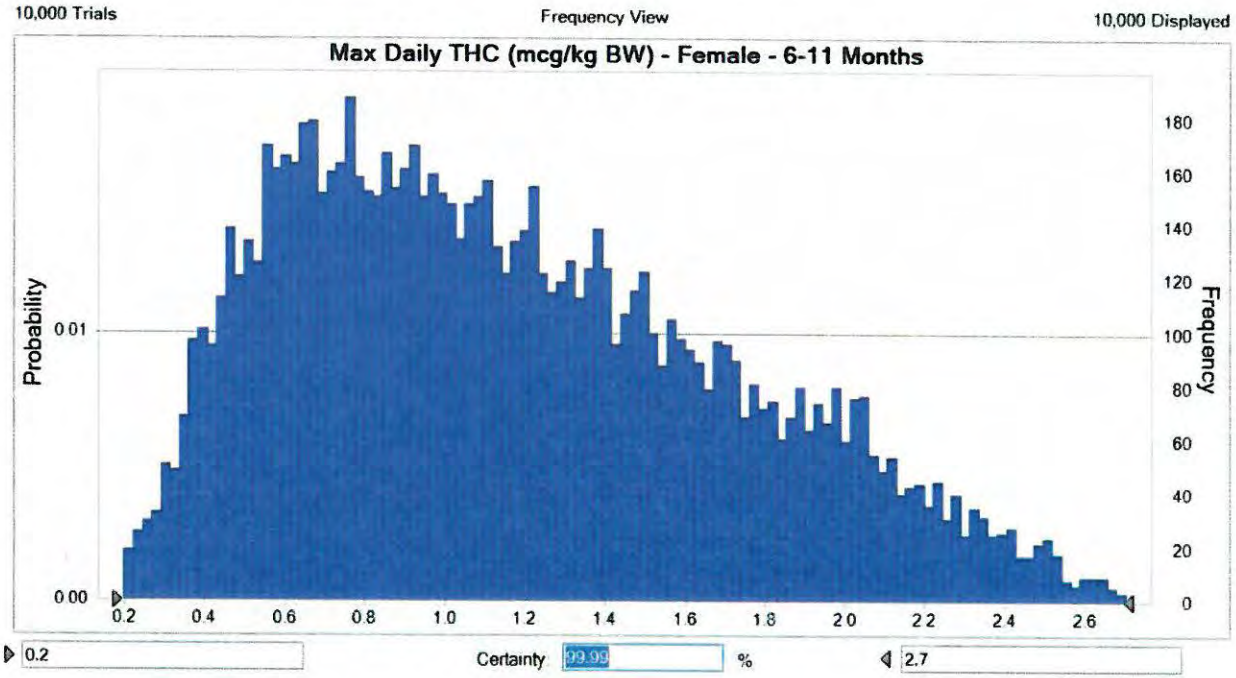
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seed will see no more than 2.5µg/kg for males age 6 to 11 months.

Figure 25 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight - Males Age 6 to 11 Months

Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	1.1
Median	1.0
Mode	—
Standard Deviation	0.5
Variance	0.3
Skewness	0.4883
Kurtosis	2.41
Coeff. of Variation	0.4699
Minimum	0.2
Maximum	2.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.2
10%	0.5
20%	0.6
30%	0.7
40%	0.9
50%	1.0
60%	1.2
70%	1.4
80%	1.6
90%	1.9
100%	2.5

Figure 26 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 6 to 11 Months



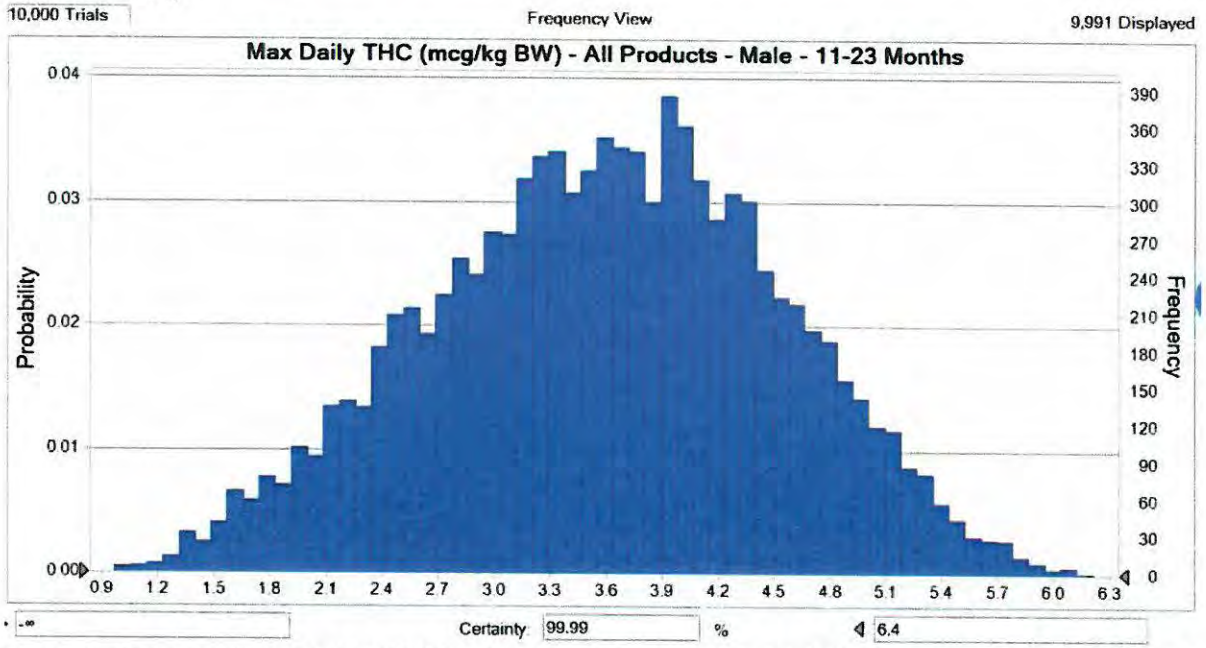
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seed will see no more than 2.7µg/kg for females age 6 to 11 months.

Figure 27 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight Females Age 6 to 11 Months

Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	1.2
Median	1.1
Mode	---
Standard Deviation	0.5
Variance	0.3
Skewness	0.4883
Kurtosis	2.41
Coeff. of Variation	0.4699
Minimum	0.2
Maximum	2.7
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.2
10%	0.5
20%	0.7
30%	0.8
40%	0.9
50%	1.1
60%	1.3
70%	1.4
80%	1.7
90%	2.0
100%	2.7

Figure 28 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Males Age 11 to 23 Months (modelled after 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 6.4µg/kg for males ages 11-23 Months.

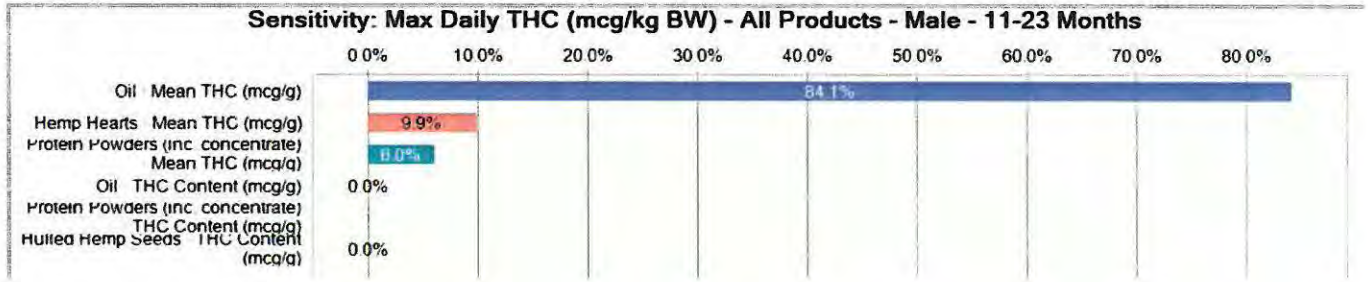
Figure 29 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	3.5
Mean	3.6
Median	3.6
Mode	—
Standard Deviation	0.9
Variance	0.9
Skewness	-0.0949
Kurtosis	2.57
Coeff. of Variation	0.2606
Minimum	0.7
Maximum	6.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.7
10%	2.3
20%	2.8
30%	3.1
40%	3.4
50%	3.6
60%	3.9
70%	4.1
80%	4.4
90%	4.8
100%	6.5

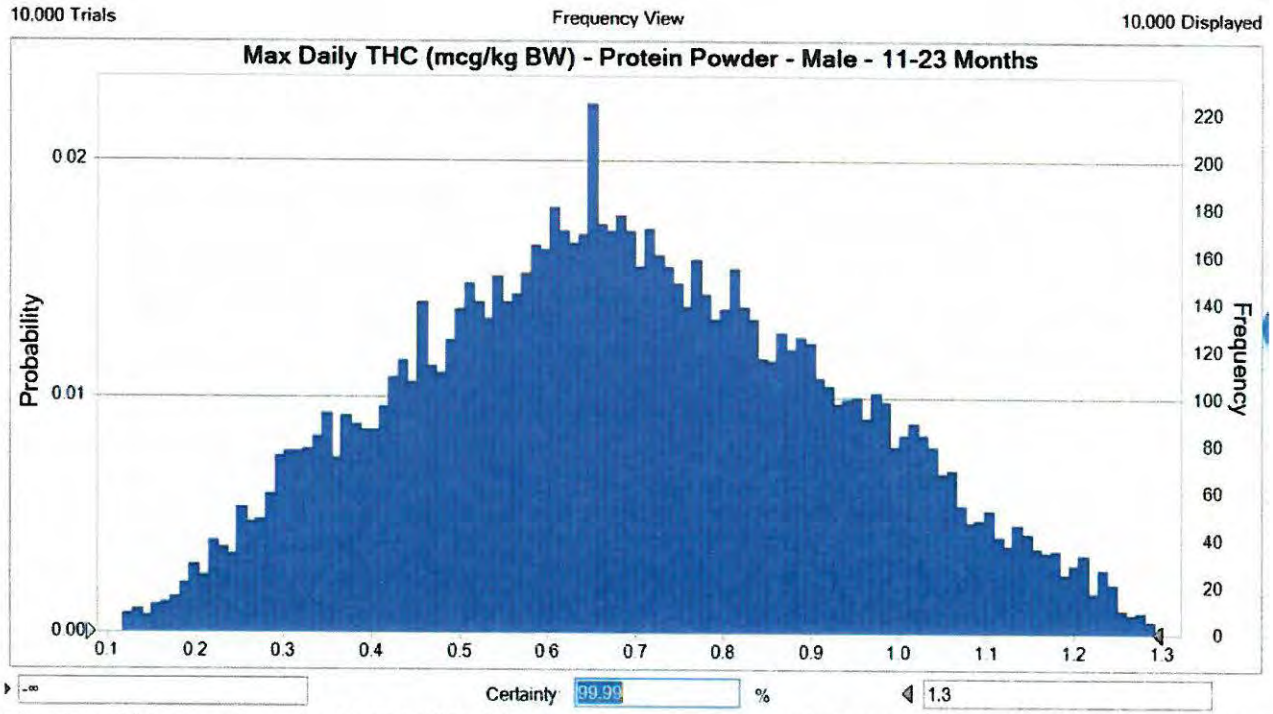
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 84% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 10% and Protein Powders make up 6%

Figure 30 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)



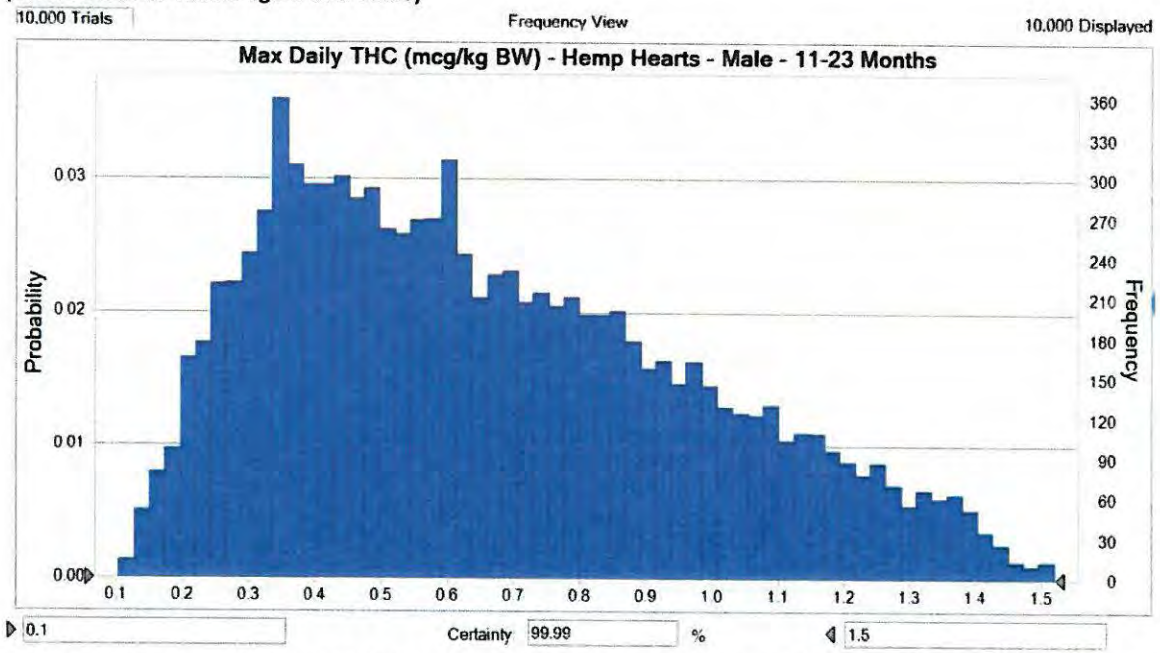
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (protein powder) of THC at a 90th percentile intake level will see no more than 1.3µg/kg for males ages 11-23 Months.

Figure 31 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.7
Mean	0.7
Median	0.7
Mode	---
Standard Deviation	0.2
Variance	0.1
Skewness	0.0999
Kurtosis	2.40
Coeff. of Variation	0.3512
Minimum	0.1
Maximum	1.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.4
20%	0.5
30%	0.6
40%	0.6
50%	0.7
60%	0.7
70%	0.8
80%	0.9
90%	1.0
100%	1.3

Figure 32 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)



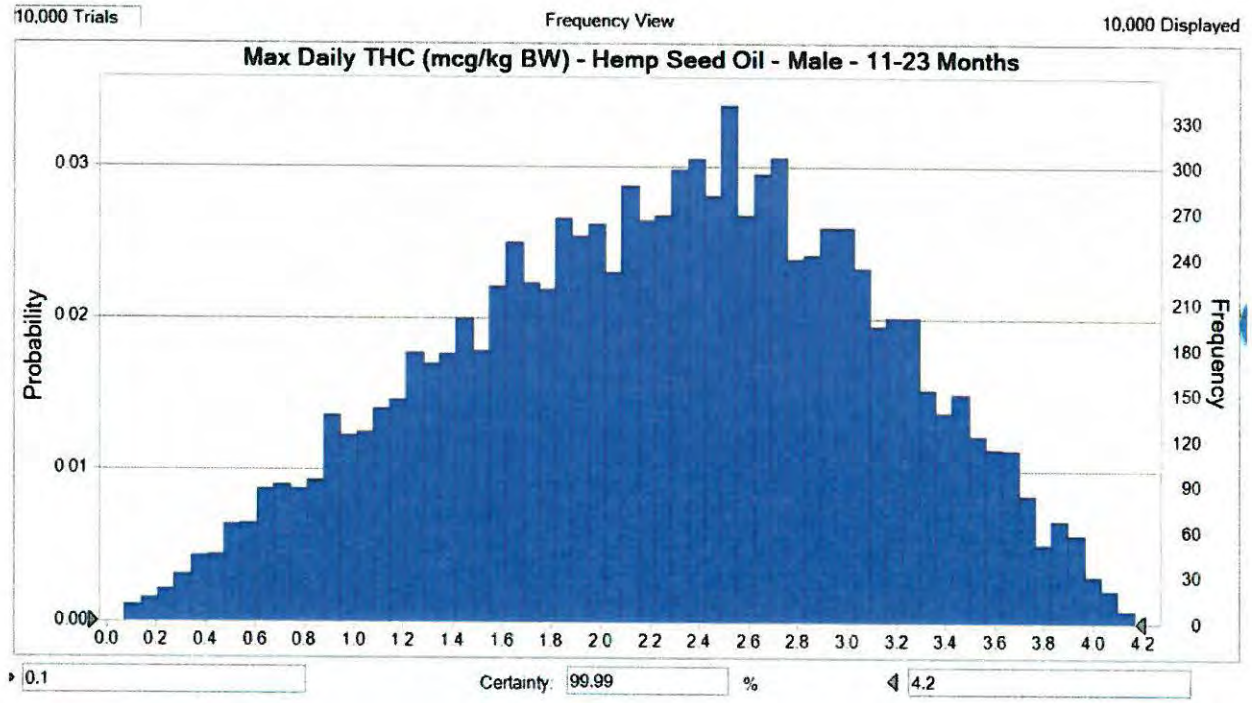
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (hemp hearts) of THC at a 90th percentile intake level will see no more than 1.5µg/kg for males ages 11-23 Months.

Figure 33 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.3
Mean	0.7
Median	0.6
Mode	—
Standard Deviation	0.3
Variance	0.1
Skewness	0.5087
Kurtosis	2.40
Coeff. of Variation	0.4761
Minimum	0.1
Maximum	1.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.4
30%	0.4
40%	0.5
50%	0.6
60%	0.7
70%	0.8
80%	1.0
90%	1.1
100%	1.5

Figure 34 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)



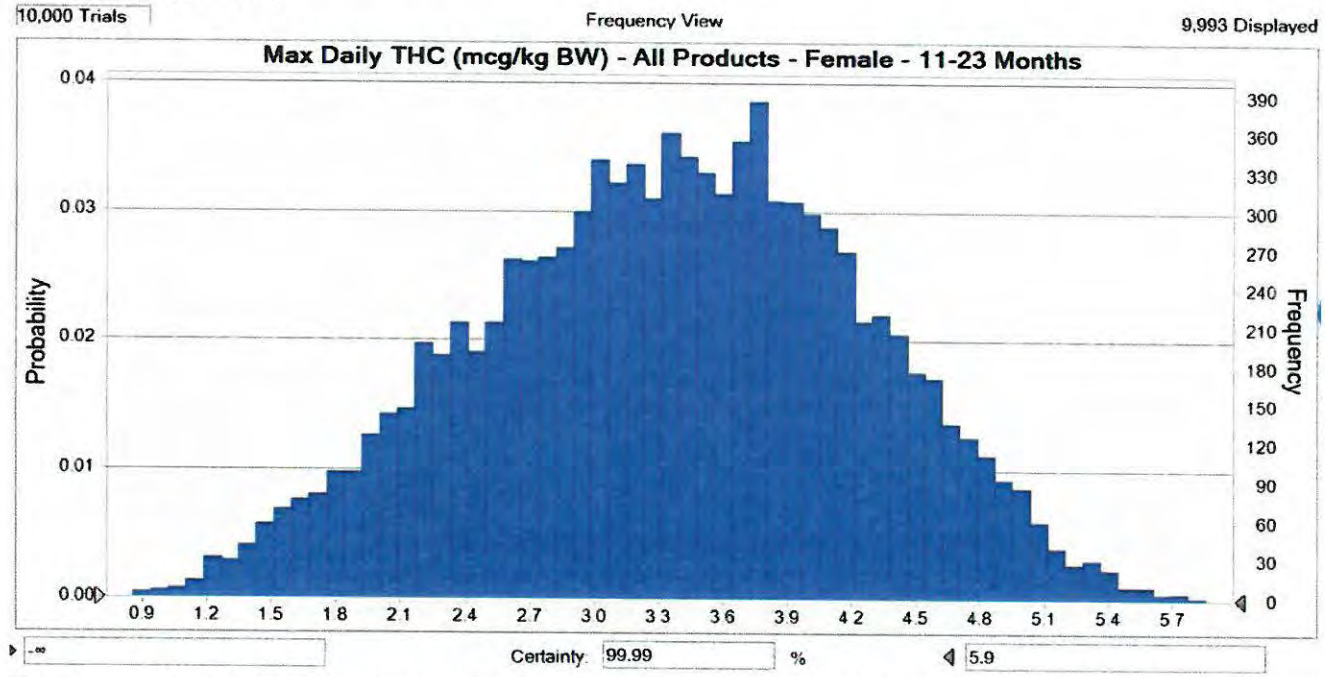
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (hemp seed oil) of THC at a 90th percentile intake level will see no more than 4.2µg/kg for males ages 11-23 Months.

Figure 35 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Males Age 11 to 23 Months (modelled after Males age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	2.5
Mean	2.2
Median	2.3
Mode	—
Standard Deviation	0.8
Variance	0.7
Skewness	-0.1663
Kurtosis	2.36
Coeff. of Variation	0.3788
Minimum	0.1
Maximum	4.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	1.1
20%	1.5
30%	1.8
40%	2.0
50%	2.3
60%	2.5
70%	2.7
80%	3.0
90%	3.3
100%	4.2

Figure 36 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

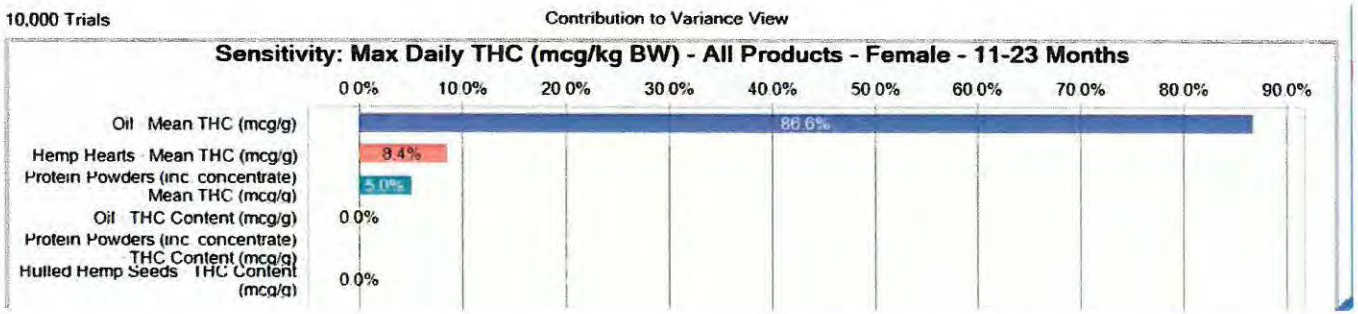


The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (All Products) of THC at a 90th percentile intake level will see no more than 5.9µg/kg for females ages 11-23 Months.

Figure 37 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

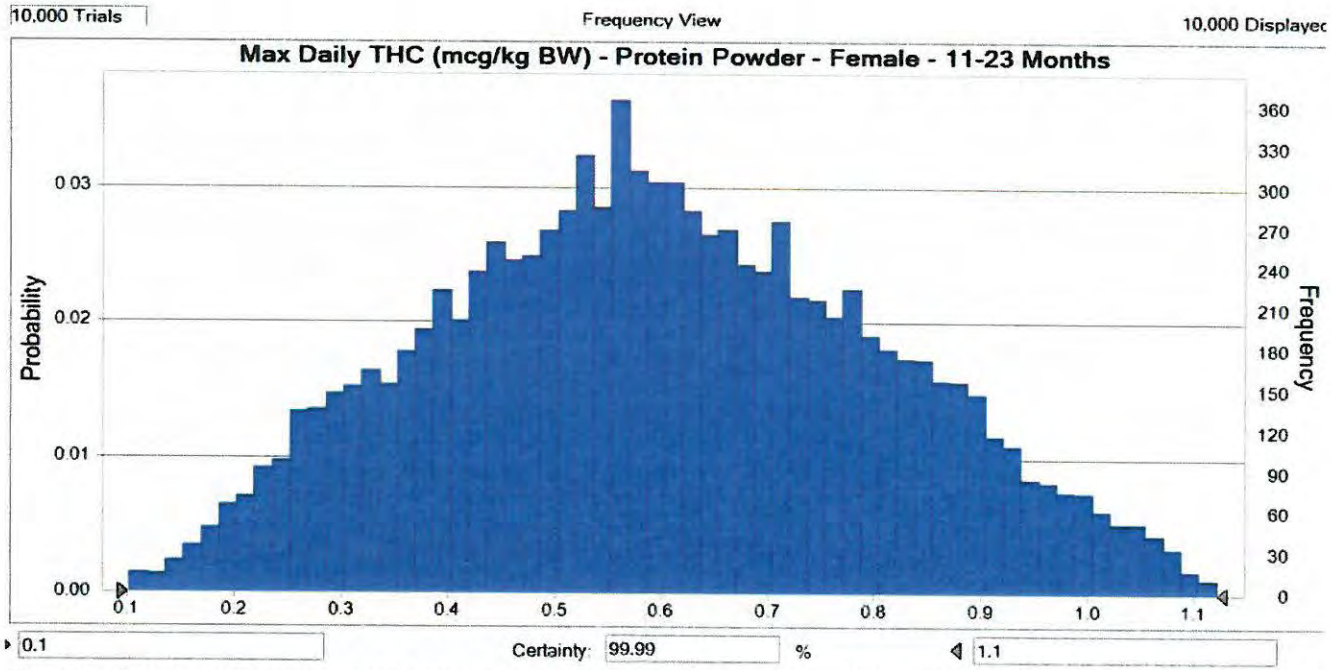
Statistic	Forecast values
Trials	10,000
Base Case	3.3
Mean	3.4
Median	3.4
Mode	—
Standard Deviation	0.9
Variance	0.8
Skewness	-0.1058
Kurtosis	2.54
Coeff. of Variation	0.2660
Minimum	0.6
Maximum	6.1
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.6
10%	2.2
20%	2.6
30%	2.9
40%	3.1
50%	3.4
60%	3.6
70%	3.9
80%	4.1
90%	4.5
100%	6.1



Variability in THC within Hemp Oil makes up 87% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 8% and Protein Powders make up 5%

Figure 38 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)



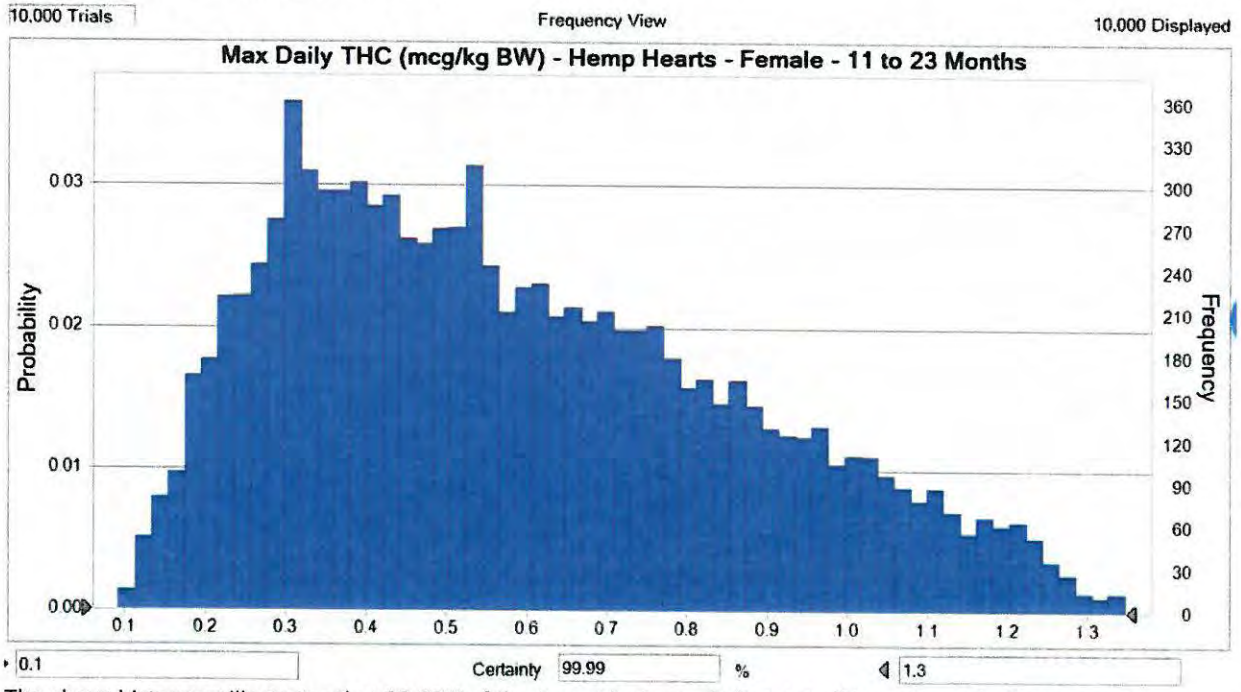
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Protein Powders) of THC at a 90th percentile intake level will see no more than 1.1µg/kg for females ages 11-23 Months.

Figure 39 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.6
Mean	0.6
Median	0.6
Mode	—
Standard Deviation	0.2
Variance	0.0
Skewness	0.0999
Kurtosis	2.40
Coeff. of Variation	0.3512
Minimum	0.1
Maximum	1.1
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.4
30%	0.5
40%	0.5
50%	0.6
60%	0.6
70%	0.7
80%	0.8
90%	0.9
100%	1.1

Figure 40 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)



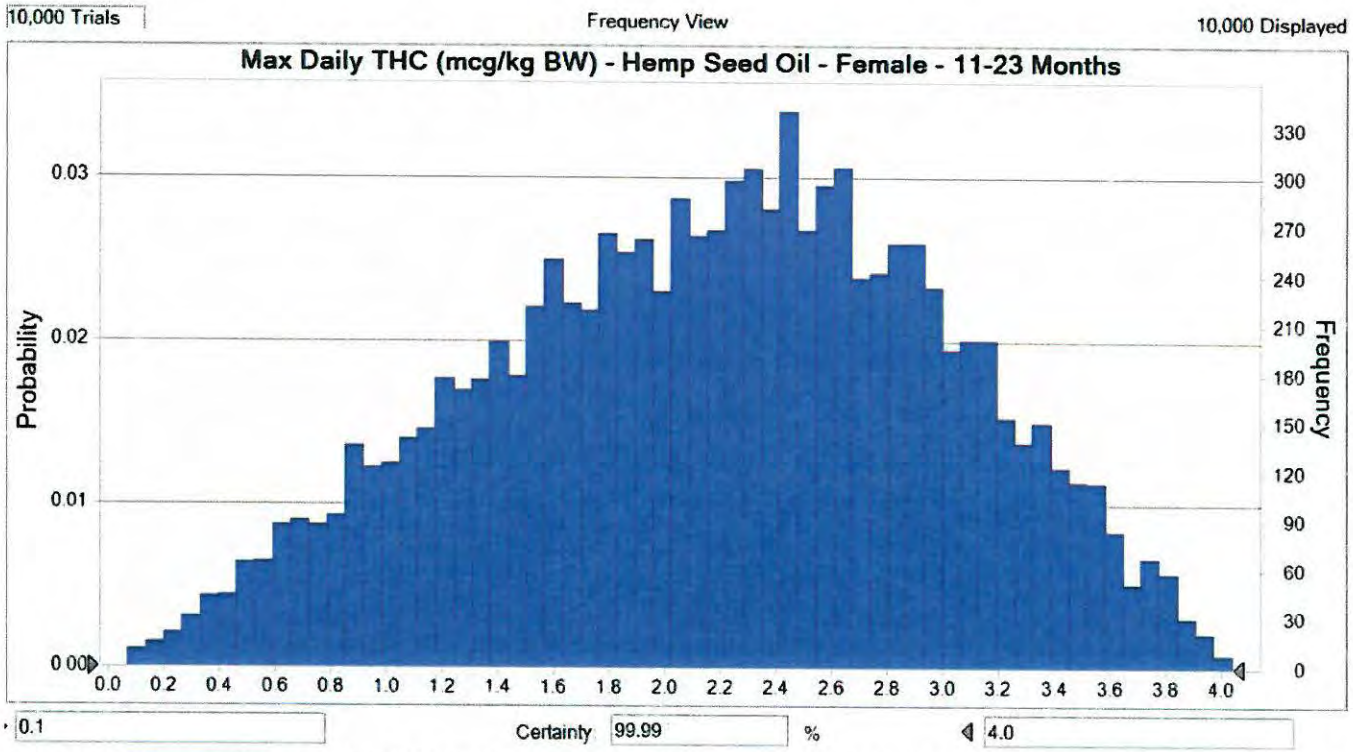
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Hemp Hearts) of THC at a 90th percentile intake level will see no more than 1.3µg/kg for females ages 11-23 Months.

Figure 41 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.3
Mean	0.6
Median	0.5
Mode	—
Standard Deviation	0.3
Variance	0.1
Skewness	0.5087
Kurtosis	2.40
Coeff. of Variation	0.4761
Minimum	0.1
Maximum	1.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.3
30%	0.4
40%	0.5
50%	0.5
60%	0.6
70%	0.7
80%	0.8
90%	1.0
100%	1.3

Figure 42 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)



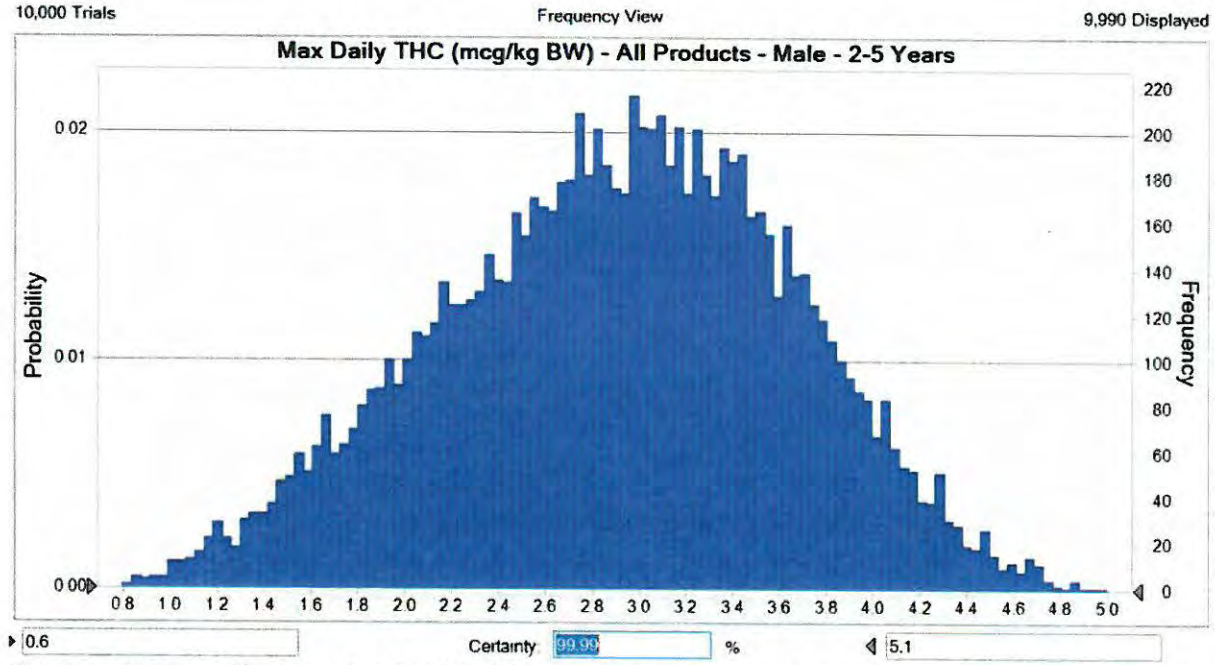
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Hemp Seed Oil) of THC at a 90th percentile intake level will see no more than 4.0µg/kg for females ages 11-23 Months.

Figure 43 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Females Age 11 to 23 Months (modelled after Females age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	2.5
Mean	2.2
Median	2.2
Mode	---
Standard Deviation	0.8
Variance	0.7
Skewness	-0.1663
Kurtosis	2.36
Coeff. of Variation	0.3788
Minimum	0.1
Maximum	4.0
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	1.0
20%	1.4
30%	1.7
40%	2.0
50%	2.2
60%	2.4
70%	2.7
80%	2.9
90%	3.2
100%	4.0

Figure 34 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – 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 5.1µg/kg for males ages 2-5.

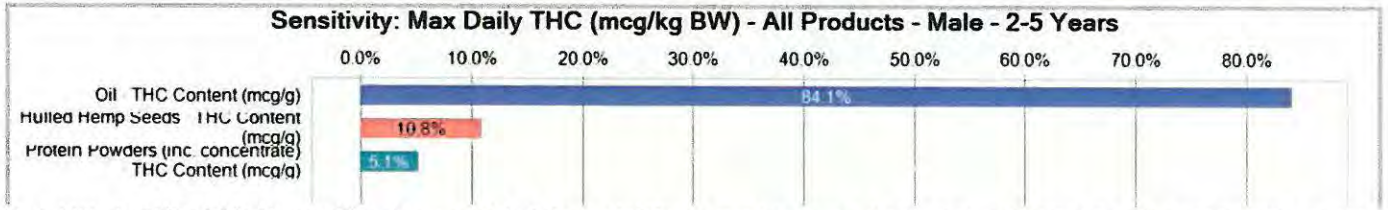
Figure 45 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	2.2
Mean	2.9
Median	2.9
Mode	---
Standard Deviation	0.7
Variance	0.6
Skewness	-0.1609
Kurtosis	2.59
Coeff. of Variation	0.2589
Minimum	0.6
Maximum	5.1
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.6
10%	1.9
20%	2.2
30%	2.5
40%	2.7
50%	2.9
60%	3.1
70%	3.3
80%	3.6
90%	3.8
100%	5.1

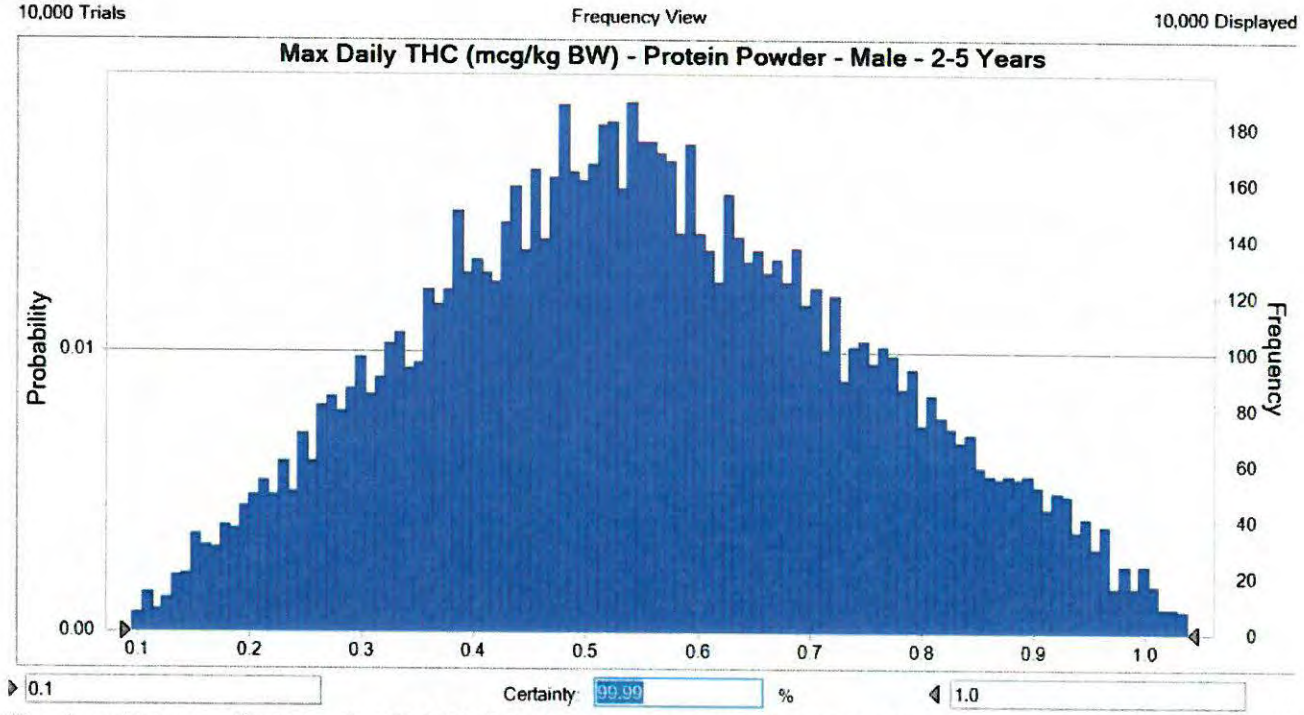
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 84% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 11% and Protein Powders make up 5%

Figure 46 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Males Age 2 to 5 Years)



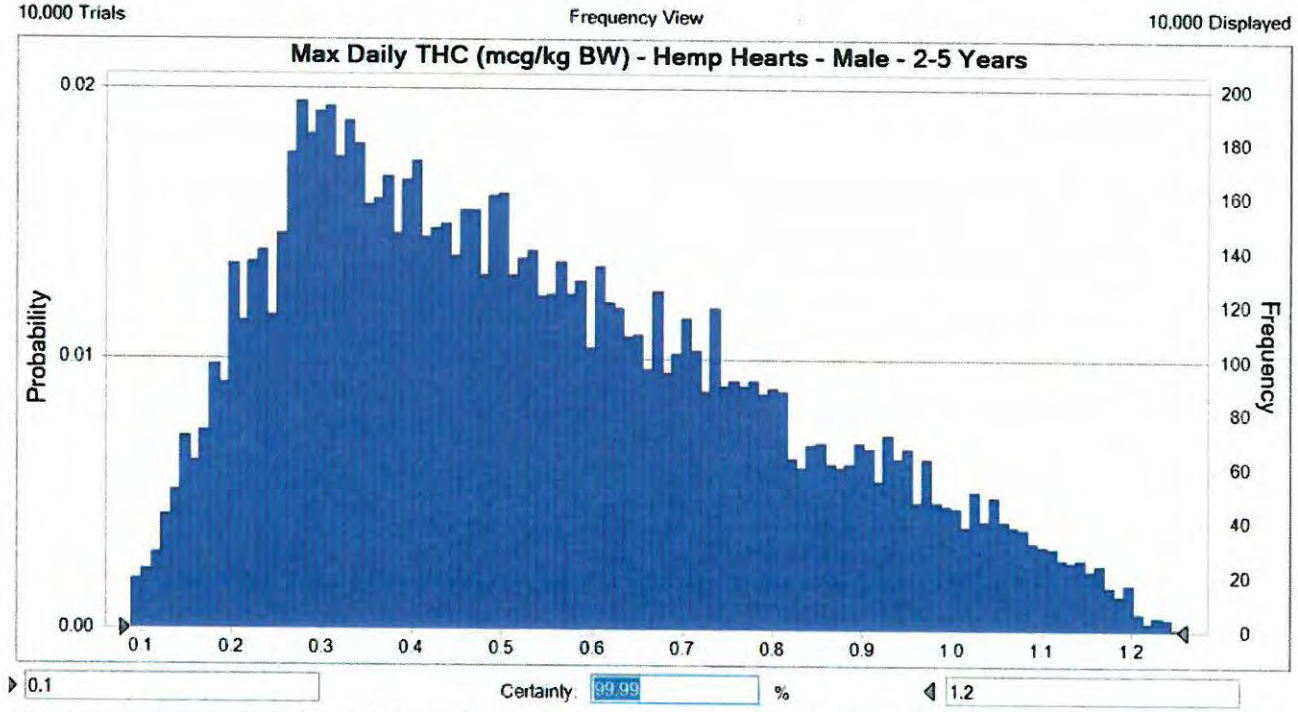
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (protein powder) of THC at a 90th percentile intake level will see no more than 1.0µg/kg for males ages 2-5.

Figure 47 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.3
Mean	0.6
Median	0.5
Mode	---
Standard Deviation	0.2
Variance	0.0
Skewness	0.1123
Kurtosis	2.41
Coeff. of Variation	0.3562
Minimum	0.1
Maximum	1.0
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.4
30%	0.4
40%	0.5
50%	0.5
60%	0.6
70%	0.7
80%	0.7
90%	0.8
100%	1.0

Figure 1 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 2 to 5 Years)



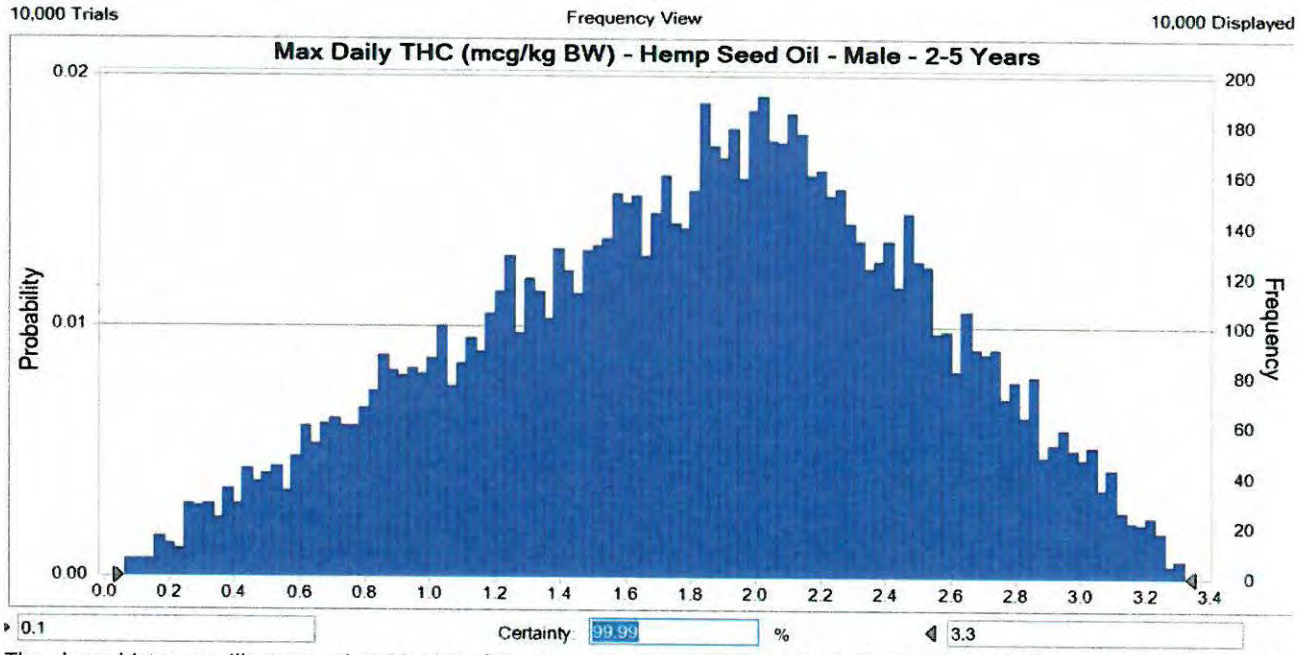
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (hemp hearts) of THC at a 90th percentile intake level will see no more than 1.2µg/kg for males ages 2-5.

Figure 49 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.5
Median	0.5
Mode	—
Standard Deviation	0.3
Variance	0.1
Skewness	0.5224
Kurtosis	2.42
Coeff. of Variation	0.4797
Minimum	0.1
Maximum	1.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.2
20%	0.3
30%	0.4
40%	0.4
50%	0.5
60%	0.6
70%	0.7
80%	0.8
90%	0.9
100%	1.3

Figure 50 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Males Age 2 to 5 Years)



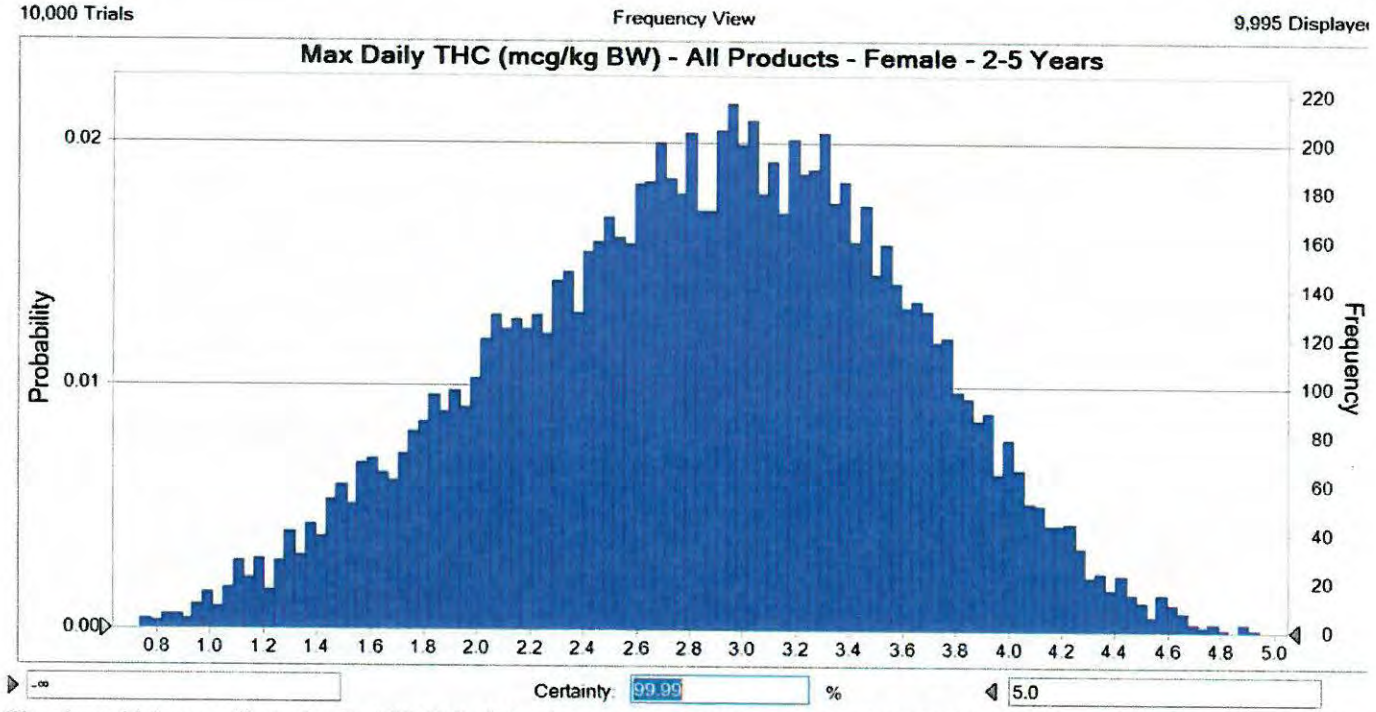
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (oil) of THC at a 90th percentile intake level will see no more than 3.3µg/kg for males ages 2-5.

Figure 51 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Males Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	1.7
Mean	1.8
Median	1.9
Mode	---
Standard Deviation	0.7
Variance	0.5
Skewness	-0.2092
Kurtosis	2.41
Coeff. of Variation	0.3772
Minimum	0.1
Maximum	3.3
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.8
20%	1.2
30%	1.4
40%	1.7
50%	1.9
60%	2.0
70%	2.2
80%	2.4
90%	2.7
100%	3.3

Figure 52 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – Females Age 2 to 5 Years)



The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (All Products) of THC at a 90th percentile intake level will see no more than 5.0µg/kg for females ages 2-5 years.

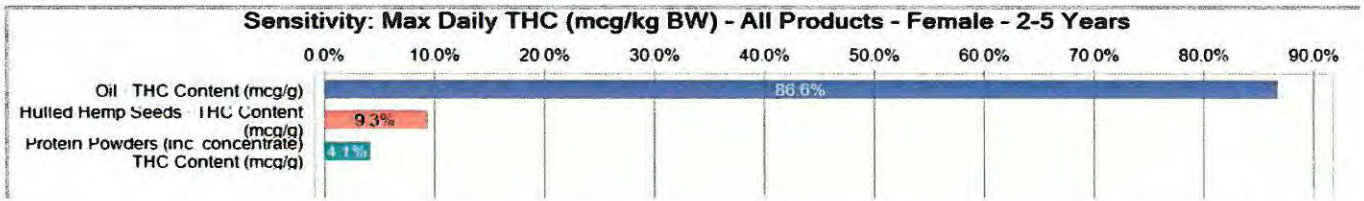
Figure 53 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	2.2
Mean	2.8
Median	2.9
Mode	---
Standard Deviation	0.8
Variance	0.6
Skewness	-0.1726
Kurtosis	2.56
Coeff. of Variation	0.2642
Minimum	0.6
Maximum	5.0
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.6
10%	1.8
20%	2.2
30%	2.4
40%	2.7
50%	2.9
60%	3.1
70%	3.3
80%	3.5
90%	3.8
100%	5.0

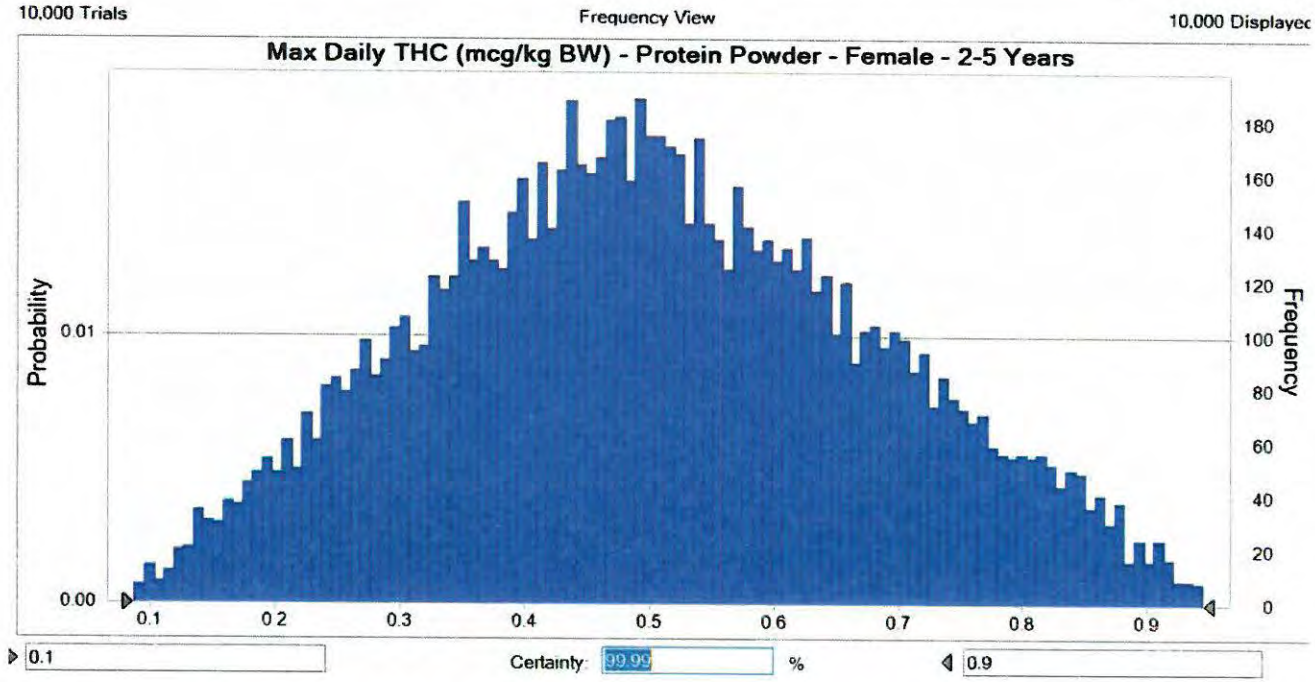
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 87% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 9% and Protein Powders make up 4%

Figure 542 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Females Age 2 to 5 Years)



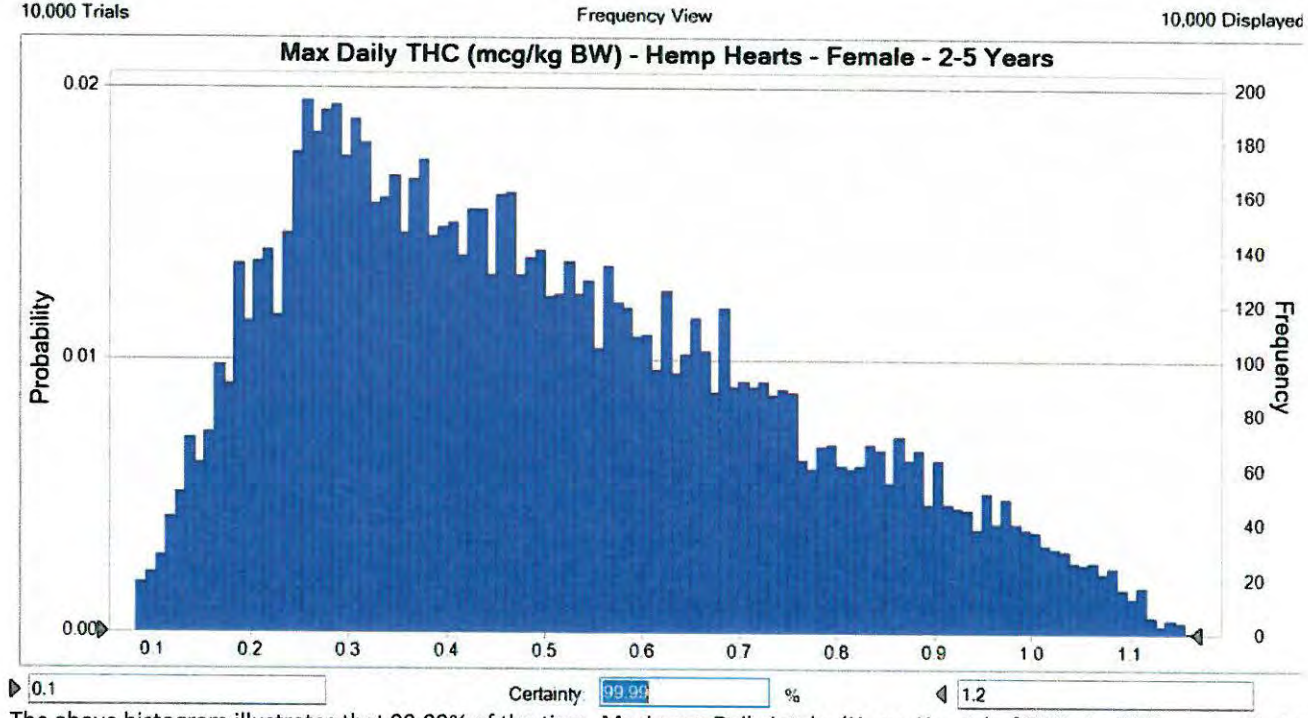
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Protein Powders) of THC at a 90th percentile intake level will see no more than 0.9µg/kg for females ages 2-5 years.

Figure 553 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.5
Median	0.5
Mode	---
Standard Deviation	0.2
Variance	0.0
Skewness	0.1123
Kurtosis	2.41
Coeff. of Variation	0.3562
Minimum	0.1
Maximum	0.9
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.3
20%	0.3
30%	0.4
40%	0.5
50%	0.5
60%	0.5
70%	0.6
80%	0.7
90%	0.7
100%	0.9

Figure 564 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 2 to 5 Years)



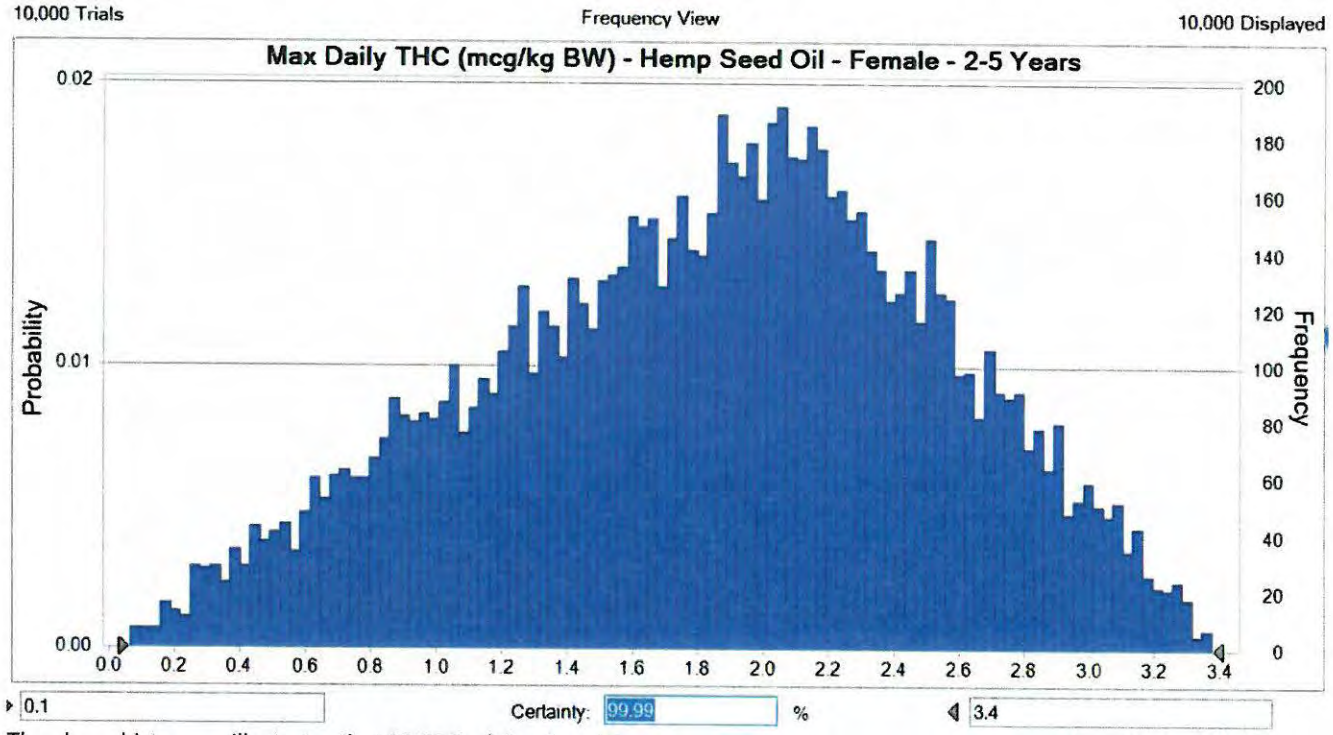
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Hemp Hearts) of THC at a 90th percentile intake level will see no more than 1.2µg/kg for females ages 2-5 years.

Figure 57 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.5
Median	0.5
Mode	—
Standard Deviation	0.2
Variance	0.1
Skewness	0.5224
Kurtosis	2.42
Coeff. of Variation	0.4797
Minimum	0.1
Maximum	1.2
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.2
20%	0.3
30%	0.3
40%	0.4
50%	0.5
60%	0.5
70%	0.6
80%	0.7
90%	0.9
100%	1.2

Figure 58 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Females Age 2 to 5 Years)



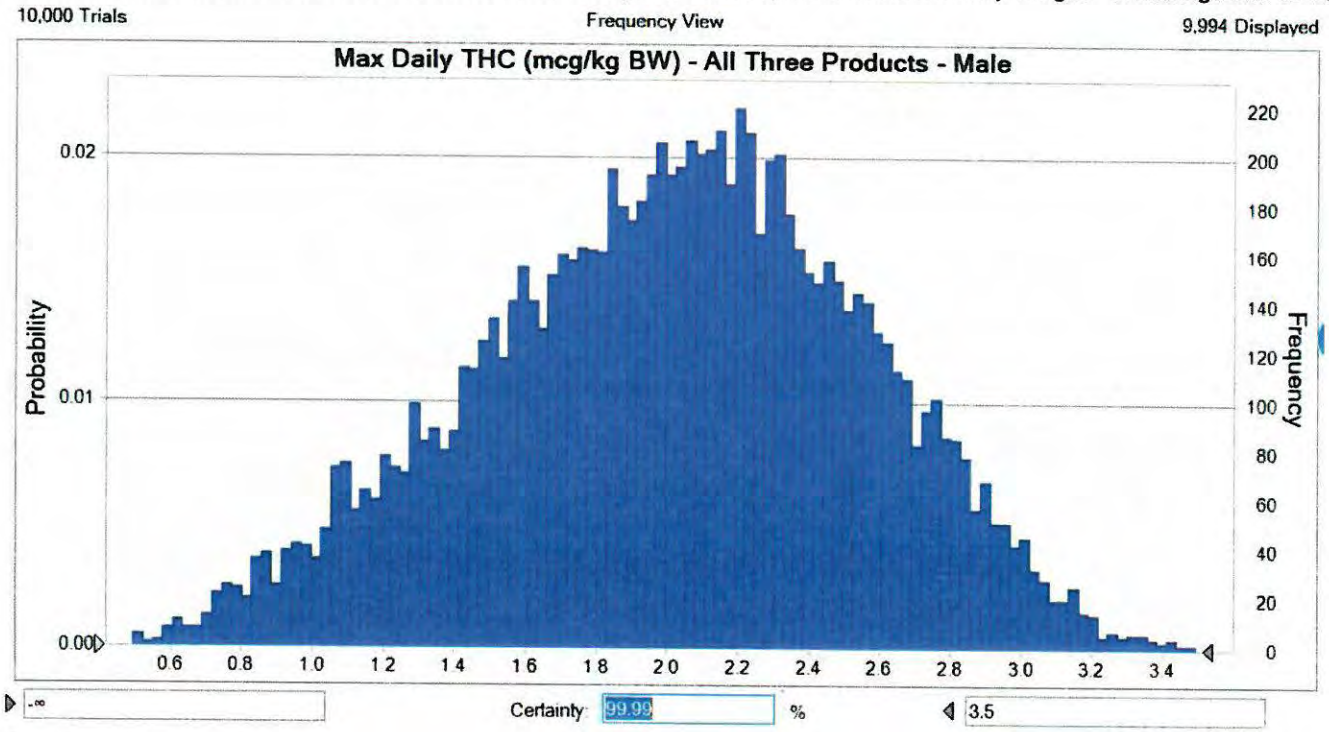
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake (Hemp Seed Oil) of THC at a 90th percentile intake level will see no more than 3.4µg/kg for females ages 2-5 years.

Figure 59 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Females Age 2 to 5 Years)

Statistic	Forecast values
Trials	10,000
Base Case	1.7
Mean	1.8
Median	1.9
Mode	—
Standard Deviation	0.7
Variance	0.5
Skewness	-0.2092
Kurtosis	2.41
Coeff. of Variation	0.3772
Minimum	0.1
Maximum	3.4
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.9
20%	1.2
30%	1.5
40%	1.7
50%	1.9
60%	2.1
70%	2.2
80%	2.5
90%	2.7
100%	3.4

Figure 60 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – 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 3.5µg/kg for males age 6-11.

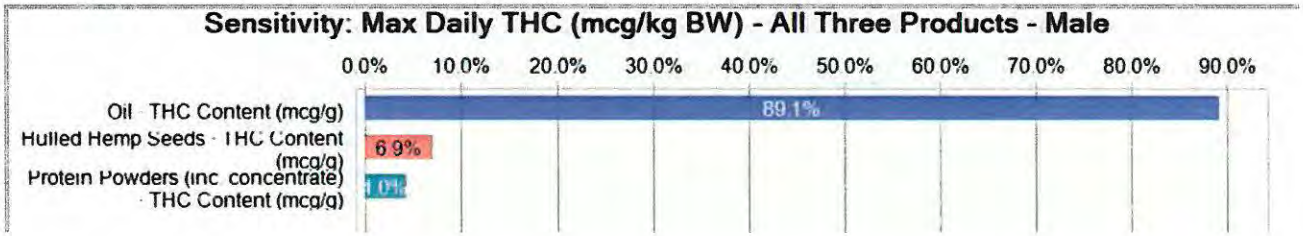
Figure 61 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	1.6
Mean	2.0
Median	2.0
Mode	---
Standard Deviation	0.5
Variance	0.3
Skewness	-0.1738
Kurtosis	2.60
Coeff. of Variation	0.2690
Minimum	0.4
Maximum	3.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.4
10%	1.3
20%	1.5
30%	1.7
40%	1.9
50%	2.0
60%	2.2
70%	2.3
80%	2.5
90%	2.7
100%	3.5

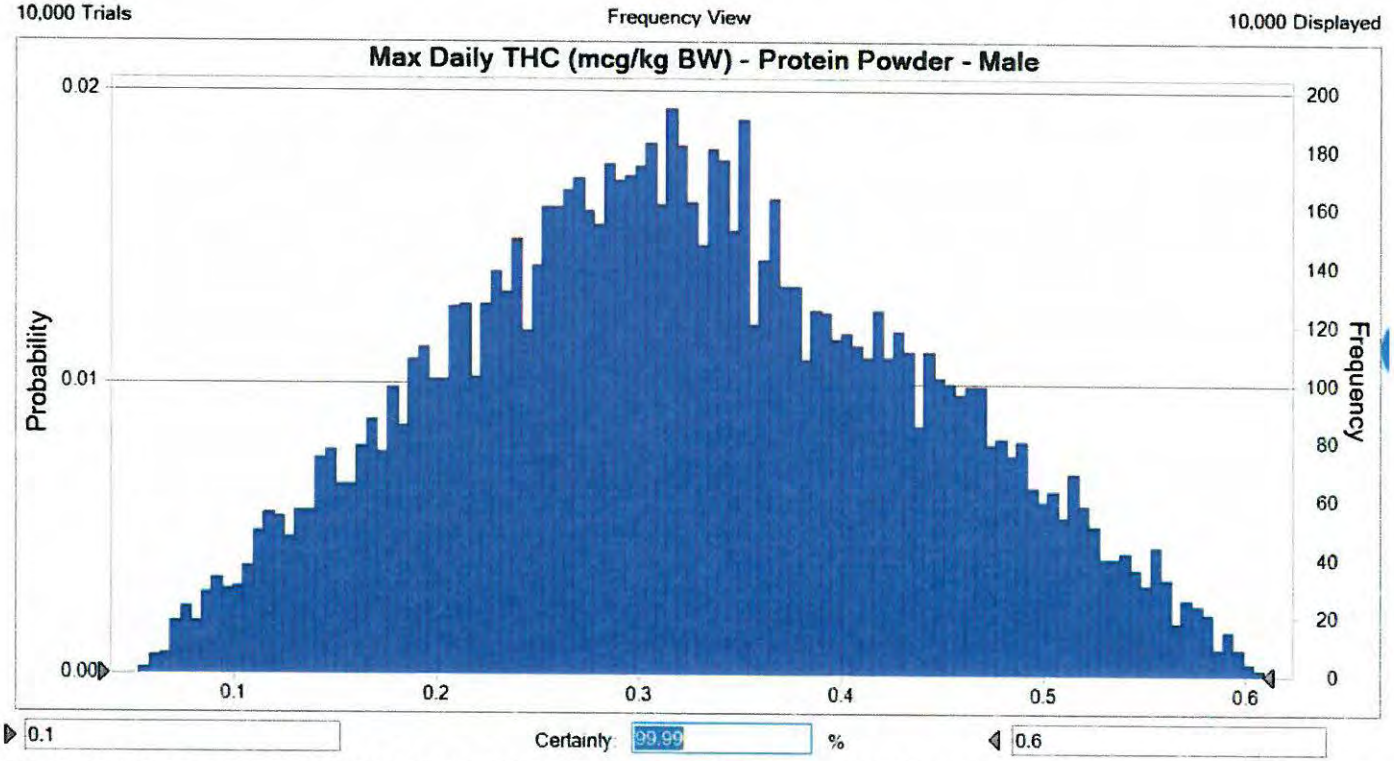
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 89% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 7% and Protein Powders make up 4%.

Figure 62 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Males Age 6 to 11 Years



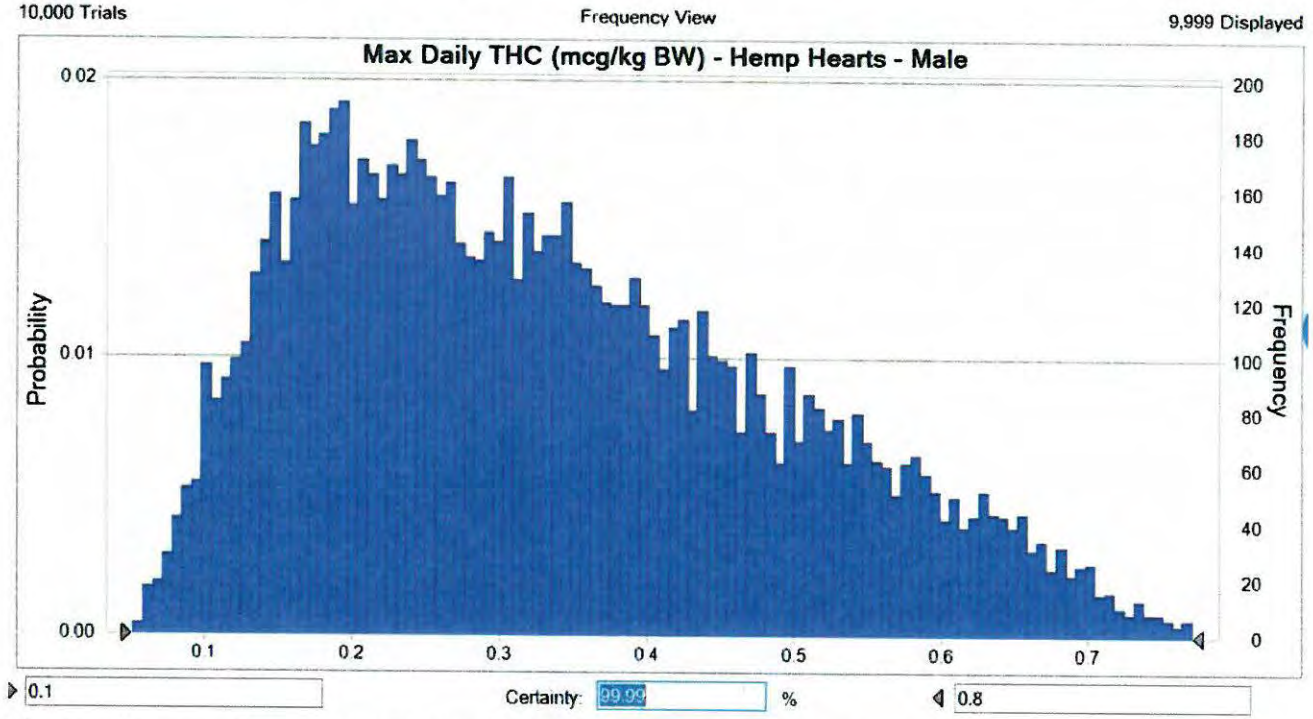
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.6µg/kg for males age 6-11.

Figure 63 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.3
Median	0.3
Mode	---
Standard Deviation	0.1
Variance	0.0
Skewness	0.0971
Kurtosis	2.39
Coeff. of Variation	0.3551
Minimum	0.1
Maximum	0.6
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.2
20%	0.2
30%	0.3
40%	0.3
50%	0.3
60%	0.3
70%	0.4
80%	0.4
90%	0.5
100%	0.6

Figure 64 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Males Age 6 to 11 Years



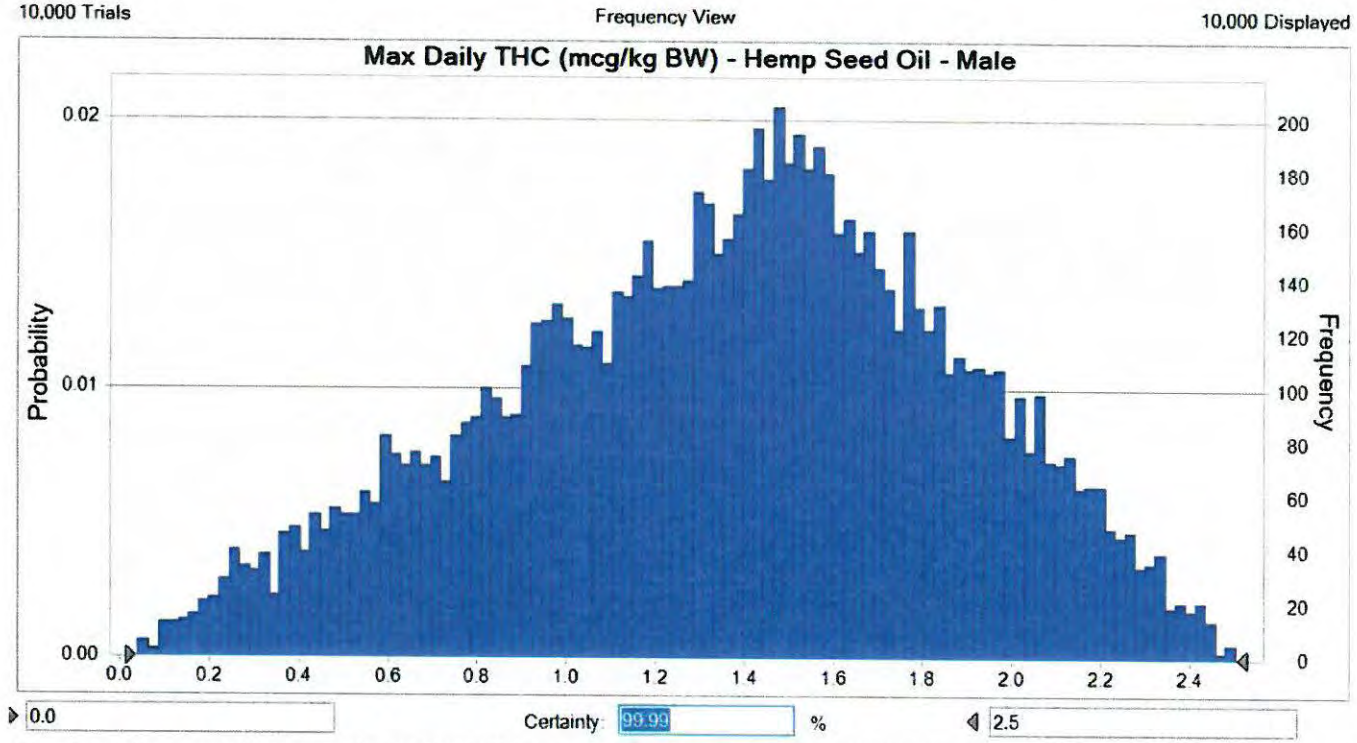
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.8µg/kg for males age 6-11.

Figure 65 Hulled Hemp Seed Consumption - THC Exposure Forecast Based on Body Weight – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.1
Mean	0.3
Median	0.3
Mode	---
Standard Deviation	0.2
Variance	0.0
Skewness	0.5183
Kurtosis	2.44
Coeff. of Variation	0.4728
Minimum	0.1
Maximum	0.8
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.1
20%	0.2
30%	0.2
40%	0.3
50%	0.3
60%	0.4
70%	0.4
80%	0.5
90%	0.6
100%	0.8

Figure 66 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – Males Age 6 to 11 Years



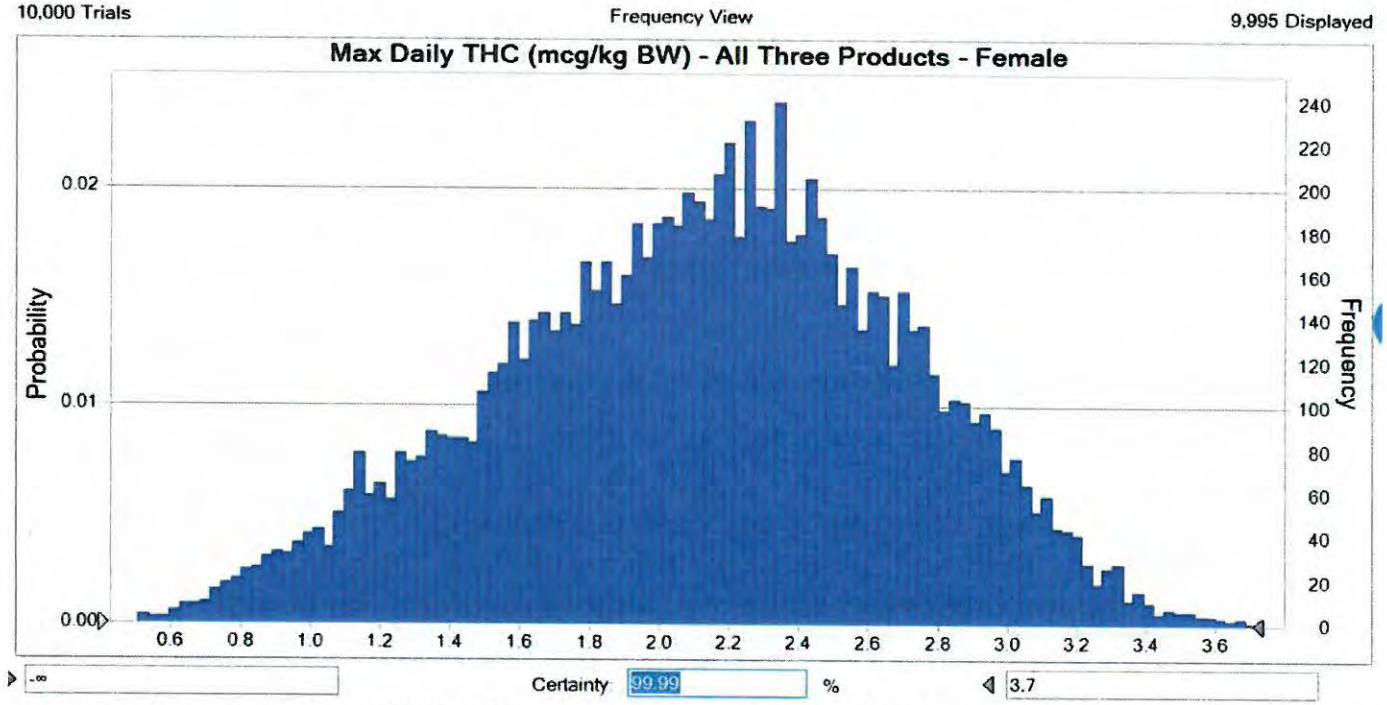
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from oil at 90th percentile intake level will see no more than 2.5µg/kg for males age 6-11.

Figure 67 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Males Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	1.3
Mean	1.4
Median	1.4
Mode	—
Standard Deviation	0.5
Variance	0.3
Skewness	-0.2254
Kurtosis	2.46
Coeff. of Variation	0.3744
Minimum	0.0
Maximum	2.5
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.6
20%	0.9
30%	1.1
40%	1.3
50%	1.4
60%	1.5
70%	1.6
80%	1.8
90%	2.0
100%	2.5

Figure 68 Monte Carlo Model – Cumulative Hemp Consumption - THC Exposure Based on Body Weight – 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 3.7µg/kg for females age 6-11.

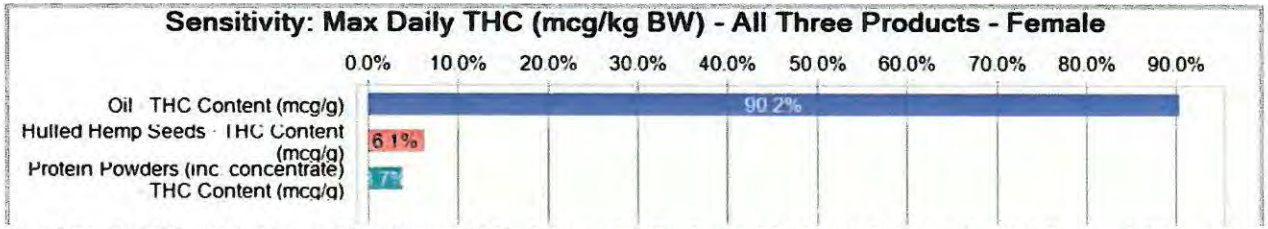
Figure 69 Cumulative Hemp Consumption - THC Exposure Forecast Based on Body Weight – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	1.7
Mean	2.1
Median	2.2
Mode	—
Standard Deviation	0.6
Variance	0.3
Skewness	-0.1800
Kurtosis	2.59
Coeff. of Variation	0.2718
Minimum	0.4
Maximum	3.7
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.4
10%	1.3
20%	1.6
30%	1.8
40%	2.0
50%	2.2
60%	2.3
70%	2.4
80%	2.6
90%	2.9
100%	3.7

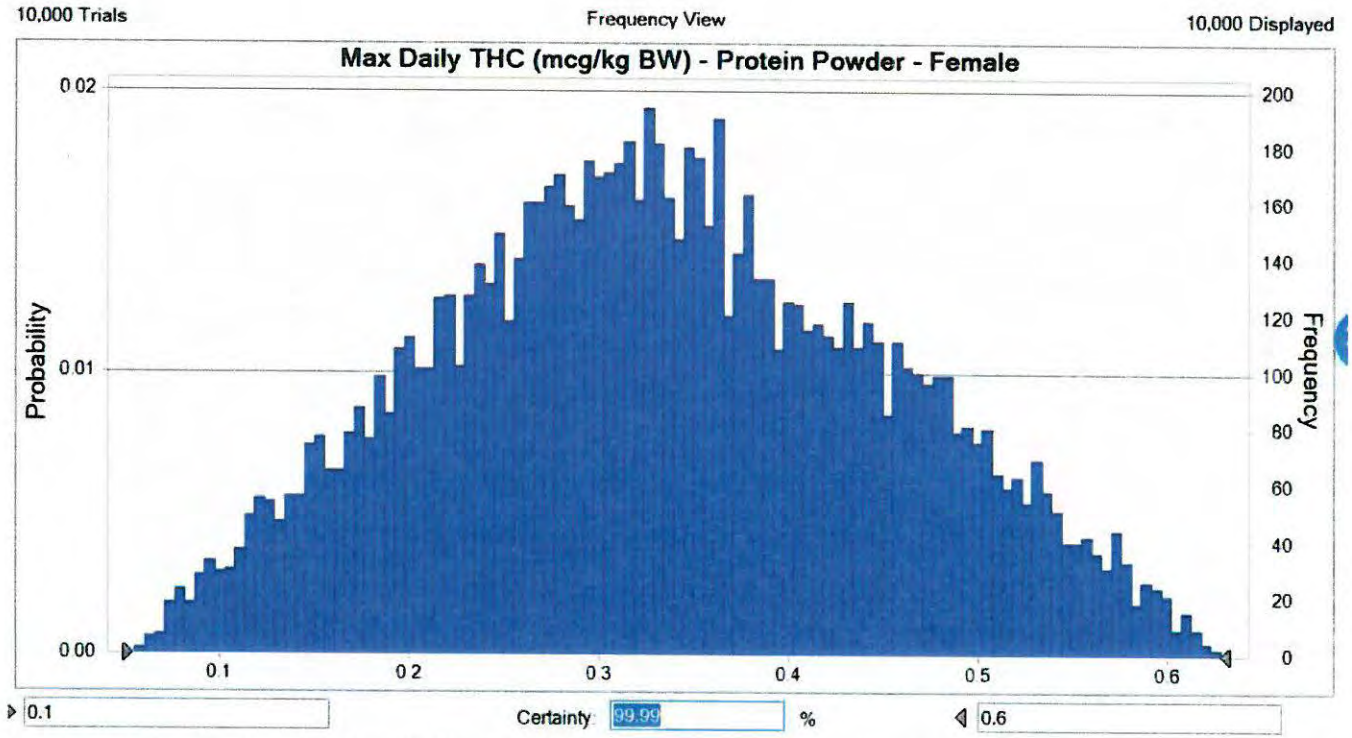
10,000 Trials

Contribution to Variance View



Variability in THC within Hemp Oil makes up 90% of the variability in our Maximum Daily Intake Distribution (all ingredients), whereas Hulled Hemp Seeds make up 6% and Protein Powders make up 4%

Figure 70 Monte Carlo Model – Hemp Protein Powder Consumption - THC Exposure Based on Body Weight – Females Age 6 to 11 Years



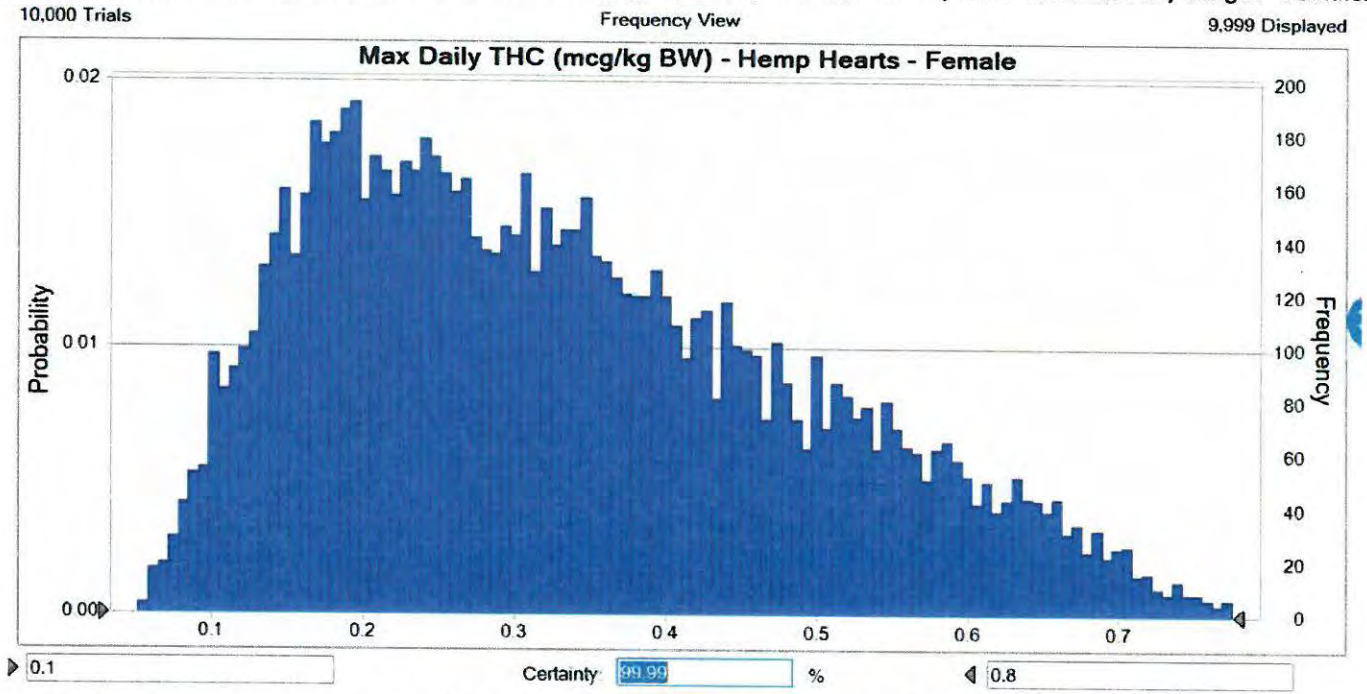
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from protein powders at 90th percentile intake level will see no more than 0.6µg/kg for females age 6-11.

Figure 71 Hemp Protein Powder Consumption - THC Exposure Forecast Based on Body Weight – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.2
Mean	0.3
Median	0.3
Mode	---
Standard Deviation	0.1
Variance	0.0
Skewness	0.0971
Kurtosis	2.39
Coeff. of Variation	0.3551
Minimum	0.1
Maximum	0.6
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.2
20%	0.2
30%	0.3
40%	0.3
50%	0.3
60%	0.4
70%	0.4
80%	0.4
90%	0.5
100%	0.6

Figure 72 Monte Carlo Model – Hulled Hemp Seed Consumption (Hemp Hearts) - THC Exposure Based on Body Weight – Females Age 6 to 11 Years



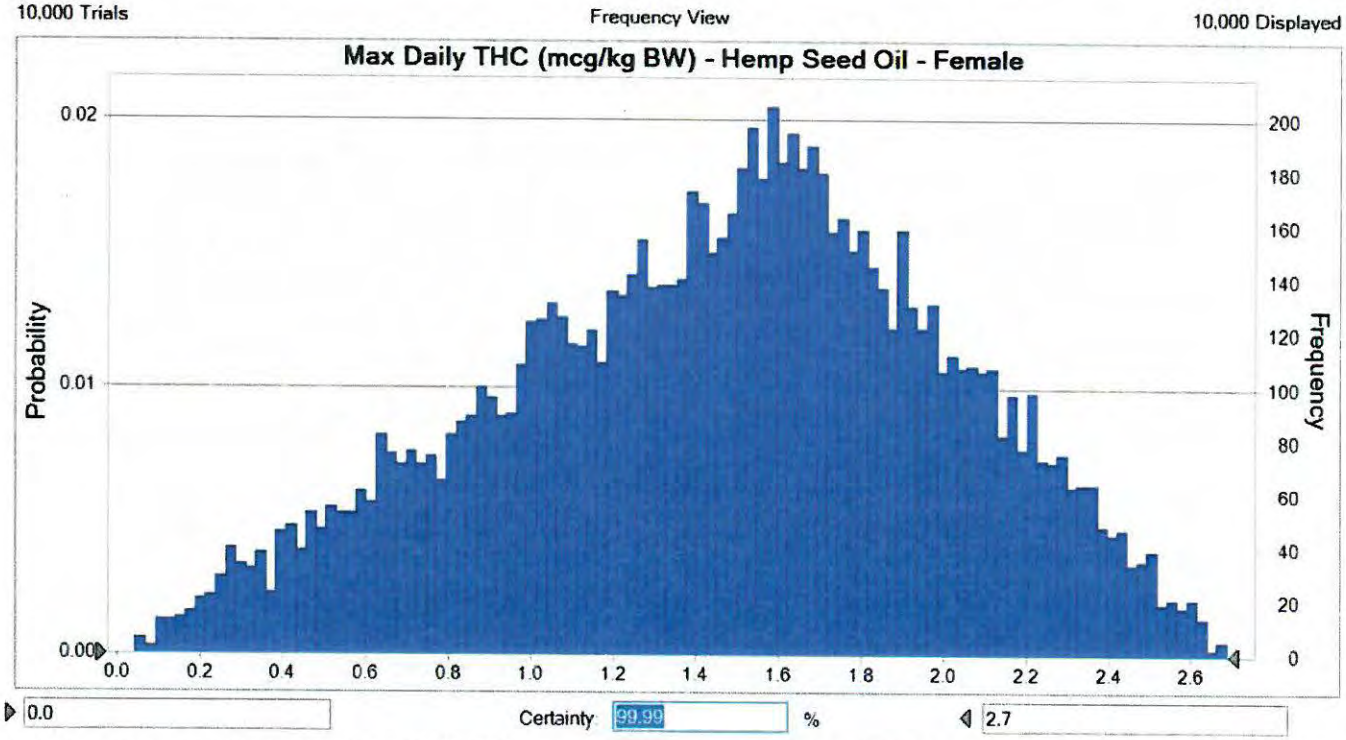
The above histogram illustrates that 99.99% of the time, Maximum Daily Intake of THC from hulled hemp seeds at 90th percentile intake level will see no more than 0.8µg/kg for females age 6-11.

Figure 73 Hulled Hemp Seed Consumption - THC Exposure Forecast at Based on Body Weight – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	0.1
Mean	0.3
Median	0.3
Mode	---
Standard Deviation	0.2
Variance	0.0
Skewness	0.5183
Kurtosis	2.44
Coeff. of Variation	0.4728
Minimum	0.1
Maximum	0.8
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.1
10%	0.1
20%	0.2
30%	0.2
40%	0.3
50%	0.3
60%	0.4
70%	0.4
80%	0.5
90%	0.6
100%	0.8

Figure 74 Monte Carlo Model – Hemp Oil Consumption - THC Exposure Based on Body Weight – 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 2.7µg/kg for females age 6-11.

Figure 75 Hemp Oil Consumption - THC Exposure Forecast Based on Body Weight – Females Age 6 to 11 Years

Statistic	Forecast values
Trials	10,000
Base Case	1.3
Mean	1.5
Median	1.5
Mode	—
Standard Deviation	0.5
Variance	0.3
Skewness	-0.2254
Kurtosis	2.46
Coeff. of Variation	0.3744
Minimum	0.0
Maximum	2.7
Mean Std. Error	0.0

Percentile	Forecast values
0%	0.0
10%	0.7
20%	1.0
30%	1.2
40%	1.3
50%	1.5
60%	1.6
70%	1.8
80%	1.9
90%	2.2
100%	2.7

Adapted

TIMELINE

Cannabis in History

12,000 bce The earth begins to warm as the Holocene Epoch begins, and plants and animals begin to recolonize Eurasia from glacial refugia.

8000 bce Antecedents of Japanese Jōmon culture already using hemp seed and leaving remains.

5000 bce Earliest European hemp seed remains deposited in Germany.

5000–4000 bce *Cannabis* seed imprints in pottery, Dniester-Prut region, Moldova

4000 bce Ancient Egyptians build the first sailing ships.

3000 bce Hemp seed remains appear in the Baltic region.

2800 bce Earliest hemp seed remains from China, and the first assumed written record of *Cannabis* use for medicine is in the pharmacopoeia of Emperor Shen Nung, the legendary father of Chinese medicine.

2700 bce Remarkably well-preserved *Cannabis* flowers, seeds, stems, and leaves are left in a Yanghai burial tomb of a shaman in western China.

2200 bce Ancient Yellow River civilization begins to consolidate power in northern China, and *Cannabis* is an important multipurpose, cultivated plant.

2000 bce First hemp seed evidence from the Balkan region.

600 bce Phoenicians pioneer the first sea trade routes in the eastern Mediterranean and Red Seas.

500 bce *Cannabis* is described in the Persian Zoroastrian *Avesta* sacred text.

500 bce Earliest hemp seed remains from the Korean Peninsula.

420 bce Hemp seed offerings left in Scythian kurgan tombs in Central Asia.

325 bce Greek geographer and astronomer Pytheas makes first recorded sojourn to England and Scandinavia by sail.

100 bce Chinese make first paper from *Cannabis* and mulberry.

70 ce Roman physician Dioscorides records *Cannabis*'s medical properties.

600 ce Papermaking spreads to Korea.

640 ce The Koran, Islam's central religious text, tolerates *Cannabis* use but forbids alcohol.

900 ce Viking expeditions begin reaching Iceland, Greenland, and Newfoundland.

950 ce Muslim Moors introduce papermaking with *Cannabis* to Spain from North Africa.

1000 ce The English word "hempe" first listed in a dictionary.

1023 Chinese Song dynasty issues the first paper money.

1149 Oxford University is founded in Oxford, England.

1160 Hildegard von Bingen writes *Physica* describing the medicinal use of *Cannabis*.

1200s The magnetic compass commonly used on Chinese oceangoing ships.

1206 Genghis Khan leads the Mongol armies and conquers much of Eurasia.

(*continued*)

1241	Gunpowder introduced to Europe by the Mongols.
1250	European sailors begin to use the magnetic compass.
1275	Marco Polo starts on his alleged 20-year trip to China and reports use of hemp fiber for paper making, caulking of Chinese ships, and cultivation near oases in eastern Turkestan.
1315	The Great Famine begins in Europe.
1346	The bubonic plague starts in China and spreads westward through Europe killing at least one-quarter of Europe's population.
1440s	German inventor Johann Gutenberg revolutionizes knowledge transfer by combining the printing press, movable metal type, and an oil-based ink.
1492	Spanish explorer Christopher Columbus lands in the Bahamas, leading ultimately to the colonization of the New World and introduction of several Old World plants including *Cannabis*.
	First paper mill in England started.
1495	Portuguese explorer Vasco da Gama sails to India via southern Africa and the Cape of Good Hope.
1498	
1533	King Henry VIII issues his first royal decree ordering each farmer to set aside a quarter acre of land for every 60 acres he controlled to cultivate hemp as a strategic crop.
	Spanish bring hemp cultivation to Chile for cordage and cloth.
1545	The Little Ice Age strikes Europe; crops fail and many starve.
1550–1850	Queen Elizabeth I decrees that land owners must grow hemp or pay a £5 fine.
1563	King Philip orders hemp to be grown throughout the Spanish Empire from Argentina to Oregon.
1564	
1569	Mercator publishes his cylindrical projection map of the earth.
1602	Dutch United East India Company (VOC) founded.
1606	British begin to grow hemp in Canada for maritime use.
1611	British begin to grow hemp in Virginia colony.
1619	Virginia becomes first American colony to make hemp growing mandatory.
1630s	Hemp traded throughout the American Colonies.
1735	Carolus Linnaeus introduces his taxonomic system for naming species.
1750s to 1790s	George Washington and Thomas Jefferson experiment with growing hemp on their farms.
1753	*Cannabis sativa* described and classified by Linneaus.
1778	After visiting Australia, James Cook is the first European to travel to Hawai'i.
1783	*Cannabis indica* described and classified by Lamarck.
1791	President Washington imposes import duties on hemp to encourage domestic industry, and Thomas Jefferson urges farmers to grow hemp instead of tobacco.
1807	Napoleon signs treaty with Russia severing all legal Russian hemp trade with Britain. American sailors commence illegal trade in Russian Hemp.
1812	Napoleon invades Russia hoping to control the supply of hemp.
1841	Scotsman William O'Shaunghnessy learns of the medical use of *Cannabis* in India.
1845	Frenchman Jacques-Joseph Moreau de Tours documents the medical benefits of *Cannabis*.
1857	Fitz Hugh Ludlow's *The Hasheesh Eater* is published.

(continued)

1872–76	Scientific Challenger expedition makes many discoveries and established oceanography; the expedition's, mother vessel, HMS Challenger, was supplied with 291 km (181 miles) of Italian hemp for depth sounding.
1859	Charles *Darwin* publishes his classic *The Origin of Species* describing evolution by natural selection and opens the ongoing debate of "evolution versus creationism."
1860	Ohio State Medical society conducts first governmental study of *Cannabis* use and health.
1860s	Augustinian friar Gregor Mendel lays the foundation for modern genetics.
1869	University of California established.
1870	*Cannabis* is listed in the United States Pharmacopoeia as a treatment for various ailments.
1881	Charles and Sir Francis Darwin publish *The Power of Movement in Plants*, investigating fundamental aspects of plant growth.
1890	Queen Victoria's personal physician, Sir Russell Reynolds, prescribes *Cannabis* for menstrual cramps and claims that when pure preparations of *Cannabis* are administered carefully, it is a most valuable medicine.
1894	The *Indian Hemp Drugs Commission Report* concludes that *Cannabis* has medical uses, no addictive properties, and a number of positive emotional and social benefits.
1916	United States Department of Agriculture calls for expansion of hemp acreage to replace timber use by the paper pulp industry.
1925	The *Panama Canal Zone Report* concludes that there is no evidence that *Cannabis* use is habit-forming or deleterious and recommends that no action be taken to prevent its use.
1938	Popular Mechanics magazine publishes an article written before the Marijuana Transfer Tax was passed extolling the virtues of "Hemp—the New Billion Dollar Crop."
1942	United States Department of Agriculture releases the movie Hemp for Victory, encouraging American farmers to resume hemp cultivation to support the war effort.