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Tetrahydrocannabinol (THC) and Other Cannabinoids in Foods, Cosmetics and Nutraceuticals Made with Industrial Hemp

- A Risk Assessment -

Prepared for Health Canada, November 23, 1999

Tetrahydrocannabinol (THC) and Other Cannabinoids in Foods, Cosmetics and Nutraceuticals Made with Industrial Hemp - A Risk Assessment -

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EXECUTIVE SUMMARY

The objectives of this risk assessment were to:

- ascertain the state of the science in research into the potential health effects of low levels of tetrahydrocannabinol (THC) and other cannabinoids found in *Cannabis sativa*;
- identify key health hazards that may be associated with the presence of THC and other cannabinoids in consumer products made with industrial hemp (*C. sativa* cultivars with <0.3% (w/w) THC);
- assess the human health safety of the Canadian limit of 10 ug/g THC for raw materials and products made from industrial hemp; and
- to identify uncertainties and critical data gaps in the risk assessment.

Of the more than 60 cannabinoids identified in *C. sativa*, the toxicity of THC is the best characterized. Limited toxicity data have been reported for two other cannabinoids, cannabidiol (CBD) and cannabinol (CBN), but there are no toxicity data on the remaining cannabinoids.

Two key hazards of cannabinoid exposure are neuroendocrine disruption and neurological impairment. Neuroendocrine disruption by low levels of cannabinoids during developmental stages (perinatal, prepubertal, pubertal) leads to permanent adverse effects on brain and reproductive system development in animals. The lowest observed effect level (LOEL) for neuroendocrine disruption by THC was 1 ug/kg/d derived from a study in rats (no suitable human studies were available). Such effects could occur in humans. Similarities in the types of adverse effects, the cannabinoid receptor distribution in the brain, and the pharmacokinetics and metabolism of cannabinoids among humans and animal species support the extrapolation from animal data to humans for the purposes of risk assessment. Neurological impairment is manifested as deficits in performance with respect to cognitive and motor skills. The LOEL for neurological impairment by THC was 70 ug/kg based on data from a dose-response study in which human subjects who had a history of marihuana use received a single oral dose of THC, and cognitive and motor skills and perception of psychoactive effects were measured.

It was not deemed possible to develop a tolerable daily intake (TDI) due to the lack of a no observed effect level (NOEL), lack of data on chronic exposure and lack of data on the potential contribution of other cannabinoids to the adverse effects. Potential health risks of foods made with industrial hemp ingredients were

characterized by estimating the amount of food from various food categories that would need to be eaten to reach a dose of THC equal to the LOELs for neurological impairment in humans and neuroendocrine effects in animals. Potential health risks from use of cosmetics and personal care products and nutraceuticals made with industrial hemp oil were characterized by comparing exposure to THC through product use with the LOELs for neurological impairment in humans and neuroendocrine effects in animals. These exposure estimates were based on the assumption that the THC concentration in industrial hemp-based in ingredients was 10 ug/g, the current Canadian guideline.

The direct comparison of exposure results with the LOELs does not address:

- the bioaccumulative potential of THC with repeated dosing or consumer use;
- the lack of an identified NOELfor THC for neuroendocrine disruption or neurological impairment;
- the potential that some individuals may be more sensitive to THC than the adults with a history of marihuana use for which the LOEL of 70 ug/g for neurological impairment was observed;
- the possibility that humans could be more sensitive to THC than the rats in the study used to derive the LOEL of 1 ug/kg for neuroendocrine disruption; and,
- the potential for neuroendocrine disruption or neurological impairment by other cannabinoids (i.e. CBD, CBN and others) that would be present in industrial hemp-based products (concentrations of these have not been measured).

In consideration of the above uncertainties, the conclusions from the risk characterization were as follows:

Food: Risk of neuroendocrine disruption: Likely.

Risk of neurological impairment and psychoactivity: Likely, particularly for children.

With respect to neurological impairment, the amount of each food type that would need to be consumed to deliver a dose of THC equal to the LOEL exceeded the mean daily intake and "serving size" which may suggest an absence of risk. In the case of the child; however, some foods (dairy substitutes and candy) were identified that could be consumed in sufficient quantities on occasion in a single day or a single sitting to cause neurological impairment, or even psychoactive effects. For example 2.3 ice cream bars could deliver a dose of THC of 70 ug/kg (the LOEL for neurological impairment) and 4.6 ice cream bars could deliver a dose of 140 ug/kg (the LOEL for psychoactivity) for a 33.9 kg child.

Cosmetics: Risk of neuroendocrine disruption: Possible

Risk of neurological impairment: Unlikely

The risk of neurological impairment cannot be excluded entirely, particularly in the case of children without further information on the relative sensitivities of children vs adults, the relative sensitivities of marihuana users vs non users, the effects of repeated exposure over a long time period, the effects and concentrations of cannabinoids other than THC and the extent of dermal penetration and systemic exposure of topically applied cannabinoids under conditions of actual product use.

Nutraceuticals: Risk of neuroendocrine disruption: Likely

Risk of neurological impairment: Possible, particularly in children.

Major shortcomings related to key data gaps identified in the assessment that preclude the development of definitive conclusions regarding the degree of potential risk are:

- the inability to consider the potential contribution of cannabinoids other than THC (limited toxicity data for other cannabinoids indicate their ability to cause neuroendocrine disruption) to the overall health risks;
- the inability to consider the long term effects of bioaccumulation of THC over time from repeated low dose exposure due to lack of chronic low level toxicity studies and lack of data on the steady-state pharmacokinetics of THC;
- the inability to consider the effects of THC and other cannabinoids after multi-generation long term exposure;
- the inability to determine the degree of exposure to the developing fetus and nursing infant; and
- the lack of analytical data for THC and other cannabinoid concentrations, at detectable levels, in raw materials and finished products made from industrial hemp.

At greatest risk of long term effects of neuroendocrine disruption are the developing fetus, nursing infant and prepubertal/pubertal child. This conclusion is based on animal data that document adverse and permanent effects on brain function and the reproductive system caused by cannabinoid induced neuroendocrine disruption during development. The peripubertal period in children is a period of major development of the brain and reproductive system which is controlled by neuroendocrine signals. In rats, the density of cannabinoid receptors was found to be greatest during the pubertal period, suggesting a underlying basis for the

increased sensitivity to the adverse effects of cannabinoids during this period. Concern is warranted for THC exposure of the developing fetus and nursing infant through maternal use of these industrial hemp products based on the knowledge that THC is rapidly transferred from the mother to the fetus crossing both the placental and blood brain barriers within in minutes of maternal exposure, and that THC accumulates and is transferred via human breast milk to the infant.

On the basis of currently available data it is concluded that the present Canadian limit of 10 ug/g THC in raw materials and products made from industrial hemp (*Cannabis sativa* cultivars with <0.3% THC) would likely not protect the Canadian consumer using industrial hemp-based food, cosmetic and personal care, and nutraceutical products from potential health risks of neurological impairment and neuroendocrine disruption associated with low level exposure to THC and other cannabinoids.

1.0 INTRODUCTION

A number of industrial hemp-based products have recently become available in Canada and many more are available from the U.S. and abroad through internet marketing. These include a wide range of personal care products (i.e. hemp hand and body moisturizing lotions, hemp massage oil, hemp sunblock, hemp lip balm, hemp soap and hemp shampoo), food ingredients, such as hemp oil, hemp seeds, hemp nut and hemp flour, hemp food products (i.e. hemp snack bars, hemp candy, hemp baked goods, hemp pasta, hemp burgers, hemp milk, hemp salad oil and hemp beverage) and nutraceuticals containing hemp oil. These products are all prepared from *Cannabis sativa* cultivars that have very low content (<0.3%) of tetrahydrocannabinol (THC). Marihuana also comes from *Cannabis sativa,* but the cultivars from which drug products are produced contain greater concentrations of THC (>0.3%).

Because of the low concentration of THC in industrial hemp-based products, it has been generally thought to be unlikely that use or consumption levels could approach those that could cause psychoactive effects. Prevention of physiological effects (observed to occur in a 70 kg adult after a single oral dose of 5 mg THC; effects were not defined) is the basis of the Canadian regulatory guideline of 10ug THC/g in industrial hemp products.[1] This limit does not consider the bioaccumulative nature of THC and the potential for cumulative exposure from repeated use or multiple use of products made with industrial hemp materials (i.e. foods, cosmetics and personal care products, and nutraceuticals). It was suggested that, even at the 10 ppm THC limit, a warning should be issued to consumers about cumulative effects that could occur after a long period of consumption industrial hemp oil containing THC at this concentration (B. Lodge, Bureau of Drug Surveillance, Jan. 31/98).

Although psychoactivity is the effect that is most commonly associated with marihuana use and exposure to THC, there are other adverse health effects and pharmacological effects that have been reported in the literature. Many of these have been associated with THC as well as with other cannabinoids. More than 60 cannabinoids have been identified in *Cannabis sativa* (Turner et al., 1979). Several hundred more chemicals have been identified in the cannabis plant, including hydrocarbons, steroids, terpenoids, phenols and others (Turner et al., 1979). The chemical that has been studied in the greatest detail is THC, while other

[1]Industrial Hemp Regulations, Schedule No. 1089, Canada Gazette, April 1, 1998. For a discussion of the derivation of this THC limit see Annex I, Section 3.6.1

cannabinoids including cannabinol (CBN) and cannabidiol (CBD) have been studied to a much lesser degree. Some cannabinoids, including cannabigerol and cannabichromene have been studied a little and the majority of the cannabinoids have not been studied. The structures of some cannabinoids are shown in Figure 1.

The purpose of this human health risk assessment has been to ascertain the potential for risks of adverse health effects associated with the use of industrial hemp products sold as foods, food ingredients, nutraceuticals, and cosmetics and personal care products. This assessment is not intended to address issues related to the use of marihuana as a drug or issues related to the therapeutic use[2] of THC or other cannabinoids. Information pertaining to potential nutritional benefits of industrial hemp-based foods was not considered. The main focus of this assessment has been the hazard, exposure and risk associated with THC. This is because THC is the most widely studied chemical constituent of *Cannabis sativa*, it is known to cause psychoactive effects as well as other toxicological and pharmacological effects, and thus a large database exists on the adverse effects of THC. With respect to exposure, it was possible to assess only THC, since no other cannabinoids have been measured in terms of their concentration in industrial hemp seeds or industrial hemp oil, the starting materials for food, cosmetic and nutraceutical products. Other cannabinoids were considered in the assessment to the degree possible, although the available data did not permit as comprehensive an assessment as was possible with THC.

[2] See (Joy et al., 1999) for a discussion of issues related to the medicinal use of marihuana.

Figure 1 -structures of cannabinoids

2.0 OBJECTIVES

The objectives of this risk assessment were to ascertain the state of the science in research into the potential health effects of low levels of THC and other cannabinoids, to identify key hazards that may be associated with the presence of cannabinoids in cosmetics, foods and nutraceuticals made with industrial hemp ingredients and to determine whether use and/or consumption of these products could be associated with risks of adverse health consequences in Canadian consumers.

3.0 METHODS

3.1 Methods - Hazard Assessment

The approach taken in obtaining data for the hazard assessment was to conduct a detailed literature search and review of relevant literature (see Annex IV for search strategy). The literature review identified over 1900 references, over 600 of which were reviewed. The review did not consider the bulk of the data on effects in humans related to marihuana smoking, since these were not considered relevant to the assessment of health risks that might occur at the much lower doses associated with the use of foods, nutraceuticals and cosmetics made with industrial hemp materials. The data considered included pharmacokinetics and metabolism data from humans and other species, oral data from human studies, epidemiology studies of children exposed to cannabinoids through maternal marihuana smoking, and toxicology, mechanistic and biochemistry data from animal studies. Where comprehensive review articles were available these were reviewed and any primary literature cited therein that could pertain to low dose exposure or the dose-response relationship was obtained and reviewed. The goals of the hazard assessment were as follows:

- identify key hazards associated with cannabinoid exposure;
- characterize dose-response relationships for key hazards;
- identify lowest effect or no-effect levels;
- ascertain relevance of findings in animal studies for humans;
- establish basis for extrapolation of experimental data to consumer use risk assessment;
- identify data gaps.

3.2 Methods Exposure Assessment

The exposure assessment of products made with industrial hemp materials was conducted for three main categories:

- food products made with industrial hemp;
- cosmetics and personal care products made with industrial hemp; and
- nutraceuticals made with industrial hemp.

The goals of the exposure assessment were:

- to identify within each product category types of products available to the Canadian consumer and to determine the range of concentrations of THC present in these categories of products made from industrial hemp;

- to determine the relative ratios of other cannabinoids (specifically CBD and CBN) to THC in *Cannabis sativa* and products derived from industrial hemp;

- to identify factors that influence THC levels in *Cannabis sativa* and raw materials made from industrial hemp;

- to determine the amount of food (assumed to be made from industrial hemp ingredients that contain 10 ppm THC[3]) to be consumed by an individual that would equal: i) the single dose LOEL of 70 ug THC/kg body weight for neurological impairment[4]; and ii) the LOEL of 1 ug THC/kg body weight/day for neuroendocrine disruption[5];

- to estimate the dermal exposure of a consumer to THC through the use of cosmetics and personal care products made with industrial hemp oil (assumed to contain 10 ppm THC[6]);

- to estimate the oral exposure of a consumer to THC through the use of nutraceuticals made of industrial hemp oil (assumed to contain 10 ppm THC[7]);

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[3] The Canadian defacto limit of 10 ppm THC in industrial hemp and products made from industrial hemp (Industrial Hemp Regulations, Schedule No. 1089, Canada Gazette, April 1, 1998.

[4] See Section 4.1.4.1 for discussion of basis of LOEL for neurological impairment.

[5] See Section 4.1.4.2 for discussion of basis of LOEL for neuroendocrine effects.

[6] The Canadian defacto limit of 10 ppm THC in industrial hemp and products made from industrial hemp (Industrial Hemp Regulations, Schedule No. 1089, Canada Gazette, April 1, 1998.

[7] The Canadian defacto limit of 10 ppm THC in industrial hemp and products made from industrial hemp (Industrial Hemp Regulations, Schedule No. 1089, Canada Gazette, April 1, 1998.

- to assess the potential exposure of the nursing infant through maternal use of products made from industrial hemp; and,

- to identify data gaps.

3.2.1 General Approach

A survey was conducted to identify types of products for each product category listed above made with industrial hemp that are currently available to the Canadian consumer. This was done through Internet searching of commercial industrial hemp websites, and information provided by industrial hemp industry associations and industrial hemp manufacturers. Next, analytical data were collected from industrial hemp oil/seed manufacturers as facilitated by the industrial hemp industry associations on concentrations of THC in raw materials of industrial hemp:

- industrial hemp oil,
- industrial hemp seed
- industrial hemp flour,
- industrial hemp meal,
- industrial hemp nut.

No analytical data on the concentrations of any cannabinoids other than THC in industrial hemp materials/products were available from industrial hemp manufacturers. Relative amounts of industrial hemp ingredient(s) in various product formulations/food recipes were determined based on manufacturer's data or hemp recipes. In addition to these industry data, published data on concentrations of THC and cannabinoids in *Cannabis sativa,* industrial hemp materials and finished hemp products were tabulated. A review of the literature on *Cannabis sativa* relevant to factors affecting concentrations of THC in plant materials, seeds and oil was performed.[8]

Concentration of THC

[8] See Annex I, Sections 3.2.2, 3.3, 3.3.2 and 3.3.3

Exposure estimates to THC were based on the current Canadian "defacto limit" of 10 ppm for "total THC" in industrial hemp oil, industrial hemp seed, industrial hemp meal and industrial hemp nut produced in or imported to Canada.[9]

Concentration of Other Cannabinoids

Concentrations of CBN and CBD could be approximated based on their relative ratios[10] to THC of 0.1 to 1.3:1 and of 10 to 30: 1, respectively. These concentrations served as the basis for the discussion of possible exposures to these cannabinoids in industrial hemp-based products but quantitative assessment was not possible due to insufficiency of the data.

Consumers of Concern

For the exposure assessment three hypothetical consumers of concern were identified and characterized using Health Canada data:[9]

- Adult female (+ 20 years) ;
- Adult male (+ 20 years); and
- Child (aged 5 to 11 years).

For each of the three consumers of concern the following exposure scenarios were assessed:

- Consumption of Foods Made with Industrial Hemp Materials
- Dermal Use of Cosmetics and Personal Care Products Made with Industrial Hemp Oil
- Nutriceuticals of Industrial Hemp Oil

[9] Industrial Hemp Regulations, Schedule 1089, Canada Gazette, April 1, 1998; for a discussion see Annex I, Section 3.6.1

[9] see Annex I, Section 3.2, Table 3.2-1 and Table 3.2-2 for concentrations of THC and other cannabinoids in *Cannabis sativa.*

3.2.2 Absorption

Absorption refers to the amount of chemical that enters the systemic circulation.

3.2.2.1 Oral Absorption of THC

THC is well absorbed following ingestion. In human studies, the percent of ingested THC absorbed from the gastrointestinal tract was 95% after ingestion of THC in an oil vehicle (Wall et al., 1983) and 90-95% after ingestion of THC in a cherry syrup vehicle (Lemberger et al., 1972). The absorption was determined in these studies by measuring the amount of THC excreted unmetabolized in feces, thus the possible contribution to the presence of metabolites of microbial conversion or acid hydrolysis in the g.i. cannot be excluded. These findings from the human studies are consistent with those of a study using fasted Rhesus monkeys, in which nearly 100% absorption was observed after ingestion of THC in a cookie (Perlin et al., 1985). In this case the extent of absorption was determined based on the area under the concentration (AUC) curve for THC plus the major metabolite 11-OH-THC, and provides evidence that the high degree of absorption observed in the human studies was also due to systemic absorption and was not an artefact of g.i. tract conversion. Based on the evidence from these studies it is assumed that oral absorption from the g.i. tract is 100% for the purposes of this exposure assessment.

3.2.2.2 Dermal Absorption of THC

The term dermal absorption as used in the exposure assessment refers to the percent of the total THC applied to the skin that would permeate the outer dermal layers, rendering it potentially available to systemic circulation. There is considerable uncertainty about the percent dermal absorption of THC in human skin.[10] For this reason three values for dermal absorption were considered in the exposure assessment. These were 33%, 1% and 100%. Exposure estimates presented in tables of this report Section 4.2.2 are those calculated for healthy skin using 33% dermal absorption of THC, which at the present time was considered to be the best estimate of dermal absorption given the limitations of the data. This value was determined using data from the only identified dermal study with human skin, albiet an *in vitro* radio-labelled study (Touitou et al., 1988).[11] Merits of the *in vitro* study by Touitou et al (1988) were:

- used human skin;
- used a drug formulation containing oleic acid, a known dermal penetration enhancer and component of hemp oil; and
- measured value.

The uncertainties associated with the derivation of 33% dermal absorption and those associated with the alternatives 1% and 100% are discussed in Section 5.7 of this report. The dermal permeability of THC in mouse skin *in vitro* (Touitou and Fabin, 1988) was increased by 10-fold in the presence of water, by 6-fold by 3% oleic acid, and by about 14-fold in the presence of water and oleic acid. Since a known constituent of industrial hemp oil is oleic acid,[12] and many cosmetics and personal care products are used with water these findings are directly relevant to the exposure assessment of THC in industrial hemp products. For personal care products that are rinsed-off or diluted in water an additional factor of 10 was applied to approximate the increased dermal permeability under aqueous conditions. Lastly, dermal absorption through damaged skin (e.g. chapped, psoriasis, eczematous, dermatitis, rash) has been reported to be generally two-fold greater than that of intact healthy skin[13]; therefore to estimate exposure to THC across compromised skin an additional factor of 2

[10] See Annex I, Section 3.5.2 and Annex I- Appendix A, SectionA.1.1.1.2 for a detailed discussion of the dermal absorption of THC.

[11] For a discussion of the Touitou et al., (1988) study and its shortcomings see Annex I, Section 3.5.2 and Annex I-Appendix A, Section 1.1.1.2

[12] Oleic acid content of industrial hemp oil is about 9 to 15% (see Annex I, Section 3.2.4, Table 3.2.4-1).

[13] See Annex I - Appendix A, Section 1.1.1.2

was applied in the determination of exposure estimates through the use of salves made with industrial hemp oil (as salves would be applied to injured or damaged skin).

3.2.4 Methods Exposure Assessment - Foods Made with Industrial Hemp Materials

A wide variety of foods can be made with industrial hemp materials.[14] THC has been detected in foods made with industrial hemp materials, these concentrations are published in the scientific literature and data have been tabulated.[15] Corresponding concentrations of other cannabinoids (i.e., CBN, CBD, CBC and others) in these products have either not been determined or were not reported in the literature reviewed. The relative amount (% v/v) of industrial hemp ingredients in foods was determined on the basis of recipes and these have been summarized.[16]

The amount of hemp foods (grams) consumed by the adult female, adult male and child (5 to 11 years) that would result in a THC intake (ug/kg) equivalent to the LOEL for acute neurological impairment or to the LOEL for neuroendocrine disruption was calculated according to the following equation:

Consumption (g/kg) = LOEL (ug/kg bw) or LOEL ug/kg bw/d x BW(kg) / C_{HF} (ug/g)x AF_{oral} (unitless)

where,

LOEL for acute neurological impairment = 70 ug/kg (see Section 4.1.4.1 of this report);
LOEL for neuroendocrine disruption = 1 ug/kg (see Section 4.1.4.2 of this report);
BW = body weight (kg) (see Section 3.4.2);
C_{HF} = Concentration of THC in Food made with Industrial Hemp Ingredients (ug/g);
AF_{oral} = Oral Absorption of THC (1, unitless) (see Section 3.2.3.1);

and

C_{HF} = sum of ($C_{THC\ in\ hemp\ oil/hemp\ seed/nut.....}$ x $\%Hemp_{oil/seed/nut}$.... +.....)

where, $C_{THC\ in\ hemp\ oil/hemp\ seed/nut}$ = concentration (ug/g) of THC in industrial hemp ingredient (assumed to be 10 ppm),
$\%Hemp_{oil/seed/nut}$ = relative % industrial hemp ingredient in hemp food to other ingredients

[14] See Annex I, Section 3.6, Table 3.6-1.

[15] See Annex I, Section 3.6, Table 3.6-2

[16] See Annex I, Section 3.6.3

Calculated food/food group consumption (grams) for each age group equivalent to the LOEL for neurological impairment or to the LOEL for neuroendocrine disruption were subsequently compared with the mean daily intakes for the adult female (+20 years) and the adult male (+20 years) (Nutrition Canada, unpublished data, 1999) and the mean and 95th daily intakes for the child (5 to 11 years) based on the 1994-1996 Continual Survey of Food Intakes by Individuals (CSFII) (U.S. Department of Agriculture). An additional comparison was made of calculated food/food group consumption (grams) with "per serving size" noted for various foods (e.g. cookies) on commercial food packages.

3.2.5 Methods Exposure Assessment - Cosmetics and Personal Care Products Made with Industrial Hemp Oil

Cosmetic and personal care products made with industrial hemp oil accessible to the Canadian consumer[17] and selected for assessment include:

- hand and body moisturizers
- massage oil
- bath oil
- body lotions
- soaps
- shampoos and conditioners;
- sunscreen
- lip balms
- body milk
- creme
- salves

[17] See Annex I, Section 3.7.1

The of analytical data on concentrations of THC in these products was summarized.[18] No analytical data for cannabinoids other than THC were measured in these products. The percent industrial hemp oil in the final product was determined based on results of a survey of alternative oils used in the manufacture of cosmetics and personal care products, as well as direct input from manufacturers of cosmetic/personal care products containing industrial hemp oil.[19] Generally for skin care products 10% or less hemp oil is used (hemp industry and cosmetic industry communication). Massage oils however, may be made with <10% hemp oil content upwards to 100%.

Assumptions regarding the average amount of product (grams) and the frequency of use per day were based on a summary of use data prepared for the Cosmetic, Toiletry and Fragrance Association (CTFA), by Environ Corp (1985).[20] These data are consistent with those provided by manufacturers of hemp cosmetic and personal care products. The application rate (g/m^2) of personal care products, directly applied to skin surface, was calculated by dividing the average amount of product (g) used per application (Environ. Corp. 1985) by the surface area of the body to which it is applied.

A detailed discussion of the dermal exposure analysis of cosmetics and personal care products containing industrial hemp oil is presented in Annex I, Section 3.7.

[18] See Annex I, Section 3.7.2

[19] See Annex I, Section 3.7.3

[20] See Annex I, Section 3.7.4

For the assessment of exposure to THC through the use of personal care products the following equations were used:

For those products that are used by:

- **Direct Application To Skin (*i.e.* lotions, creams, soaps)**

The following equation was used to estimate exposure from **rinse-off** products (soap, shampoo) and **leave-on** products (hand, face, body moisturizer, massage oil, lip balm, sunscreen products and salves).

Internal Dose (ug/kg bw/day) = C_{THC} x Application Rate x SA x AF x D_{exp} x day/24h x F_{app} x 1/BW

Where,

C_{DEA} = concentration of THC in product (ug/g);
Application Rate = amount applied to skin surface divided by the body surface area (g/m^2) to which it is applied;*[a typical application rate for lotions is about 2 mg/cm^2 or about 20 g/m^2 (Dr. B. Bronaugh, FDA, 1998, personal communication*)];
SA = Surface area of skin in contact with product (m^2);
AF = absorption factor (unitless) (% THC absorbed) (see Section 3.2.3.2);
D_{exp} = duration of exposure or contact time (hours/day);
F_{app} = frequency of application (/day);
BW = body weight (kg).

This equation assumes steady-state conditions for dermal uptake and therefore may overestimate dermal exposure, particularly for incidences involving short-term exposure (*i.e.* hand washing). No equations have been identified that estimate dermal uptake under non-steady-state conditions (U.S. EPA, 1992), nor endorsed by Canadian or U.S. regulatory agencies.

- **Dilution in Water[21] (*i.e.* bath oil)**

  Internal Dose (ug/kg/day)= C_w x 2PC x $(6LT \times DE/3.14)^{0.5}$ x SA x 1000L/m^3/BW

  Where,

  C_w = concentration of THC in water (ug/L);
  PC= permeability constant in water (m/h) = 1.3 x 10^{-6} m/h (see Annex I, Section 3.5.2);
  LT= lag time to reach steady state rate (h) = 8.5 h (see Annex I, section 3.5.2);
  DE= duration of exposure (h);
  SA= body surface area of skin in contact with water (m^2); and
  BW= body weight (kg).

The above equation assumes non-steady-state conditions prevail during the exposure scenario as the estimated time to reach steady-state (TSS) would be greater than the duration of the event (*i.e.* length of bath assumed to be 0.5 hours). Furthermore, as the chemical is in solution rather applied directly to the skin, the equation also assumes that there is an infinite amount of chemical in the surrounding water and thus exposure to the chemical is continual throughout the duration of the exposure event (U.S. EPA, 1992). Therefore, this equation would provide a conservative estimate of exposure and would be more realistic than using a steady-state relationship (which would likely over-estimate exposure). To estimate exposures for conditions of damaged or compromised skin an additional factor of x2 would be applied to the above equations.[22]

3.2.6 Methods Exposure Assessment - Nutraceuticals of Industrial Hemp Oil

The exposure to THC from ingestion of hemp oil nutraceuticals was estimated based on the recommended dose range from 15 to 60 ml/day (Struempler et al. 1997; Costantino et al, 1997) which is consistent with dosage information for one commercial industrial hemp oil product.[23] The general equation below was used to estimate exposures to THC through use of nutraceuticals:

[21] An additional factor of x10 was applied to products diluted in water (i.e. bath oil); see Section 3.2.3.2

[22] See Section 3.2.3.2 re: dermal absorption of damaged skin

[23] See Annex I, Section 3.8

Internal dose (ug/kg body weight/day) = C_{THC} (ug/g) x AF_{oral} x NC (g/d) x 1/BW (kg^{-1})

where, Internal dose = ug THC/kg body weight/day
C_{THC} (ug/g) = Concentraion of THC in Nutraceutical; assumed to be 10 ppm (Canadian limit)
AF_{oral} = Oral absorption of THC (unitless) (see Section 3.2.3.1)
NC (g/d) = amount of nutraceutical consumed daily
BW (kg) = body weight

3.2.7 Methods Exposure Assessment - the Adolescent and Teenager

The assessment of exposure of the adolescent and teenager was done qualitatively based on the literature reviewed pertaining to consumer use habits and sensitivity of various age groups to the potential health effects of THC and other canabinoids.

3.2.8 Methods Exposure Assessment - Nursing Infant

This exposure assessment was done qualitatively on the basis of human and animal studies that document the relationship of maternal exposure to THC and subsequent exposure of the suckling infant.[24]

4.0 RESULTS

4.1 Results - Hazard Assessment

4.1.1 Hazard Identification

Two key hazards were identified. The first hazard is neuroendocrine disruption and the second is neurological impairment.

Neuroendocrine Disruption

[24] See Section 4.1.2 of this report

Cannabinoids have been demonstrated to disrupt the hypothalamus-pituitary-gonadal axis and/or to affect related neurotransmitters in adult monkeys (Smith et al., 1978), adult rats (Daley et al., 1974; Demiguel et al., 1998; Diana et al., 1998; Murphy et al., 1990a; Rodriguez de Fonseca et al., 1992; Steger et al., 1990; Tyrey, 1980; Wenger et al., 1988), and adult human females (Bauman, 1980; Dornbush et al., 1978; Mendelson et al., 1986; Mendelson et al., 1985a; Mendelson et al., 1985b; Murphy et al., 1990a).[25]

Manifestation of neuroendocrine disruption can result in long term effects on brain development, the reproductive system and the immune system, particularly if this disruption occurs during development (i.e. during gestation, childhood or adolescence). The neuroendocrine and immunological systems are closely linked and perturbations of one are likely to affect the other (Draca, 1995). The effects of cannabinoids on the immune system appear to occur at higher doses than those that affect the neuroendocrine system, and are likely secondary to neuroendocrine disruption. Immune system effects are not considered as a primary hazard for the purposes of this risk assessment and will not be discussed further.[26] Evidence for permanent cannabinoid-induced effects on reproduction and/or behaviour in animals comes from 15 studies in which monkeys or rodents were exposed *in utero* and/or during lactation and then were not exposed further, but were kept for observation until adulthood (Corchero et al., 1998; Dalterio, 1980; Dalterio and Bartke, 1979; Dalterio et al., 1984a; Dalterio et al., 1984b; García Gil et al., 1997; Golub et al., 1982; Hatoum et al., 1981; Kumar et al., 1990; Kumar et al., 1986; Mokler et al., 1987; Molina-Holgado et al., 1997; Navarro et al., 1994; Vela et al., 1995; Vela et al., 1998). In the rodent studies exposure occurred for several days. Permanent effects reported in rodents in these studies included reduced sensitivity to morphine, increased self-administration of morphine, changes in density of brain opioid receptors, changes in brain catecholamines, increased corticosterone release in response to stimulus of the hypothalamus-pituitary-adrenal axis, enhanced response to novelty in behavioural tests in males, reduced copulatory behaviour in males, inhibition of testosterone release in response to a receptive female, abnormal estrus and altered hypothalamic regulation of gonadotropin secretion in females. In the monkey study, exposure occurred *in utero* and through nursing from mothers exposed orally to THC for 3.5 months. Offspring were observed to have altered visual attention at 1 and 2 years of age (Golub et al.,1982).[27]

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[25] See Annex I, Section 2.5.6 for additional details of the effects of cannabinoids on human neuroendocrine and reproductive parameters in humans.

[26] See Annex I, Section 2.7 for more details on immunological effects of cannabinoids.

[27] See Annex I, Section 2.5.4 and Appendix A Table A-5.2-1 for further details on the studies discussed in this

It has been suggested that given the potent effect of cannabinoids on the neuroendocrine system, that neuroendocrine mediated behaviours would be more likely to be affected in humans than learning and memory, the endpoints studied in traditional testing protocols (Brake et al., 1987). Neuroendocrine-related endpoints have not been specifically studied in humans exposed *in utero*, but sexual development and cognitive functioning in the Ottawa Prenatal Prospective Study (OPPS) cohort described below are currently being studied (Fried, in progress).

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paragraph.

In addition to the evidence from animal studies that perinatal exposure to cannabinoids causes permanent effects on brain development, there is also evidence from human studies of similar effects in the offspring of mothers who smoked marihuana during pregnancy. Although the evidence is equivocal that links marihuana exposure to adverse effects on pregnancy outcome and on neonates, there is more consistency with respect to the influence of *in utero* marihuana exposure and subtle neurobehavioural changes in older children (Fried, 1995; Fried, 1996; Richardson et al., 1995).[28] These findings are relevant to the current risk assessment because they provide information on the types of effects that may occur in humans exposed to cannabinoids *in utero* and through nursing.

[28] See Annex I, Section 2.5.7 for further discussion of prenatal studies in humans.

The findings of greatest significance come from a prospective study known as the Ottawa Prenatal Prospective Study (OPPS). This study began in 1978 and has been the subject of numerous reports and reviews (Fried, 1980; Fried, 1982; Fried, 1995; Fried, 1996; Fried et al., 1983; Fried and Makin, 1987; Fried and O'Connell, 1987; Fried et al., 1992; Fried and Watkinson, 1988; Fried and Watkinson, 1990; Fried and Watkinson, 1990; Fried and Watkinson, 1992; Fried et al., 1992; Fried et al., 1998; Fried et al., 1984; O'Connell and Fried, 1984; O'Connell and Fried, 1991). The most recent published results from this study involved the evaluation of cognitive functioning in 9-12 year-olds (Fried et al., 1998). Cognitive functioning and sexual development in this cohort is currently under study (Fried, in progress). The OPPS study is the only study which has provided data on children past 3 years old who were exposed to marijuana *in utero*. The subjects in the OPPS study constitute a low-risk sample, since they are all from middle class homes and the adverse influences of poverty and heavy drug use (other than marihuana) did not play a role in the development of the children. Because the OPPS study provides the most comprehensive evaluation of the effects of prenatal marihuana exposure, provided statistical control for all major confounding variables, used a large sample size from a low-risk population and studied children up to age 12, it is considered that this study has generated the most relevant and reliable data available.[29]

A negative impact of *in utero* marihuana exposure was also observed in 9-12 year olds in tests designed to measure impulse control, visual analysis and hypothesis testing. These are higher order cognitive processes considered to fall into the category of executive function. Executive function is defined as, "the cognitive ability to maintain an appropriate problem-solving set for attainment of a future goal, and involves the integration of cognitive processes" (Fried, 1995). Decrements in executive function were also associated with prenatal marihuana exposure in the OPPS subjects at age six. The affected behaviours included problems with self-regulation, problems maintaining attention and decreased ability to act on accumulated knowledge (Fried, 1995; Fried et al., 1992).

It is not possible to prove unequivocally an association between an environmental exposure and an adverse effect in a human population using data from epidemiology studies. This is because the impacts of confounding factors cannot be completely understood or ruled out entirely using statistical methods; however, the reported association between neurocognitive changes in 9-12 year olds and maternal marihuana smoking provides a strong suggestion that the association is causal (Fried et al., 1998). This conclusion is strengthened by data

[29] The methods and results of this study are discussed in more detail in Annex I, Section 2.5.7

from other areas of research. The conclusions of Fried et al. (1998) that prenatal exposure to marihuana is associated with neurocognitive changes in children is supported according to the Hill criteria for causality (Hill, 1965) because there is a temporal association between the cause and the effect, there is a plausible biological mechanism through which the effect could have been caused, the specific adverse effects have been well correlated with similar exposures in animals, there is concordance among effects across species, there is consistency in findings among epidemiology studies and the cohort being studied has consistently shown effects over the years.[30]

[30] Supporting evidence is discussed in detail in Annex I, Section 2.5.7.

The data discussed above serve to demonstrate the basis for the conclusion that neuroendocrine disruption represents a key hazard of exposure to cannabinoids. The majority of studies involved exposure to THC, although there were some that used CBD and/or CBN, and these other cannabinoids have also been observed to cause neuroendocrine disruption[31]. It was noted that adverse effects were observed in all studies at all doses tested, with no negative findings with respect to THC exposure and neuroendocrine disruption being reported in the literature.[32] Overall the findings from these studies indicate that the developing fetus and the neonate are very sensitive to neuroendocrine changes induced by THC and that these can lead to permanent effects on behaviour and reproductive parameters. Dose-response assessment and discussion of the basis for extrapolation to humans are discussed in sections 4.1.4, 4.1.5 and 4.1.6.

Neurological Impairment

The second hazard considered for this risk assessment is neurological impairment. This is manifested as decrements in performance in a battery of tests designed to evaluate motor and cognitive skills. Performance decrements have been observed in three studies from the same research group in which volunteer subjects received a single oral dose of THC (Belgrave et al., 1979; Chesher et al., 1990; Chesher et al., 1977).[33] Neurological impairment as defined above for this report is considered distinct from psychoactivity. Psychoactive effects are interpreted by the subject as a feeling of being "stoned". Based on the results of a dose-response study (Chesher et al., 1990) it is assumed that neurological impairment occurs at a lower dose than psychoactivity, thus protection from neurological impairment will protect from psychoactivity. Generally a risk assessment is conducted on the basis of the adverse effect that occurs at the lowest effect dose. In this case, neurological impairment is considered as a key hazard even though it occurs in humans at much higher doses than does neuroendocrine disruption in animals. This endpoint requires specific consideration because of the attention that has been given to the importance of maintaining THC concentrations in products made from industrial hemp at concentrations below those that could cause neurological effects, including psychoactivity.

[31] Studies of the effects of CBN and CBD on neuroendocrine and reproductive parameters are discussed in Annex I, sections 2.5.4.5, 2.5.5.4 and 2.5.6.2

[32] See Annex I, Appendix A, Table A-5.2-1 for a comprehensive listing of all studies.

[33] See Annex I, Section A-2.1 for details of acute studies in humans.

4.1.2 Absorption, Distribution, Metabolism, Excretion and Pharmacokinetics

The absorption, distribution, metabolism, excretion (ADME) and pharmacokinetics of the cannabinoids has been extensively studied.[34] Details of the derivation of oral and dermal absorption values used in the exposure section are presented in sections 3.2.3.1 and 3.2.3.2 of this report. Information useful to the risk assessment that comes from the ADME and pharmacokinetic data are briefly summarized below.

- THC is well absorbed from the GI tract following ingestion (Lemberger et al., 1972; Perlin et al., 1985; Wall et al., 1983).
- The major metabolite if THC is 11-OH-THC, and is produced in the liver through the action of P450 enzymes primarily in the liver (Agurell et al., 1986).
- Non-microsomal processes convert the 11-OH-THC to 11-carboxy-THC, which is not toxic (Agurell et al., 1986).
- The major metabolic pathways appear to be the same in animals and humans (Yamamoto et al., 1995).
- 11-OH-THC is at least as psychoactive and pharmacologically active as THC (Di Marzo et al., 1998; Karler and Turkanis, 1987; Lemberger et al., 1972; Perez-Reyes et al., 1972; Wall et al., 1976; Watanabe et al., 1990).
- THC undergoes extensive first-pass metabolism following ingestion (Hunt and Jones, 1980).
- Metabolism of THC to 11-OH-THC occurs to a greater degree after oral dosing than after i.v. dosing with the ratio of metabolite to parent being 1:10 or 1:20 after i.v. dosing and 1:1 or 1:2 after oral dosing (Wall and Perez-Reyes, 1981; Wall et al., 1983).
- Enterohepatic recirculation of metabolites has been found to be an important process in mice (Harvey et al., 1980), dogs (Garrett and Hunt, 1977) and humans (Wall and Perez-Reyes, 1981; Wall et al., 1983). The high degree of enterohepatic recirculation explains the dominance of fecal excretion and may also contribute to the slow rate of excretion.
- Excretion of THC occurs slowly, with mean terminal half lives in humans reported as 2.6-12.6 days (Johansson et al., 1989a), 1-10 days (Cridland et al., 1983), 8 days (Hunt et al., 1981), 6.2 days (Kelly and Jones, 1992) and 1.8-2.5 days (Huestis and Cone, 1998).
- THC accumulates in fat (Bronson et al., 1984; Harvey et al., 1982; Hunt and Jones, 1980; Johansson et al., 1989b; Nahas et al., 1981; Rawitch et al., 1979), with no metabolism of THC occurring in fat (Bronson et al., 1984).

[34] Detailed discussions are presented in Annex I, Section 2.1 and Annex I, Appendix A, Section A-1.0

- The slow excretion and long half life of THC in plasma is probably due to its storage in fat with subsequent slow release to the blood stream (Hunt and Jones, 1980; Johansson et al., 1989a).

- Human infants appear to have a lower capacity for metabolism of THC compared to adults as evidenced by the absence of 9-carboxy-THC in the urine of an infant exposed to THC through breast milk from a marihuana using mother (Perez-Reyes and Wall , 1982).

- THC concentrations may persist in neonates because of immaturity of the hepatic microsomal enzyme system (Asch and Smith, 1986).

- THC has a high affinity for plasma lipoprotien, and 88-99% of THC in plasma is associated with protein in humans (Hunt and Jones, 1980). 11-OH-THC is also highly bound to protein, with 97% of that in blood being bound to lipoproteins (Harvey, 1984).

- In rabbits, it has been found that protein binding and plasma clearance of drugs that bind to proteins are slower in neonates than in adults, resulting in higher concentrations of active drug (McNamara et al., 1991; McNamara et al., 1992). Similar studies have not been conducted in humans; however, these data indicate that neonates could be exposed to higher effective concentrations of drugs, such as THC, that bind to proteins.

- Significant exposure to the brain can occur after exposure to CBN, THC, and 11-OH-THC enters the brain more quickly than THC (data from studies with monkeys and rodents) (Ho et al., 1973; McIsaac et al., 1971; Perez-Reyes et al., 1976; Shannon and Fried, 1972).

- Concentrations of THC plus metabolites in the brain have been found to be higher than or similar to those in plasma soon after dosing in rats (Berrendero et al., 1998; Bronson et al., 1984; Leighty, 1973; Nahas et al., 1981).

- It appears that 11-OH-THC also penetrates more quickly than THC into the brains of humans as evidenced by the more rapid loss from blood and the faster appearance of pharmacological effects after injection of 11-OH-THC compared to THC (Perez-Reyes et al., 1976).

- Radioactivity from radiolabelled THC accumulates is the frontal cortex in monkeys and rats (McIsaac et al., 1971; Shannon and Fried, 1972). The frontal cortex has also been found to contain the highest concentration of cannabinoid receptors in the rat (Herkenham et al., 1991; Musty et al., 1995).

- Localization has been noted in the adrenal gland (Kennedy and Waddell, 1972; Kennedy and Waddell, 1972; Ryrfeldt et al., 1973), and it has been suggested that this may indicate the potential for THC to interfere with the action or metabolism of steroid hormones (Kennedy and Waddell, 1972).

- Localization has also been observed in gonadal tissues in male and female rodents (Bronson et al., 1984; Morrill et al., 1983; Nahas et al., 1981; Rawitch et al., 1979).

- THC and its metabolites are distributed to breast milk in animals (Ahmad and Ahmad, 1990; Chao et al., 1976; Dalterio, 1980; Jakubovic et al., 1973; Jakubovic et al., 1974) and humans (Perez-Reyes and Wall , 1982).

- The concentration of THC in human milk can be much higher than the concentration in maternal plasma (Perez-Reyes and Wall , 1982), and in monkeys serum levels of THC in suckling infants can be higher than maternal serum levels (Asch and Smith, 1986). These data indicate the potential for significant exposure to nursing infants.

- THC and its metabolites distribute to the fetus of dogs, sheep and monkeys within minutes of maternal exposure by inhalation or injection (Abrams et al., 1985; Bailey et al., 1987; Martin et al., 1977).

- THC distributes to the fetus to a lower degree after oral than injection exposure in the rat (Hutchings et al., 1989).

- In dogs and monkeys THC and not 11-OH-THC can cross the placenta (Bailey et al., 1987; Martin et al., 1977), while in humans there is evidence of fetal exposure and/or metabolism, based on the detection of both 11-OH-THC and its metabolite 9-carboxy-THC in the feces of a nursing infant of a marihuana-smoking mother (Perez-Reyes and Wall , 1982).

- The single dose pharmacokinetics of cannabidiol (CBD) (Ohlsson et al., 1986) and cannabinol (CBN) (Johansson et al., 1987) in humans were found to be very similar to those of THC, with all three showing fast clearance from blood, large distribution volume and slow elimination from the body.

- Both CBN and CBD are extensively metabolized and the majority of the dose is excreted in feces (Chiang and Rapaka, 1987).

- CBD can cross the blood brain barrier in the mouse (Bornheim et al., 1995).

4.1.3 Mechanism of Action

Numerous mechanisms through which cannabinoids may exert their neurotoxic and other effects have been suggested, and although the operation of none are completely understood, it is likely that many different mechanisms of action may contribute to the observed effects. Many of the adverse effects of cannabinoids are thought to occur as result of binding to a specific cellular receptor. Effects of cannabinoids on neurological function and development may be mediated though their influence on neurotransmitter systems. This mechanism is discussed in more detail below. Several other of the proposed mechanisms are discussed in Annex I, Section 2.8.

The existence of a cannabinoid receptor has been unequivocally proven, and the history of this discovery and supporting evidence have been reviewed (Howlett et al., 1992; Matsuda, 1997; Pertwee, 1993).

Cannabinoid receptors in the brain are most abundant in the cortex, cerebellum, hippocampus and striatum (Bidaut-Russell et al., 1990).[35] The distribution of cannabinoid receptors in the brain are correlated with the adverse effects of cannabinoids on cognition, memory and control of movement (Felder and Glass, 1998; Herkenham, 1992; Herkenham et al., 1991). Cannabinoid receptor localization within the brain is similar in humans, monkey, dog and guinea pig (Herkenham et al., 1990)and similar in fetal, neonatal and adult human brains (Glass et al., 1997). In the human brain, the number of receptors has been reported to be higher in the fetal and neonatal brain than in the adult brain (Glass et al., 1997). An earlier study found similar levels of receptor binding in adult and infant human brain (Mailleux and Vanderhaeghen, 1992). Differences between these studies might be due to interindividual variation, since small numbers of infant brains were studied. The period of peak receptor density in the rat brain was found to be during puberty (Rodríguez de Fonseca et al., 1993). Receptor density during puberty has not been measured in humans.

Endogenous ligands have been identified that can bind to the cannabinoid receptor and recent reviews have provided detailed descriptions of the discovery of these endogenous ligands and evidence for functional roles for this system (Axelrod and Felder, 1998; Di Marzo and Fontana, 1995; Di Marzo et al., 1998; Felder and Glass, 1998; Mechoulam et al., 1998). Various roles have been suggested for the endogenous cannabinoid system including neuromodulation (Axelrod and Felder, 1998; Di Marzo et al., 1998), neuroprotection (Mechoulam et al., 1998), immunomodulation in the brain (Sinha et al., 1998), immunomodulation (Di Marzo and Fontana, 1995), modulation of reproductive function (Di Marzo and Fontana, 1995) and endocrine function (Pertwee, 1993), control of motor activity (Felder and Glass, 1998), functioning of perception, cognition, memory and learning, control of mood, emotion, food intake, regulation of body temperature (Pertwee, 1993) and regulation of blood pressure (Mechoulam et al., 1998). Further research is required to fully elucidate the role of the endogenous cannabinoid system. It is to be expected that exogenous chemicals that can bind to the cannabinoid receptor would have the potential to disrupt the normal functioning of the cannabinoid system.[36]

[35] Details on the functioning of the cannabinoid receptor are presented in Annex I, Section 2.8.1.

[36] More detailed information on cannabinoid receptors and the endogenous cannabinoid system is presented in Annex I, Section 2.8.1.

It has not been possible to correlate the psychoactive effects of cannabinoids with the receptor-dependent actions since non-psychoactive cannabinoids can bind to the receptor equally well or better than THC (Howlett et al., 1992).

Evidence has been presented that the effects of cannabinoids may be mediated through their influence on neurotransmitter systems. Neurotransmitters and neuromodulators that have been found to be affected by cannabinoid exposure include dopamine, serotonin, acetylcholine, gamma-aminobutyric acid (GABA), norepinephrine, histamine, prostaglandins and opioid peptides, and evidence for this has been reviewed (Pertwee, 1990; Pertwee, 1992). Several studies have reported alterations in brain neurotransmitters as a result of perinatal exposure to cannabinoids.[37] Mechanisms through which cannabinoids may influence neurotransmitter systems include, modulation of transmission through effects on synthesis, release or reuptake of neurotransmitters, effects on affinity of the neurotransmitters for their receptors or effects on the second messenger systems of the neurotransmitters (Pertwee, 1992). A detailed description and diagram of a proposed mechanism whereby THC and anandamide (an endogenous cannabinoid ligand) may influence neurotransmitter function is provided by Di Marzo et al. (1998).[38]

4.1.4 Dose Response Assessment

4.1.4.1 Dose Response Assessment - Neurological Impairment

A summary of the doses associated with acute effects in humans in various studies is presented in Table 4.1.4.1-1.[39] Psychoactive effects in humans given a single oral dose of THC have been consistently reported in the dose range of 120-140 ug/kg (Isbell et al., 1967; Chesher et al., 1990; Leweke et al., 1998) with one study reporting a NOEL of 70 ug/kg (Chesher, 1990). No repeat dosing studies using oral exposure to THC in humans have been reported in the literature.

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[37] Studies demonstrating effects of cannabinoids on neurotransmitters are summarized in Annex I, Table 2.5.1-1 and Annex I, Appendix A, Table A-5.2-1)

[38] Neurotransmitter disruption by cannabinoids is discussed in more detail in Annex I, Section 2.8.6.

[39] Additional details on the methods and results of these studies are presented in Annex I, Section 2.2.1 and Annex I, Appendix A, Section A-2.1.

Table 4.1.4.1-1: Summary of Acute Effects of Oral Dosing in Humans

Route	THC Dose (ug/kg)	Effects	NOEL, LOEL or Only Dose Tested	Reference
oral	120, 480	psychoactive effects	120 (LOEL)	(Isbell et al., 1967)
oral	70, 140, 215, 286	impaired performance on test battery	70 (LOEL)	(Chesher et al., 1990)
oral	70, 140, 215, 286	psychoactive effects	70 (NOEL)	(Chesher et al., 1990)
oral	320	impaired performance on test battery	320 (only dose)	(Belgrave et al., 1979)
oral	215	impaired performance on test battery	215 (only dose)	(Chesher et al., 1977)
oral	137	no effects; observation time not long enough	137 (only dose)	(Chesher et al., 1976)
oral	126	psychoactive effects	126 (only dose)	(Leweke et al., 1998)
oral *	71	dizziness, euphoria, thinking abnormalities	71 (only dose)	(Beal et al., 1995)

* this was a repeat dosing study using Drabinol (a synthetic cannabinoid) at a dose of 2.5 mg twice daily for at least four weeks in male AIDS patients; assumed body weight of 70 kg for dose calculation; all other studies in table are single dose studies

The most definitive of these studies is that conducted by Chesher et al. (1990).[40] This was a double blind dose-response study with 16 subjects of both sexes per dose group. Subjects were given oral doses of 0, 5, 10, 15 or 20 mg THC in sesame oil vehicle in gelatine capsules after consuming a light breakfast. Subjects were given a battery of tests to measure performance, including standing steadiness, hand-eye coordination, reaction time (3 separate tests) and simple mathematics (speed and accuracy). The tests were given before drug exposure and at 80, 140, 200 and 260 minutes after exposure. Subjects were also asked to report their degree of intoxication on

[40] Additional discussion of the study by Chesher et al. (1990) is presented in Annex I, Section 2.2.1.

a scale of 1-10. All subjects had previous experience with marihuana intoxication. Subjective evaluation of intoxication revealed psychoactive effects beginning at the 10 mg dose. The slope of the regression line relating performance to dose at time zero (predosing) was compared with the slopes of the regression lines at each of the other 4 time points. This analysis was done for the centroid (unweighted mean) of the scores on the set of measures and also for each individual measure. All individual measures showed a significant decrement associated with THC dosing, except complex reaction time (visual and auditory reaction time both showed decrements). There was a dose-response, with the centroid of performance scores on the test battery significantly reduced even at the lowest dose. The slope of the dose-response curve was similar at 80, 140 and 200 minutes after dosing and was less steep 260 minutes after dosing. The lowest dose used in this study was 70 ug/kg. This study indicates a significant decrement in performance scores after a single, low oral dose that persisted for 3 hours after dosing. The results of this study are considered to be relevant to the assessment of human risk from ingestion of products containing industrial hemp with the caveat that this was a single dose study, only THC and not a complex mixture of cannabinoids was given and the subjects were experienced marihuana users. Based on the results of this study the LOEL for neurological impairment is taken to be 70 ug/kg, the NOEL for psychoactivity is taken to be 70 ug/kg and the LOEL for psychoactivity is taken to be 140 ug/kg.

4.1.4.2 Dose Response Assessment - Neuroendocrine Disruption

Neuroendocrine disruption by cannabinoids in animals has been observed at much lower doses than those associated with overt behavioural effects. It is expected that in humans as well, neuroendocrine disruption would occur at much lower doses that those causing neurological impairment. Although neurological impairment is an important endpoint to be considered, it is not the most sensitive. In addition, the data indicate that there is no relationship between psychoactivity and effects on neuroendocrine, reproductive or immune system parameters since cannabinoids with no psychoactivity can cause these types of effects (Baczynsky and Zimmerman, 1983a; Baczynsky and Zimmerman, 1983b; Dalterio, 1980; Dalterio and deRooij, 1986; Dalterio and Bartke, 1979; Dalterio et al., 1984a; Dalterio et al., 1984b; Desoize et al., 1981; Kaminski, 1998; Murphy et al., 1990a; Nahas et al., 1977; Newton et al., 1993; Patra and Wadsworth, 1991; Smith et al., 1997; Steger et al., 1990; Tilak and Zimmerman, 1984; Zuardi et al., 1993). Thus the absence of psychoactivity for a cannabinoid or the absence of psychoactivity at a low dose does not imply absence of potential toxicity.

Relevant dose-response information for neuroendocrine disruption in humans are not available, since these effects have generally only been studied in relation to marihuana smoking. Adverse effects on neurological and reproductive system development in animals have been shown to occur at low doses as a result of neuroendocrine disruption during fetal and neonatal development in animals.[41] Other studies have demonstrated adverse effects on neuroendocrine parameters and/or related neurotransmitters in animals exposed after the perinatal period.[42] Most of these studies were conducted at high doses, not relevant to exposure levels that could occur through the use of food, cosmetics and nutraceuticals made from industrial hemp. Those studies that used doses of 1 mg/kg or lower are summarized in Table 4.2.2.3-1. The lowest effect dose was 0.001 mg/kg/d by i.p. dosing, which caused hormonal changes in pregnant rats (Wenger et al., 1991) and caused endocrine hormone changes, delayed estrus and reductions in the number of ova in rats exposed prepubertally (Wenger et al., 1988). These studies were conducted using single dose levels, and as such shed no light on the dose-response relationship. Ideally dose-response data would be used for risk assessment, but in this case there are no suitable dose-response studies.

A frequent finding among the multiple dose level studies was a biphasic dose response, in which the response decreased with increasing dose, or opposite effects were observed at low versus high doses (Daley et al., 1974; Kumar et al., 1986; Navarro et al., 1995; Rubio et al., 1998; Smith et al., 1978). The biphasic dose-response of THC is well recognized, although not well understood (see Dewey, 1986 for review). Opposing actions appear to occur at low doses (0.2-2.0 mg/kg) compared to higher doses (5-50 mg/kg) (Dewey, 1986). The endogenous cannabinoid, anandamide, has also been found to exhibit a biphasic dose-response for a number of pharmacological and behavioural effects (Sulcova et al., 1998). It has been suggested that effects of cannabinoids at low doses may be related to receptor-dependent actions, while high dose effects may be related to effects on membrane disruption (Howlett et al., 1992; Sanchez et al., 1998). This is consistent with the expectation that neuroendocrine disturbances are induced by THC through a receptor dependent mechanism, which would be expected to be maximally operable at an optimum concentration.

[41] See Annex I, Appendix A, Table A-5.2-1 for a summary of all perinatal exposure studies in animals.

[42] See Annex I, Sections 2.5.1, 2.5.2 and 2.5.2 for discussions of studies on the effects on neuroendocrine parameters in adult animals.

Table 4.1.4.2-1: Summary of Low Dose and Dose-Response Studies on Neuroendocrine and Reproductive Effects of Cannabinoids

Species	Route	Dose mg/kg/d	Dose Schedule	Outcome and Comments	Reference
Studies of Effects of Cannabinoids on Hypothalamus-Pituitary-Gonadal Axis and Related Neurotransmitters					
monkey (ovariect-omized)	i.m.	0, 0.625, 1.25, 2.5, 5.0	single dose	reduced LH and FSH at all doses; effect on LH greatest at lowest doses; effect on FSH greatest at highest and lowest doses	(Smith et al., 1978)
rat (M)	oral	0, 0.5 THC, CBN, CBD	single dose	no effects on PRL; LH reduced at 60 min, but not at 30 or 120 min after dosing with THC; no effect of CBN or CBD on LH; hypothalamic NE turnover affected with all treatments; CBN and CBD potentiate effects of THC on LH; no effects on dopamine or serotonin	(Murphy et al., 1990b)
rat (M)	oral	0, 0.1, 1, 10 THC, CBN, CBD	single dose	plasma LH and testosterone reduced 60 min post-dosing by THC or CBN, not by CBD; no dose-relationship, all doses equally potent; no effect on plasma FSH; NE turnover reduced with THC or CBN; dose-related with THC, effects at all doses; no dose-response with CBN, all doses equally potent	(Steger et al., 1990)
rat (M)	oral	0, 0.5, 5	single dose	dose-related decrease in plasma PRL; decrease in number of dopaminergic receptors in striatum and forebrain	(Rodriguez de Fonseca et al., 1992)
rat (M)	i.v.	0, 0.0625, 0.125, 0.250, 0.5, 1	single dose	injections given cumulatively, one every 90 sec; firing rate of dopaminergic neurons was increased slightly after 1st injection and stat significantly after cumulative dose of 0.125 mg/kg	(Diana et al., 1998)
rat (M)	i.p.	0, 0.04, 4, 40	daily for 4 d	increase in pituitary wt, pituitary PRL (ug/mg) and serum PRL, but not stat signif at low dose, stat signif increase in pituitary PRL (ug/gland) at low dose	(Daley et al., 1974)
rat (M)	i.p.	0, 5	single dose	reduced plasma PRL and LH; increased GABA in medial basal hypothalamus	(Demiguel et al., 1998)

Table 4.1.4.2-1: Summary of Low Dose and Dose-Response Studies on Neuroendocrine and Reproductive Effects of Cannabinoids

Species	Route	Dose mg/kg/d	Dose Schedule	Outcome and Comments	Reference
rat (F)	i.p.	0, 0.001	postpartum day 22-day of vaginal opening	dosing during prepubertal period; effects observed 35-45 days after cessation of exposure; reduced LH and FSH; PRL increased only in animals killed on 1st day of estrus; delay in estrus, irregular estrous cycles and fewer ova in treated rats	(Wenger et al., 1988)
rat (F)	i.p.	0.001	wk 1, 2 or 3 of pregnancy	LH, progesterone and PGF1 reduced during 3rd week of pregnancy	(Wenger et al., 1988)
rat (F) (ovariect omized)	i.v.	0, 0.0312, 0.0625, 0.125, 0.250, 0.5	single dose	decrease in LH at 0.0625 mg/kg and higher; doses equipotent, but duration of effect longer at higher doses; NOEL = 0.0312 mg/kg (data for lowest dose not shown in paper)	(Tyrey, 1980)

Summary of Low Dose and Dose-Response Perinatal Exposure Studies with THC

Rat	oral	0, 1, 5, 20	GD5-d24 postnatal	enhanced behavioural response to novelty in adult offspring; reverse dose-response - greatest effect at lowest dose; males most affected; increased corticosteroid in adult male offspring in response to HPA stimulus at 1 and 5 mg/kg/d THC doses; increased morphine sensitivity in males at 1 mg/kg/d dose;	(Rubio et al., 1998)
Rat	i.p.	0, 0.001	daily in 3rd week	reduced birth weight; reduced gonad weight in pups; transitory (up to D20) inhibition of hypothalamo-pituitary-gonadal axis in pups	(Wenger et al., 1991)
Rat	i.p.	0, 0.02	daily in 3rd week	reduced birth weight; reduced survival of female pups; increased stillbirths; decreased weight of pituitary on D0 and D5; transitory (up to D20) inhibition of hypothalamo-pituitary-gonadal axis in pups; similar findings with anandamide at same dose	(Wenger et al., 1995)

Table 4.1.4.2-1: Summary of Low Dose and Dose-Response Studies on Neuroendocrine and Reproductive Effects of Cannabinoids

Species	Route	Dose mg/kg/d	Dose Schedule	Outcome and Comments	Reference
Rat	s.c.	0, 0.38, 1.9, 3.8	during 1st 5 days of life	long-lasting inhibition of postpubertal reproductive functioning as indicated by abnormal estrous cycles in treated grps age 3-10 months; altered hypothalamic regulation of gonadotropin secretion in adult females; effects at all dose levels; LHRH increased at low dose, decreased at higher doses in mediobasal hypothalamus (MBH); met-enkephalin in MBH increased at all doses, negative dose-response	(Kumar et al., 1986)

The lowest doses tested in the studies that showed a reverse dose-response were 1 mg/kg by oral dosing and 0.38 mg/kg by s.c. dosing (see Table 4.1.4.2-1). In one of these studies it was shown that early exposure to THC (0.38 mg/kg during 1st 5 days of life) could affect postpubertal reproductive functioning in adult females rats, even though dosing did not continue (Kumar et al., 1986). Similarly animals dosed perinatally with an oral dose of 1 mg/kg/d THC, exhibited enhanced behavioural response to novelty and increased sensitivity to morphine in adulthood (Rubio et al., 1998). Based on the shape of the dose-response curves and the recognition that THC can produce biphasic effects it must be concluded that even lower doses than these could cause adverse effects on the developing neurological and reproductive systems. In the absence of a clear understanding of the dose-response relationship at low doses, the occurrence of effects on the neuroendocrine system at all doses tested and the weight of evidence demonstrating that cannabinoids can affect neurological and reproductive system development, it is concluded that the LOEL of 0.001 mg/kg/d is the most reasonable choice of data upon which to base extrapolation to humans for the purposes of risk assessment. This dose caused hormonal changes in pregnant rats (Wenger et al., 1991) and caused endocrine hormone changes, delayed estrus and reductions in the number of ova in rats exposed prepubertally (Wenger et al., 1988). Information is presented in section 4.1.6 of this report that supports extrapolation from animal data to humans.

4.1.5 Dose Route Extrapolation

The dermal and oral dose routes are of concern in the assessment of human health risks associated with the use of cosmetics, foods and nutraceuticals made from industrial hemp. Data from toxicology studies that used these dose routes would obviously be the most appropriate for use as the basis of the risk assessment. Unfortunately there were no studies available that used the dermal dosing route. There were some human and animal studies in which the oral route was used, but these were not conducted at low enough doses to allow determination of a NOEL. Some studies at lower doses in animals used i.p., s.c. or i.v. dosing and provide evidence of effects at very low doses. The issues with respect to dose route extrapolation pertaining to the use of data from the studies discussed in the previous sections are discussed below.

4.1.5.1 Extrapolation for Neurological Impairment

A human oral dosing study demonstrated deficits in performance in a battery of tests of motor and cognitive skills at the lowest dose tested of 70 ug/kg (Chesher et al., 1990). These data can be considered to be relevant to the assessment of human health risk to food and nutraceutical products since the oral dose route was used.

No human data were available that were suitable for extrapolation for dermal exposure. Human data were available for i.v. dosing, but the rate of dermal absorption would probably be much lower (although there are no data to support this statement). Human data were also available for oral dosing, but this results in first pass effect and lower acute toxicity than i.v. dosing. Since the lowest available LOEL in humans is for oral dosing, and assuming that toxicity from dermal dosing would be likely to be lower than by i.v. dosing, the oral LOEL is used in this assessment for extrapolation to dermal dosing for the purposes of this risk assessment with respect to acute neurological impairment.

It must be taken into consideration that the oral study from which the LOEL was derived (Chesher et al., 1990) used only a single exposure, considered only adults, considered adults that were previous or current marihuana smokers and did not measure effects related to the most sensitive endpoint, that is, neuroendocrine disruption. Thus these data have less relevance for children, adolescents and non-users of marihuana who could ingest industrial hemp-based food and/or nutraceutical products over a prolonged period. These data are not directly relevant to the developing fetus or infants that may be exposed to cannabinoids through maternal use of products made from industrial hemp. These data also do not provide any evidence that could be used to assess the risks associated with neuroendocrine disruption.

4.1.5.2 Extrapolation for Neuroendocrine Disruption

The studies discussed in the previous section that provide the key data to be used in the risk assessment for neuroendocrine disruption involved dosing via the i.p. route. The use of the i.p. dose route has often been criticized as a route not relevant to human exposure, causative of toxicity as result of local tissue damage and peritonitis, and possibly resulting in pooling of the dose at the injection site. The very low dose i.p. studies were all reported by the same principal author (Wenger et al., 1988; 1989; 1995). In the case of these studies it does not appear that toxicity was an issue, since none was reported. In one of the studies pregnant rats were treated for a week during gestation, with no influence on pregnancy outcome if dosing was during the first or second week (Wenger et al., 1989). This indicates a lack of adverse effects related to the i.p. dosing route alone. Pharmacokinetics after i.p. dosing are more similar to those of oral than i.v. dosing as evidenced by a slow increase in plasma concentrations in rats (Ford et al., 1977). No studies of the metabolism of THC after i.p. dosing were identified; however, it would be expected that there would be slower production of the 11-OH-THC metabolite by this route compared to the oral route due to the absence of a first pass effect. Acute dosing by i.p. injection resulted in a similar degree of toxicity in mice and rats as did oral dosing (Forney, 1971). The

comparative pharmacokinetics and acute toxicity data provide some evidence that there may be a similar degree of potency with these dose two routes. It is clear from the large volume of data on the effects of THC on neuroendocrine, reproductive and behavioural parameters, that the dose route does not influence the nature of the outcome. The doses used in the studies by Wenger et al. were so low that an aqueous dosing solution could be used (Harvey, 1984), so there are no issues related to dose pooling at the injection site. It should be noted that the i.p. dosing studies, as well as the other low dose studies reviewed for this assessment, suffer from an absence of dose verification data. That is, there are no analytical data presented to allow verification that the dosing solutions contained the target doses, nor are there any studies with radiolabelled material proving that the animals received the intended doses. For the purposes of this assessment it has been assumed that the animals received the doses stated by the authors of the various papers, while it is recognized that this cannot be verified without supplementary data. Based on these arguments and after careful review of the study reports it has been concluded that the effects observed at the dose of 0.001 mg/kg/d can be attributed to the disruption of the hypothalamus-pituitary axis and that these findings are relevant to the assessment of human exposure through ingestion. It should also be noted that the studies by Wenger et al. are repeat dosing studies and as such may carry more weight than the single dose studies.

No experimental data on neuroendocrine effects based on dermal application of cannabinoids in animals or humans were available. Dermal application of THC would be expected to result in slower systemic exposure than with other routes, with no first pass effect. Since the extent of absorption is considered in this risk assessment through adjustment of administered dose to calculate delivered dose, and the data strongly indicate that the adverse effects of THC are similar regardless of dose route, it can be concluded that any dose route that does not result in a first pass effect should be more relevant than the oral route for extrapolation to humans exposed dermally. It is probable that i.v. dosing would lead to more rapid increases in plasma concentrations than would dermal dosing. It is not known how the rates of absorption of i.p. versus s.c. versus dermal dosing would compare. Although, it is possible that using data from studies that employed a dose route that resulted in faster systemic absorption could underestimate the risk from dermal exposure to THC. This is because THC acts by a receptor-dependent mechanism which exhibits a biphasic dose-response. Thus there is an optimum intracellular concentration at which maximal neuroendocrine disruption would occur. Slow absorption could lead to prolongation of the low concentrations that could lead to maximal disruption and also could lead to increased potential for relatively more of the administered dose to be sequestered into adipose tissue for later release. It should also be noted that none of the available studies provides a dosing model that mimics the human situation of total body application or immersion. Overall it can be concluded that there is a great deal of

uncertainty surrounding the selection of an appropriate animal model from which to extrapolate for use in human dermal risk assessment.

In the interest of conservatism and in the absence of any strong scientific evidence favouring the selection of data from any of the available dose routes, the i.p. dosing studies have been selected for use in this risk assessment with respect to neuroendocrine disruption.

4.1.6 Interspecies Extrapolation

Generally it is preferred to use data on blood concentrations to facilitate extrapolation of dose-response information from animals to humans. This removes a degree of uncertainty that exists due to the potential species differences in absorption, metabolism and disposition that may influence the relationship between administered and delivered doses. In the case of THC it is not possible to consider blood concentrations in relation to effects since the effects are caused by the combined effects of THC and its major metabolite 11-OH-THC and do not correlate with the blood concentration of THC. For example, after oral administration in humans the "high" was associated with a blood THC concentration of 0.02 ng/ml, while after i.v. administration the "high" was associated with a blood THC concentration of 2 ng/ml, indicating a significant contribution of metabolite to the psychoactivity after oral dosing (Harvey, 1991). It would theoretically be possible for the total blood concentration of THC plus 11-OH-THC to be used in interspecies extrapolation; however, lack of data on steady state kinetics precludes the use of this approach. Dose-response information used for human health risk assessment in this report is considered on the basis of administered dose.

The data on effects reported in humans in response to marihuana use are not suitable for direct use in the assessment of risks from the use of industrial hemp-based foods, cosmetics or nutraceuticals because the doses from smoking are unknown, the influence of smoking-related factors cannot be considered and pharmacokinetics and metabolism of THC are different after smoking compared to oral and presumably dermal exposure. The types of effects noted in humans are listed here to illustrate that similar effects of cannabinoid exposure have been observed in both animals and humans, thus providing support for the use of data from studies using animal models under controlled exposure conditions for extrapolation in human health risk assessment. Effects that have been associated with marihuana use in humans that are not related to psychoactive effects include adverse effects on endocrine and reproductive parameters in males and females, immune suppression, and neurocognitive deficits in the offspring of mothers who used the drug during

pregnancy (Cabral and Dove Pettit, 1998; Day et al., 1994; Edmondson, 1985; Fried and Watkinson, 1988; Griffith et al., 1994; Hollister, 1986; Klein et al., 1998a; Klein et al., 1998b; Lee, 1998; Little et al., 1992; Maykut, 1985; Mendelson et al., 1986; Mendelson et al., 1985b; Richardson et al., 1993; Tennes, 1984; Vescovi et al., 1992). These are all effects that have been associated with neuroendocrine disruption (Crisp et al., 1997). Similar effects of THC and other cannabinoids on neuroendocrine and reproductive parameters observed in humans have been reported in monkeys, rats and mice.[43] Deficits in visual attention were observed in 1- and 2-year old monkeys after perinatal exposure (Golub et al., 1982). Similarly in humans poorer abstract/visual reasoning was noted in 3-year olds who had been exposed to marihuana *in utero* and during lactation (Day et al., 1994; Griffith et al., 1994)and in a group of neonates there was an association between maternal marihuana use and poorer habituation to visual stimuli (Fried, 1980; Tansley et al., 1986).

Exposure to THC in female rodents has been shown to delay estrus and/or alter cycle lengths after repeated administration (Field and Tyrey, 1984; Kostellow et al., 1980; O'Connell et al., 1987; Wenger et al., 1988). These effects were observed at oral doses of as low as 1 mg/kg/d (Kostellow et al., 1980; O'Connell et al., 1987). Similar effects on estrus cycle and ovulation as were seen in rodents have been observed in monkeys treated with THC (Asch et al., 1981; Smith et al., 1983). Marihuana smoking has been found to affect menstrual cycle length and endocrine hormone levels in humans (Bauman, 1980; Dornbush et al., 1978; Mendelson et al., 1986; Mendelson et al., 1985a; Mendelson et al., 1985b).

In addition to there being similarities in effects among species, major metabolic pathways have been found to be essentially the same in all species studied, including humans (Bornheim et al., 1995). Distribution of THC to the brain, the fetus and to breast milk appears to be similar among rodents and primates.[44] As well, cannabinoid receptor distribution in the brain was found to be similar among species, including humans (Herkenham, 1991; Pertwee, 1997). In dogs and monkeys there is evidence that 11-OH-THC does not cross the blood brain barrier and is not produced from THC in the fetus (Bailey et al., 1987; Martin et al., 1977).

Given the similarities between animals and humans in types of response, cannabinoid receptor distribution, metabolism, tissue distribution and pharmacokinetics, the weight of available evidence supports the use of

[43] see Annex I, Appendix A, Tables A-2.2-1, A-3.2-1, A-5.1.1-1, A-5.2-1 and Sections A-5.3 and A-5.4 for summaries of many animal studies.

[44] see Annex I, Section 2.1.3.4 and Annex I, Appendix A, Section A-1.3 for details of tissue distribution studies

interspecies extrapolation from animal data for the purposes of human health risk assessment. It should be noted, however, that there are no data on the relative sensitivities of animals versus humans with respect to cannabinoid-induced neurological disruption, nor are there data to demonstrate the predictive validity of the rat model used in the studies by Wenger et al. from which the LOEL was derived.

4.1.7 Cannabinoids Other Than THC

The majority of the data discussed above pertains to THC, since other cannabinoids have been studied less extensively or not at all. It is recognized that, while THC is the major psychoactive component of marihuana, other components certainly contribute to the psychoactivity and pharmacological activity as well (Carlini et al., 1974). In addition, data indicate that non-psychoactive cannabinoids can cause effects on neuroendocrine, reproductive and/or immune system parameters (Baczynsky and Zimmerman, 1983a; Baczynsky and Zimmerman, 1983b; Dalterio, 1980; Dalterio and deRooij, 1986; Dalterio and Bartke, 1979; Dalterio et al., 1984a; Dalterio et al., 1984b; Desoize et al., 1981; Kaminski, 1998; Murphy et al., 1990a; Nahas et al., 1977; Newton et al., 1993; Patra and Wadsworth, 1991; Smith et al., 1997; Steger et al., 1990; Tilak and Zimmerman, 1984; Zuardi et al., 1993).[45] Thus the absence of psychoactivity for a cannabinoid or the absence of psychoactivity at a low dose does not imply absence of potential toxicity. THC is not the only active principle in marihuana, or by extension, in food, nutraceutical or cosmetic products produced from Cannabis sativa. Insufficient data exist for rigourous assessment of the potential impacts of other cannabinoids in humans.

Contradictory results of the influence of CBD and CBN on metabolism and pharmacokinetics of THC have been reported.[46] Insufficient data exist to allow the integration of data on the potential influence of other cannabinoids on the actions of THC into the current human health risk assessment.

Given the structural similarities among THC, CBN and CBD and the similarities in their pharmacokinetics and metabolism (see Section 4.1.2) it is reasonable to assume that the oral and dermal absorption and potential to

[45] Studies of neuroendocrine disruption of other cannabinoids are summarized in Annex I, Table 2.5.1-1 and 2.5.4.5-1; acute toxicity studies are discussed in Annex I, Appendix A, Section 2.2.2 and genotoxicity studies are discussed in Annex I, Appendix A, Section 2.6.2.

[46] See Annex I, Section 2.1.3 for a discussion of the potential interaction between cannabinoids.

cross the blood brain barrier and potential for fetal transfer and transfer to infants through breast milk would be similar for all three cannabinoids. The potential for transfer of CBD across the blood brain barrier has been demonstrated experimentally (Bornheim et al., 1995). No data on the toxicity, pharmacokinetics or metabolism of other natural cannabinoids were identified in the literature.

Data are not available to allow adequate characterization of the dose-response relationship of other cannabinoids; however, there have been comparisons made among the effects of THC, CBN and CBD (Dalterio et al., 1982; Dalterio et al., 1984a; Dalterio et al., 1984b; Murphy et al., 1990a; Patra and Wadsworth, 1991; Steger et al., 1990; Zimmerman et al., 1979). An evaluation of the various comparisons supports the conclusion that both CBN and CBD have the potential to cause adverse neuroendocrine and reproductive effects and that CBN is equipotent with THC in many parameters and more potent in some measures.[47]

Overall the data suggest that CBN is as potent as THC in inducing neuroendocrine and reproductive effects, while CBD is less potent. It is not possible to consider the possible interactions among the various cannabinoids for this assessment.

4.1.8 Carcinogenesis Assessment

[47] See Annex I, Section 2.11.2 for a discussion of the comparative toxicity of THC and other cannabinoids, and see Annex I, Table 2.5.4.4-1 for a summary of studies comparing the effects of THC and other cannabinoids on neuroendocrine and reproductive parameters.

Three long term animal carcinogenicity studies have been conducted with THC. One of these studies reported tumours at the injection site, the lung and the adrenal cortex after s.c. injection at a dose of 20 ug/mouse (0.8 mg/kg/d for a 25g mouse) for life (Szepsenwol et al., 1980). The methods and results of this study were not fully reported and no incidence or pathology data are given. No increased tumour incidences were observed in 2-year rat cancer study conducted by NTP (1996).[48] In a 2-year mouse study, thyroid tumour incidence was statistically significantly increased in the low dose group and a reverse dose-response was observed for follicular cell hyperplasia, adenoma an neoplasia (NTP, 1996). Hormone levels were not measured in mice, but rats in a companion study treated at lower doses showed evidence of endocrine disruption. Endocrine disruption has been reported in the literature in mice exposed to THC at lower doses than were used in the NTP study (see Table 4.1.4.2-1). Since endocrine disruption is a known cause of thyroid follicular cell tumours in rodents and since biphasic dose-response relationships have been observed for many effects of THC (Dewey, 1986), it seems likely that the thyroid tumours in THC-treated mice were related to treatment. In addition the possibility that thyroid tumour incidence may be greater at even lower doses cannot be ruled out. Increased tumour incidences were not observed in other tissues in rats or mice treated with THC for 2 years (NTP, 1996). The doses used in the mouse study were well above the doses of THC that could be potentially experienced by humans, even through marihuana smoking, and thyroid tumours did not develop in rats exposed to lower doses. There has been no reported epidemiological evidence of increased incidences of thyroid tumours among marihuana smokers, although this potential association has not been specifically examined. For these reasons it seems unlikely that THC poses a thyroid tumour risk in humans; however the possibility cannot be excluded entirely without further study.

Three case control studies have implicated maternal marihuana use with cancer in offspring. The types of cancer under investigation in these studies were astrocytoma (Kuitjen et al., 1992), rhabdomyosarcoma (Grufferman et al., 1993) and nonlymphoblastic leukemia (Robison et al., 1989). None of these studies can be considered to provide conclusive evidence of causality.[49]

It is not expected that epidemiology studies would be able to prove a link between human cancer and exposure to marihuana or cannabinoids, even if such a link did exist. This is because of the difficulty in addressing the

[48] The methods and results of the NTP study are discussed in detail in Annex I, Section 2.4.2.

[49] Human epidemiology studies suggesting an association between maternal marihuana use and cancer in offspring are discussed in more detail in Annex I, Section 2.9.

potential impacts of confounding factors and the difficulty in obtaining accurate exposure information. According to an editorial in the Journal of the National Cancer Institute, "It has taken over half a century to prove that tobacco causes human cancers and to provide sufficient evidence to convince the public" (Mao and Oh, 1998). The tobacco case had reliable and abundant exposure data, where these data are difficult to obtain for marihuana given its status as an illicit drug.

Evidence from genotoxicity studies suggests that THC would not be carcinogenic through a genotoxic mechanism.[50] Among the effects considered to be possibly caused in humans by exposure to endocrine disrupting chemicals are breast cancer in women, prostate and testicular cancer in men (Crisp et al., 1997). No studies of these types of cancers have been conducted in humans exposed to cannabinoids. The most plausible mechanism for carcinogenesis of cannabinoids is through secondary effects of endocrine disruption; therefore, to protect the public from a hypothetical cancer risk, exposure must be kept below the threshold for endocrine disruption.

4.2 Results - Exposure Assessment

4.2.1 Results - Exposure Assessment - Foods Made with Industrial Hemp Materials

In food production, industrial hemp may be used in the following forms:

- industrial hemp seed (often roasted);
- industrial hemp nut (dehulled seed);
- industrial hemp seed meal (the pressed hemp seed remaining after oil extraction);
- industrial hemp flour (made from seed);
- industrial hemp milk [e.g. seed/nut is soaked in water, blended in blender (optional) and strained through cheese cloth]; and
- industrial hemp flowers and leaves (used as a flavour in drinks and pastilles).

Consequently, a wide variety of foods can be made with industrial hemp materials (Table 4.2.1-1) for which the relative percentages (%v/v) of industrial hemp ingredients in foods have been summarized based on hemp food recipes[51] .

[50] Genotoxicity studies are summarized in Annex I, Appendix A, Section A-6-1.

[51] For a discussion of foods made from industrial hemp see Annex I, Section 3.6.3

The relative amounts of ingredients derived from industrial hemp in foods selected for assessment are presented in Table 4.2.1-2.

Table 4.2-1: Food Ingredients and Foods Made of Industrial Hemp

Ingredients	**Ice cream/ Frozen deserts Made with Industrial Hemp Ingredients**
	Hemp-Scream
Industrial Hemp Flour (substitute for other flours)	**Salad Dressings and Sauces Made with Industrial Hemp Ingredients**
Industrial Hemp Oil	Salad dressings
Industrial Hemp Seeds (substitute for flour and other nuts/seeds e.g. sunflower seeds)	Mayonnaise
Industrial Hemp Milk (substitute for milk)	Sauces, such as tahini sauce and pesto sauce
Baked Goods Made with Industrial Hemp Ingredients	**Milk and Dairy Substitutes Made with Industrial Hemp Ingredients**
Brownies, cakes, muffins	Butter
Cookies, rice-crispie-like squares	Milk
Pies	Cheese
Breads	Yogurt
Quick Breads Made with Industrial Hemp Ingredients	Other fermented milk products (e.g. sour cream, yop)
Pancakes	**Hot Cereal Made with Industrial Hemp Ingredients**
Pizza crust	Cream of Wheat, porridge, oatmeal
Main Course Made with Industrial Hemp Ingredients	**Candy Made with Industrial Hemp Ingredients**
Loafs, casseroles (e.g. meat loaf; veggie loaf)	Chocolate nut bars; healthy bars
Burgers	Dried fruit and nut bars; granola-type bars
Soup	
Roast	**Snack food Made with Industrial Hemp Ingredients**
Pasta	Pretzels (hempzels)

Table 4.2-1: Food Ingredients and Foods Made of Industrial Hemp

Beverages Made with Industrial Hemp Ingredients	Trail mix; shelled roasted nuts, such as sunflower; granola-type cereal or sundae topping
fruit drinks and lemonades	**Hot drinks Made with Industrial Hemp Ingredients**
Beer, Wine	Coffee, Hot chocolate
Energy drinks (e.g. Boost)	

Table 4.2.1-2: Relative Amounts of Industrial Hemp Ingredients in Foods Selected for Assessment

Hemp Food/ Food Group[a]	% Hemp Oil[b]	% Hemp Seed[b]	% Hemp Meal[b]	% Hemp Nut[b]
Breads		10 to 25 %[e]		
Cakes, Cookies, Pastries and Pies		10 to 25 % seed or flour		
Cakes, Cookies, Pastries and Pies		3 %	7 %	
Cakes, Cookies, Pastries and Pies				10 %
Pancakes, Quick Breads		12 to 25 %		
Pancakes, Quick Breads			17 %	
Hot Cereal		25 %		
Pasta	0.3 %	47.7 %		
Burgers		10 to 15 %		
Loafs	3 %	22 %		
Loafs		15 %		
Loafs			10 %	
Salad Dressings	72 %			
Salad Dressings		2 %		
Salad Dressings			5 %	

Table 4.2.1-2: Relative Amounts of Industrial Hemp Ingredients in Foods Selected for Assessment

Hemp Food/ Food Group[a]	% Hemp Oil[b]	% Hemp Seed[b]	% Hemp Meal[b]	% Hemp Nut[b]
Salad Dressings	5 %	21 %		
Salad Dressings	31 %			
Salad Dressings				12 %
Sauces	10%			
Sauces		99%		
Sauces	19%	8%		
Mayonnaise	72 %			
Cheese		80%		
Yogurt		80%[d]		
Soup		10 %		
Milk and Milk Drinks		8 to 23 %		
Milk and Milk Drinks	4 %	17 % flour		
Milk and Milk Drinks				23 %
Milk/Frozen Deserts		10 to 80 %[e]		
Milk/Frozen Deserts				23 %[j]
Snacks:				
Hempzels, Crackers		10 to 25 %[f]		
Nuts and Seeds		50 to 100%		
Nuts and Seeds				50 to 100%
Candy		25 to 80 %		
Beverages:				
Fruit Drinks		1 to 10 %[g]		
Energy Drinks		10 to 25 %[h]		
Beer		<5 ng THC/ml[i]		
Wine		<5 ng THC/ml[j]		
Coffee		5 to 10 %[k]		

[a] based on hemp foods identified in Table 3.6-1.
[b] as determined according to hemp recipes summarized in Table 3.6-2.
[c] assumed the hemp content to be the same as other baked goods (i.e., cookies, cakes, and pies).
[d] assumed the hemp content to be similar to hemp cheese.
[e] assumed the hemp content to be similar to cheese and milk.
[f] assumed the hemp content to be similar to quick breads.
[g] no data; assumed hemp content to be 1%.
[h] assumed to be similar to milk and milkshakes.
[i] measured data (Commercial Brewery of Hemp Beer, personal communication)
[J] assumed the hemp content to be similar to that of hemp beer.
[k] hemp seeds are mixed with coffee beans; assumed hemp content was 1 %.

4.2.1.1 Calculated Consumption Equal to the LOEL for Acute Neurological Impairment

The calculated consumption expressed in grams of foods made with industrial hemp ingredients (oil, seeds, meal and nut) containing 10 ug THC/g[52], that when consumed would be equal to the single dose LOEL of 70 ug THC/kg body weight/day for acute neurological impairment for the adult female, adult male and child are presented tables Tables 4.2.1.1-1 to 4.2.1.1-3, respectively. The estimated THC content in hemp foods was directly proportional to the relative percent of industrial hemp ingredients which is reflected in the calculated hemp food consumption amount for each consumer.

Hemp beer is made using the hemp seed meal as a flavouring ingredient (Hemp Brewery, personal communication). Hemp seed meal consists of the hemp seed material that is left-over after all the oil has been extracted. The beer is further processed prior to bottling. Given the lipophilic characteristic of THC, any THC in the seed meal and or unfinished beer would be expected to partition to the organic/ fatty phase and therefore would not be expected to be present in finished beer. Analytical data for hemp beer support this hypothesis, since non-detectable levels of THC were reported for hemp at a analytical detection limit of 5 ng/ml. The calculated consumption of hemp beer by the adult female and adult male was determined assuming a THC concentration in the finished product of equal to or one-half the detection limit of 5 ng/ml. No data was available on THC content of hemp wines. Assuming concentrations would be similar to those determined for hemp beer, the calculated consumption of wine equal to the LOEL for neurological impairment in humans would also be similar.

Tables 4.2.1.1-1 to 4.2.1.1-3 also include a comparison of the calculated consumption (g) per food/food group equivalent to the LOEL for acute neurological impairment of THC with the mean daily intake (g/day) for the adult female or adult male (Nutrition Canada, personal communication) per food/food group, and the mean daily intake (g/day) for the child (5 to 11 years) [1994-1996 data of the Continual Survey of Food Intakes by Individuals (CSFII), U.S. Dept. of Agriculture], and “per serving size” of foods/food groups according to commercial food labels. This comparison provides a frame of reference with respect to realistic quantities that could be consumed in a single serving or day.

[52] Or 10 ppm the Canadian limit for THC in industrial hemp raw materials and products made from industrial hemp; see Annex I, Section 3.6.1

Table 4.2.1.1-1: Adult Female: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Female: Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Adult Female: Mean Daily Intake[e] (g/d)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Breads	0%	10 - 25 %	0%	0%	1767 - 4417	55.72	90 g (2 slices)
Cookies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	1767 - 4417		30 g or two 15 g cookies
Cakes, Cookies, Pastries and Pies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	1767 - 4417	113.86	28 - 83 g (brownie/cake mix)
Pancakes, Quick Breads	0%	0 - 25 %	0 - 17%	0%	1767 - 2598	94.01	32 g (2 pancakes)
Hot Cereal	0%	25 %	0%	0%	1767	39.40	30 g (1/3 cup)
Pasta	0.3 %	48 %	0%	0%	920	215.12	85 g
Burgers	0%	10 - 15 %	0%	0%	2945 - 4417	98.87	114 g (1/4 lb)
Loafs	0 - 3 %	0 -22 %	0 - 10%	0%	1767 - 2598	98.87[g]	na
Salad Dressings	0 -72 %	0 - 21%	0 - 5%	0 - 12%	613 - 22,085	18.48	15 ml (1TBSP)
Sauces	0 - 19%	0 - 99%	0%	0%	448 - 4417	24.65	na
Hemp Mayonnaise	0 -72 %	0%	0%	0%	616	18.48[h]	na

Table 4.2.1.1-1: Adult Female: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Female: Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Adult Female: Mean Daily Intake[e] (g/d)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Hemp Cheese	0%	80%	0%	0%	553	30.97	na
Hemp Yogurt	0%	80%	0%	0%	553	146.61	175 g (yogurt cup)
Soup	0%	10 %	0%	0%	4417	136.85	250 ml
Hemp Milk and Hemp Milk Drinks	0%	0 - 23 %	0%	0-23%	1918 - 5523	83.14	250 ml (8oz cup)
Hemp Milk/Frozen Deserts	0%	0 - 80 %	0%	0 - 23%	553 - 4417	93.28	125 ml
<u>Snacks:</u>							
Hempzels, Crackers	0%	10 - 25 %	0%	0%	1767 - 4417	41.63	17 - 28 g (crackers, approx. 9 pretzels, 11 chips)
Nuts and Seeds	0%	50 - 100%	0%	50 -100%	442 - 883	15.7	na
Candy	0%	25 - 80%	0%	0%	553 - 1767	23.48	32 -64 g (candy bar)
<u>Beverages:</u>							

Table 4.2.1.1-1: Adult Female: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Female: Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Adult Female: Mean Daily Intake[e] (g/d)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Fruit Drinks	0%	1%	0%	0%	44170	316.83	250 ml (8 oz cup)
Energy Drinks	0%	10 - 25 %	0%	0%	1767 - 4417	39.69	250 ml (8 oz cup)
Coffee	0%	1%	0%	0%	44170	536.67	250 ml (8 oz cup)

[a]see Sections 3.2.4, 4.1.4.1 and 4.1.5.1 of this report
[b]based on hemp foods identified in Table 3.6-1.
[c] determined from hemp recipes, see section 3.6.3, Table 3.6-3 and Annex II.
[d]assuming hemp oil, hemp seed, hemp meal and hemp nut used contained 10 ug THC/g; equivalent to the "defacto limit' of < 10 ug THC/g hemp materials.
[e] most recent Nutrition Canada data (Bob Hills, Health Canada, personal communication)
[f] as specified on package labels of commercial food products.
[g] assume daily intake to be the same as burgers
[h]assume daily intake is the same as that of salad dressing.
na - no data available for "serving size"

Table 4.2.1.1-2: Adult Male: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]	Adult Male: Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Adult Male: Mean Daily intake[e] (g/kg)	"serving size"[f]

	% Hemp Oil	**% Hemp Seed**	**% Hemp Meal**	**% Hemp Nut**			
Breads	0%	10 - 25 %	0%	0%	2205 - 5516	55.72	90 g (2 slices)
Cookies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	2205 - 5516		30 g or two 15 g cookies
Cakes, Cookies, Pastries and Pies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	2205 - 5516	113.86	28 - 83 g (brownie/cake mix)
Pancakes, Quick Breads	0%	0 - 25 %	0 - 17%	0%	2205 - 3245	94.01	32 g (2 pancakes)
Hot Cereal	0%	25 %	0%	0%	2205	39.40	30 g (1/3 cup)
Pasta	0.3 %	48 %	0%	0%	1148	215.12	85 g
Burgers	0%	10 - 15 %	0%	0%	3675 - 5516	98.87	114 g (1/4 lb)
Loafs	0 - 3 %	0 -22 %	0 - 10%	0%	2205 - 5516	98.87[g]	na
Salad Dressings	0 -72 %	0 - 21%	0 - 5%	0 - 12%	763 - 27580	18.48	15 ml (1TBSP)
Sauces	0 - 19%	0 - 99%	0%	0%	560 - 5516	24.65	na
Hemp Mayonnaise	0 -72 %	0%	0%	0%	763	18.48[h]	na
Hemp Cheese	0%	80%	0%	0%	693	30.97	na
Hemp Yogurt	0%	80%	0%	0%	693	146.61	175 g (yogurt cup)
Soup	0%	10 %	0%	0%	5516	136.85	250 ml

Table 4.2.1.1-2: Adult Male: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Male: Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Adult Male: Mean Daily intake[e] (g/kg)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Hemp Milk and Hemp Milk Drinks	0%	0 - 23 %	0%	0-23%	2401 - 6895	83.14	250 ml (8 oz cup)
Hemp Milk/Frozen Deserts	0%	0 - 80 %	0%	0 - 23%	693 - 5516	93.28	125 ml
Snacks:							
Hempzels, Crackers	0%	10 - 25 %	0%	0%	2205 - 5516	41.63	17 -28 g (crackers, approx 9 pretzels, 11 chips)
Nuts and Seeds	0%	50 - 100%	0%	50 -100%	553 - 1103	15.7	na
Candy	0%	25 - 80%	0%	0%	693 - 2205	23.48	32 - 64 g (candy bar)
Beverages:							
Fruit Drinks	0%	1%	0%	0%	55160	316.83	250 ml (8 oz cup)
Energy Drinks	0%	10 - 25 %	0%	0%	2205 - 5516	39.69	250 ml (8 oz cup)

Table 4.2.1.1-2: Adult Male: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Male: Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Adult Male: Mean Daily intake[e] (g/kg)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Coffee	0%	1%	0%	0%	55160	536.67	250 ml (8 oz cup)

[a]see Sections 3.2.4, 4.1.4.1 and 4.1.5.1 of this report
[b]based on hemp foods identified in Table 3.6-1.
[c] determined from hemp recipes, see section 3.6.3, Table 3.6-3 and Annex II.
[d]assuming hemp oil, hemp seed, hemp meal and hemp nut used contained 10 ug THC/g; equivalent to the "defacto limit' of < 10 ug THC/g hemp materials.
[e] most recent Nutrition Canada data (Bob Hills, Health Canada, personal communication)
[f] as specified on package labels of commercial food products.
[g] assume daily intake to be the same as burgers
[h]assume daily intake is the same as that of salad dressing.
na - no data available for "serving size"

Table 4.2.1.1-3: Child (5 to 11 years): Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological Impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Child (5 to 11 years): Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Child (5 to 11 years): Mean Daily intake[e] (g/kg)	" serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Breads	0%	10 - 25 %	0%	0%	921 - 2303	56	90 g (2 slices)
Cookies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	921 - 2303 (or 61 cookies)		30 g or two 15 g cookies
Cakes, Cookies, Pastries and Pies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	921 - 2303	64	28 - 83 g (brownie/cake mix)
Pancakes, Quick Breads	0%	0 - 25 %	0 - 17%	0%	921 - 1358	58	32 g (2 pancakes)
Hot Cereal	0%	25 %	0%	0%	921	19.7[g]	30 g (1/3 cup)
Pasta	0.3 %	48 %	0%	0%	483	141	85 g

Table 4.2.1.1-3: Child (5 to 11 years): Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological Impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Child (5 to 11 years): Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Child (5 to 11 years): Mean Daily intake[e] (g/kg)	" serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Burgers	0%	10 - 15 %	0%	0%	1533 - 2303	134	114 g (1/4 lb)
Loafs	0 - 3 %	0 -22 %	0 - 10%	0%	921 - 2303	134[h]	na
Salad Dressings	0 -72 %	0 - 21%	0 - 5%	0 - 12%	322 - 11515	14	15 ml (1TBSP)
Sauces	0 - 19%	0 - 99%	0%	0%	231 - 2303	12.3[i]	na
Hemp Mayonnaise	0 -72 %	0%	0%	0%	322	14[j]	na
Hemp Cheese	0%	80%	0%	0%	287	34	na
Hemp Yogurt	0%	80%[i]	0%	0%	287	118	175 g (yogurt cup)
Soup	0%	10 %	0%	0%	2303	68.4[k]	250 ml

Table 4.2.1.1-3: Child (5 to 11 years): Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological Impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Child (5 to 11 years): Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Child (5 to 11 years): Mean Daily intake[e] (g/kg)	" serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Hemp Milk and Hemp Milk Drinks	0%	0 - 23 %	0%	0-23%	1001 - 2877	410	250 ml (8 oz cup)
Hemp Milk/Frozen Deserts	0%	0 - 80 %	0%	0 - 23%	287 - 2303	110	125 ml
Snacks:							
Hempzels, Crackers	0%	10 - 25 %	0%	0%	921 - 2303	33	17 - 28 g (crackers, approx. 9 pretzels, 11 chips)
Nuts and Seeds	0%	50 - 100%	0%	50 -100%	230 - 462	24	na

Table 4.2.1.1-3: Child (5 to 11 years): Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological Impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Child (5 to 11 years): Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Child (5 to 11 years): Mean Daily intake[e] (g/kg)	" serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Candy	0%	25 - 80%	0%	0%	287 - 921	33	32 - 64 g (candy bar)
Beverages:							
Fruit Drinks	0%	1%	0%	0%	23030 - 57575	336	250 ml (8 oz cup)
Energy Drinks	0%	10 - 25 %	0%	0%	921 - 2303	19.8[l]	250 ml (8 oz cup)
Coffee	0%	1%	0%	0%	23030	150	250 ml (8 oz cup)

Table 4.2.1.1-3: Child (5 to 11 years): Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the Single Dose LOEL for Acute Neurological Impairment[a] of 70 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Child (5 to 11 years): Calculated Consumption[d] (grams) of hemp food equal to 70 ug THC/kg body weight/day	Child (5 to 11 years): Mean Daily intake[e] (g/kg)	" serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			

[a]see Sections 3.2.4, 4.1.4.1 and 4.1.5.1 of this report
[b]based on hemp foods identified in Table 3.6-1.
[c] determined from hemp recipes, see section 3.6.3, Table 3.6-3 and Annex II.
[d]assuming hemp oil, hemp seed, hemp meal and hemp nut used contained 10 ug THC/g; equivalent to the "defacto limit' of < 10 ug THC/g hemp materials.
[e] most recent Nutrition Canada data (Bob Hills, Health Canada, personal communication)
[f] as specified on package labels of commercial food products.
[g] assume daily intake of child is 50% of adult daily intake
[h]assume daily intake is the same as that of burgers.
[i]assume daily intake is 12 g/d or 50% of adult daily intake of sauces which is similar to the value of 13 g/d child daily intake of fats and oils (CSFII 1996 -1997 data).
[J]assume daily intake to be the same as that of salad dressing.
[k]assume daily soup intake is 50% of adult daily intake.
[l]assume child daily intake of energy drinks is 50% of adult intake.
na -no data available for "serving size"

Results of the exposure analysis for the adult female, adult male and child consumers of foods made with industrial hemp ingredients indicated that exposures to THC through consumption of "serving size" and mean daily intake would not be expected to exceed the LOEL for acute neurological impairment of 70 ug/kg body weight/day. These results in terms of the potential for health risks are discussed further in Section 5.0 Risk Characterization.

4.2.1.2 Calculated Consumption Equal to the LOEL for Neuroendocrine Effects

The calculated consumption expressed in grams of foods made with industrial hemp ingredients (oil, seeds, meal and nut) containing 10 ug THC/g[53] that when consumed would be equal to the LOEL of 1 ug THC/kg body weight/day for neuroendocrine disruption are presented for the adult female, adult male and child in Tables 4.2.1.2-1 to 4.2.1.2-3. The calculated THC content in hemp foods was directly proportional to the relative percent of industrial hemp ingredients which is reflected in the calculated hemp food consumption amount for each consumer.

The calculated consumption of hemp beer by the adult female was determined assuming a THC concentration in the finished product of equal to or one-half the detection limit of 5 ng/ml. The calculated consumption of hemp beer equal to the LOEL for neuroendocrine disruption was >13 kg for adult females. No data were available on THC content of hemp wines. Assuming concentrations would be similar to those determined for hemp beer, the calculated consumption of wine would also be similar.

Also included in Tables 4.2.1.2 -1 to 4.2.1.2 -3 are data for the mean daily intake (g/day) per food/food group of the adult female and the adult male (Nutrition Canada, personal communication), and of the child (5 to 11 years old) [1994-1996 data of the Continual Survey of Food Intakes by Individuals (CSFII), U.S. Dept. of Agriculture], and the "serving size" of foods/food groups according to commercial food labels. This comparison provides a frame of reference with respect to realistic quantities that could be consumed in a single serving or day.

Table 4.2.1.2-1: Adult Female: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the LOEL for Neuroendocrine Disruption[a] of 1 ug THC /kg body weight/day

[53] Or 10 ppm the Canadian limit for THC in industrial hemp raw materials and products made from industrial hemp; see Annex I, Section 3.6.1

Hemp Food/ Food Group[b]	**% Hemp Ingredients Content**[c]				**Adult Female: Calculated Consumption**[d] **(grams) of hemp food equal to 1 ug THC/kg body weight/day**	**Adult Female: Mean Daily Intake**[e] **(g/d)**	**"serving size"**[f]
	% Hemp Oil	**% Hemp Seed**	**% Hemp Meal**	**% Hemp Nut**			
Breads	0%	10 - 25 %	0%	0%	25.24 - 63.1	55.72	90 (2 slices)
Cookies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	25.24 - 63.1		30 g or two 15 g cookies
Cakes, Cookies, Pastries and Pies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	25.24 - 63.1	113.86	28 to 83 g (brownie/cake mix pkg)
Pancakes, Quick Breads	0%	0 - 25 %	0 - 17%	0%	25.24 - 37.12	94.01	32 g (2 pancakes)
Hot Cereal	0%	25 %	0%	0%	25.24	39.40	30 g (1/3 cup)
Pasta	0.3 %	48 %	0%	0%	13.15	215.12	85 g
Burgers	0%	10 - 15 %	0%	0%	42.17 - 63.1	98.87	114 g (1/4 lb)
Loafs	0 - 3 %	0 -22 %	0 - 10%	0%	25.24 - 63.1	98.87[g]	na
Salad Dressings	0 -72 %	0 - 21%	0 - 5%	0 - 12%	8.76 - 315.5	18.48	15 ml (1TBSP)
Sauces	0 - 19%	0 - 99%	0%	0%	6.37 - 63.1	24.65	na
Hemp Mayonnaise	0 -72 %	0%	0%	0%	8.76	18.48[h]	na
Hemp Cheese	0%	80%	0%	0%	7.89	30.97	na

Table 4.2.1.2-1: Adult Female: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the LOEL for Neuroendocrine Disruption[a] of 1 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Female: Calculated Consumption[d] (grams) of hemp food equal to 1 ug THC/kg body weight/day	Adult Female: Mean Daily Intake[e] (g/d)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Hemp Yogurt	0%	80%	0%	0%	7.89	146.61	175 g (yogurt cup)
Soup	0%	10 %	0%	0%	63.1	136.85	250 ml
Hemp Milk and Hemp Milk Drinks	0%	0 - 23 %	0%	0-23%	27.43 - 78.88	83.14	250 ml (8 oz cup)
Hemp Milk/Frozen Deserts	0%	0 - 80 %	0%	0 - 23%	7.89 - 63.1	93.28	125 ml
Snacks:							
Hempzels, Crackers	0%	10 - 25 %	0%	0%	25.24 - 63.1	41.63	17 - 28 g (crackers, approx. 9 pretzels, 11 chips)
Nuts and Seeds	0%	50 - 100%	0%	50 -100%	6.31 - 12.62	15.7	na
Candy	0%	25 - 80%	0%	0%	7.89 - 25.24	23.48	32 - 64 g (candy bar)
Beverages:							

Table 4.2.1.2-1: Adult Female: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the LOEL for Neuroendocrine Disruption[a] of 1 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Female: Calculated Consumption[d] (grams) of hemp food equal to 1 ug THC/kg body weight/day	Adult Female: Mean Daily Intake[e] (g/d)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Fruit Drinks	0%	1%	0%	0%	631	316.83	250 ml (8 oz cup)
Energy Drinks	0%	10 - 25 %	0%	0%	25.24 - 63.1	39.69	250 ml (8 oz cup)
Coffee	0%	1%	0%	0%	631	536.67	250 ml (8 oz cup)

[a] see Sections 3.2.4, 4.1.4.2 and 4.1.5.1 of this report
[b] based on hemp foods identified in Table 3.6-1.
[c] determined from hemp recipes, see section 3.6.3, Table 3.6-3 and Annex II.
[d] assuming hemp oil, hemp seed, hemp meal and hemp nut used contained 10 ug THC/g; equivalent to the "defacto limit' of < 10 ug THC/g hemp materials.
[e] most recent Nutrition Canada data (Bob Hills, Health Canada, personal communication)
[f] as specified on package labels of commercial food products.
[g] assume daily intake to be the same as burgers
[h] assume daily intake is the same as that of salad dressing.
na - no data available for "serving size"

Table 4.2.1.2-2: Adult Male: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materi LOEL for Neuroendocrine Disruption[a] of 1 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Male: Calculated Consumption[d] (grams) of hemp food equal to 1 ug THC/kg body weight/day	Adult M Mean D Intake (g/kg
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut		
Breads	0%	10 - 25 %	0%	0%	31.52 - 78.8	55.72
Cookies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	31.52 - 78.8 (2 - 5 cookies)	
Cakes, Cookies, Pastries and Pies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	31.52 - 78.8	113.8
Pancakes, Quick Breads	0%	0 - 25 %	0 - 17%	0%	31.52 - 46.35	94.01
Hot Cereal	0%	25 %	0%	0%	31.52	39.40
Pasta	0.3 %	48 %	0%	0%	16.4	215.1
Burgers	0%	10 - 15 %	0%	0%	52.53 - 78.8	98.87
Loafs	0 - 3 %	0 -22 %	0 - 10%	0%	31.52 - 78.8	98.87
Salad Dressings	0 -72 %	0 - 21%	0 - 5%	0 - 12%	10.94 - 394	18.48
Sauces	0 - 19%	0 - 99%	0%	0%	7.96 - 78.8	24.65
Hemp Mayonnaise	0 -72 %	0%	0%	0%	10.9	18.48
Hemp Cheese	0%	80%	0%	0%	9.85	30.97
Hemp Yogurt	0%	80%	0%	0%	9.85	146.6
Soup	0%	10 %	0%	0%	78.8	136.8
Hemp Milk and Hemp Milk Drinks	0%	0 - 23 %	0%	0-23%	34.26 - 98.5	83.14
Hemp Milk/Frozen Deserts	0%	0 - 80 %	0%	0 - 23%	9.85 - 78.8	93.28
Snacks:						
Hempzels, Crackers	0%	10 - 25 %	0%	0%	31.52 - 78.8	41.63

Table 4.2.1.2-2: Adult Male: Calculated Consumption (grams) of Foods Made with Industrial Hemp Materi LOEL for Neuroendocrine Disruption[a] of 1 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Adult Male: Calculated Consumption[d] (grams) of hemp food equal to 1 ug THC/kg body weight/day	Adult M Mean D Intak (g/kg
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut		
Nuts and Seeds	0%	50 - 100%	0%	50 -100%	7.88 - 15.76	15.7
Candy	0%	25 - 80%	0%	0%	9.85 - 31.52	23.48
Beverages:						
Fruit Drinks	0%	1%	0%	0%	788	316.8
Energy Drinks	0%	10 - 25 %	0%	0%	31.52 - 78.8	39.69
Coffee	0%	1%	0%	0%	788	536.6

[a]see Sections 3.2.4, 4.1.4.2 and 4.1.5.1 of this report
[b]based on hemp foods identified in Table 3.6-1.
[c] determined from hemp recipes, see section 3.6.3, Table 3.6-3 and Annex II.
[d]assuming hemp oil, hemp seed, hemp meal and hemp nut used contained 10 ug THC/g; equivalent to the "defacto limit' of < 10 ug THC/g hemp materials.
[e] most recent Nutrition Canada data (Bob Hills, Health Canada, personal communication)
[f] as specified on package labels of commercial food products.
[g] assume daily intake to be the same as burgers
[h]assume daily intake is the same as that of salad dressing..
na - no data available for "serving size"

Table 4.2.1.2-3: Child (5 to 11 years): Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the LOEL for Neuroendocrine Disruption [a] of 1 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Child (5 to 11 years): Calculated Consumption[d] (grams) of hemp food	Child (5 to 11years): Mean Daily intake[e] (g/d)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Breads	0%	10 - 25 %	0%	0%	13.16 - 32.9	56	90 g (2 slices)
Cookies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	13.16 - 32.9 (1 to 2 cookies)		30 g or two 15 g cookies
Cakes, Cookies, Pastries and Pies	0%	0 - 25 % seed or flour	0 - 7%	0 - 10%	13.16 - 32.9	64	28 to 83 g brownie/cake
Pancakes, Quick Breads	0%	0 - 25 %	0 - 17%	0%	13.16 - 19.35	58	32 g (2 pancakes)
Hot Cereal	0%	25 %	0%	0%	13.16	19.7[g]	30 g (1/3 cup)
Pasta	0.3 %	48 %	0%	0%	6.85	141	85 g
Burgers	0%	10 - 15 %	0%	0%	21.93 - 32.9	134	114 g (1/4 lb)
Loafs	0 - 3 %	0 -22 %	0 - 10%	0%	13.16 - 32.9	134[h]	na
Salad Dressings	0 -72 %	0 - 21%	0 - 5%	0 - 12%	4.57 - 164.5	14	15 ml (1TBSP)
Sauces	0 - 19%	0 - 99%	0%	0%	3.32 - 32.9	12.3[i]	na
Hemp Mayonnaise	0 -72 %	0%	0%	0%	4.57	14[j]	na
Hemp Cheese	0%	80%	0%	0%	4.11	34	na

Table 4.2.1.2-3: Child (5 to 11 years): Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the LOEL for Neuroendocrine Disruption [a] of 1 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Child (5 to 11 years): Calculated Consumption[d] (grams) of hemp food	Child (5 to 11years): Mean Daily intake[e] (g/d)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Hemp Yogurt	0%	80%[i]	0%	0%	4.11	118	175 g (yogurt cup)
Soup	0%	10 %	0%	0%	32.9	68.4[k]	250 ml
Hemp Milk and Hemp Milk Drinks	0%	0 - 23 %	0%	0-23%	14.3 - 41.13	410	250 ml (8 oz cup)
Hemp Milk/Frozen Deserts	0%	0 - 80 %	0%	0 - 23%	4.11 - 32.9	110	125 ml
Snacks:							
Hempzels, Crackers	0%	10 - 25 %	0%	0%	13.16 - 32.9	33	17 -28 g (crackers, approx.9 pretzels, 11 chips)
Nuts and Seeds	0%	50 - 100%	0%	50 -100%	3.29 - 6.58	24	na
Candy	0%	25 - 80%	0%	0%	4.11 - 13.16	33	32 - 64 g (candy bar)

Table 4.2.1.2-3: Child (5 to 11 years): Calculated Consumption (grams) of Foods Made with Industrial Hemp Materials Equivalent to the LOEL for Neuroendocrine Disruption [a] of 1 ug THC /kg body weight/day

Hemp Food/ Food Group[b]	% Hemp Ingredients Content[c]				Child (5 to 11 years): Calculated Consumption[d] (grams) of hemp food	Child (5 to 11years): Mean Daily intake[e] (g/d)	"serving size"[f]
	% Hemp Oil	% Hemp Seed	% Hemp Meal	% Hemp Nut			
Beverages:							
Fruit Drinks	0%	1%	0%	0%	329	336	250 ml (8 oz cup)
Energy Drinks	0%	10 - 25 %	0%	0%	13.16 - 32.9	19.8[l]	250 ml (8 oz cup)
Coffee	0%	1%	0%	0%	329	150	250 ml (8 oz cup)

a amount of hemp food consumed equal to 1 ug THC/kg body weight/day see Sections 3.2.4, 4.1.4.2 and 4.1.5.1 of this report
[b]based on hemp foods identified in Table 3.6-1.
[c] determined from hemp recipes, see section 3.6.3, Table 3.6-3 and Annex II.
[d]assuming hemp oil, hemp seed, hemp meal and hemp nut used contained 10 ug THC/g; equivalent to the "defacto limit' of < 10 ug THC/g hemp materials.
[e] most recent Nutrition Canada data (Bob Hills, Health Canada, personal communication)
[f] as specified on package labels of commercial food products.
[g] assume daily intake of child is 50% of adult daily intake
[h]assume daily intake is the same as that of burgers.
[i]assume daily intake is 12 g/d or 50% of adult daily intake of sauces which is similar to the value of 13 g/d child daily intake of fats and oils (CSFII 1996 -1997 data).
[J]assume daily intake to be the same as that of salad dressing.
[k]assume daily soup intake is 50% of adult daily intake.
[l]assume child daily intake of energy drinks is 50% of adult intake.
na - no data available for "serving size".

Through a comparison of the Calculated Consumption Equal to the LOEL for Neuroendocrine Disruption for foods made with industrial hemp ingredients with 10ppm THC against values for "serving size" reported on labels of commercial foods (Tables 4.2.1.2-1 to 4.2.1.2-3), foods were identified that could be expected to result in THC exposures of the consumer in excess of the 1 ug/kg body weight/day LOEL. All foods/food groups for which information for a "serving size" was identified would be expected to result in dietary exposures of THC greater than the LOEL for neuroendocrine disruption in animals, assuming all raw ingredients derived from industrial hemp contain 10 ppm THC. The only exception was for the 78.8 kg adult male, for which consumption of cookies, pancakes, hot cereal and hempzles in "serving size"quantities would equal or approach the LOEL for neuroendocrine disruption. No data were identified for "serving sizes" of the following food groups loafs, sauces, mayonnaise, cheese and nuts and seeds; consumption of these foods by the adult female, adult male and child could likely meet or exceed the LOEL for neurodendocrine effects on the basis of a comparison of the calculated consumption levels of these foods with respective values for mean daily intake.

4.2.2 Results - Exposure Assessment - Cosmetics and Personal Care Products Containing Industrial Hemp Oil

Details of the scenarios selected for assessment of exposure to THC through the use of cosmetics and personal care products made with industrial hemp oil are provided in Annex I, Section 3.7 and have been summarized in Annex I, Section 3.7, Table 3.7-1. Estimated exposures of the adult female, adult male and child to THC through the use of cosmetics and personal care products made with industrial hemp oil, expressed as the daily internal dose of ug THC/kg body weight/day, are presented in Tables 4.2.2-1a to 4.2.2-3a, respectively. The total estimated exposure to THC through the use of multiple cosmetics and personal care products made with hemp oil was determined by the sum of the estimated exposures for the single product exposure scenarios for the maximum and minimum exposures based on application rates and percent hemp oil content of product formulations (Tables 4.2.2-1b to 4.2.2-3b).

Table 4.2.2-1a: Estimated Internal Dose of THC (ug/kg body weight/day) in Adult Female Through Use of Cosmetics and Personal Care Products Containing Industrial Hemp Oil[a]

Product Type	Amount Used	% Hemp Oil in Product	Application Rate g/m^2	Adult Female Internal Dose[b] ug/kg/day (dermal exposure)
hand lotion, moisturizer	2 ml	4%	23.5	0.0084
		10%	23.5	0.021
body moisturizer/ body lotion	3.5 g	4%	3.22	0.013
		10%	3.22	0.033
massage oil	5 ml	6%	3.1	0.0022
		100%	3.1	0.037
massage oil	10 ml	6%	6.2	0.0045
		100%	6.2	0.075
bath oil[c]	15 ml	6%	NA	9.7×10^{-5}
		100%	NA	0.0016
soap[c] (hand washing)	2.6 g	1%	30.6	2.8×10^{-5}
soap[c] (body washing)	2.6	1%	1.6	2.8×10^{-5}
shampoo[c]	16.4 g	0.5%	81.2	1.2×10^{-4}
		1%	81.2	2.4×10^{-4}
conditioner[c]	12.4 g	1%	61.4	4.5×10^{-5}
		3%	61.4	1.4×10^{-4}
sunscreen	3.18 g	2%	3.22	0.0066
		10%	3.22	0.033
lip balm	0.015 g	10%	13.6	0.00059
body milk	5 ml	4%	5.1	0.01
		10%	5.1	0.026
body milk	10 ml	4%	10.1	0.021
		10%	10.1	0.052

Table 4.2.2-1a: Estimated Internal Dose of THC (ug/kg body weight/day) in Adult Female Through Use of Cosmetics and Personal Care Products Containing Industrial Hemp Oil[a]

Product Type	Amount Used	% Hemp Oil in Product	Application Rate g/m^2	Adult Female Internal Dose[b] ug/kg/day (dermal exposure)
creme (face)	2 ml	5%	34.1	0.0052
		10%	34.1	0.01
salve	0.01 g	10%	25	0.00021
		75%	25	0.0016
salve	0.02 g	10%	25	0.00042
		75%	25	0.0031

[a]For details of each exposure scenario refer to Annex I, Section 3.7,Table 3.7-3; detailed calculations of dermal exposure assuming dermal absorption of 33%, 1% and 100% are provided in Annex I - Appendix C.

[b]estimated exposures for intact healthy skin assuming a dermal absorption of 33% and the concentration of THC in hemp oil= 10 ppm; to estimate THC exposure for damaged skin conditions, apply a factor of x2 to these values estimated for exposure of healthy skin.

[c]estimated exposure was adjusted by x10 from values in Annex I - Appendix C based on the observation that dermal permeability was increased 10-fold in the presence of water (see Annex I, Section 3.5 and Annex I -Appendix A, Section A.1.1.1.2).

NA - not applicable

Table 4.2.2-1b: Estimated Exposure of Adult Female to THC through Combined Daily Use of Cosmetics and Personal Care Products Made with Industrial Hemp Oil

Concentration of THC in Industrial Hemp Oil[a] (ug/ml)	Adult Female Estimated Total Daily Intake of THC (ug/kg body weight/d)	
	Minimum[b] Estimated	Maximum[c] Estimated
10	0.047	0.23

[a] assuming total THC (ug/g) in hemp oil equals Canadian limit for industrial hemp.
[b] Calculated as the sum total of the estimated daily internal dose (ug/kg bw/d) for each product category, corresponding to scenarios on a per product basis of the lesser amount used, lesser % hemp oil in product and a dermal absorption of 33%, to represent the minimum estimated combined exposure related to use for the exposure scenarios assessed.
[c] Calculated as the sum total of the estimated daily internal dose (ug/kg bw/d) for each product category, corresponding to scenarios on a per product basis of the greater amount used, greater % hemp oil in product and a dermal absorption of 33%, to represent the maximum estimated combined exposure related to use for the exposure scenarios assessed.

Table 4.2.2-2a: Estimated Internal Dose of THC (ug/kg body weight/day) in Adult Male Through Use of Cosmetics and Personal Care Products Containing Industrial Hemp Oil[a]

Product Type	Amount Used	% Hemp Oil in Product	Application Rate g/m^2	Adult Male Internal Dose[b] ug/kg/day
hand lotion, moisturizer	2 ml	4%	20.6	0.0067
		10%	20.6	0.017
body moisturizer/ body lotion	3.5 g	4%	2.9	0.011
		10%	2.9	0.027
massage oil	5 ml	6%	2.8	0.0018
		100%	2.8	0.03
massage oil	10 ml	6%	5.6	0.0036
		100%	5.6	0.06
bath oil[c]	15 ml	6%	NA	8.7×10^{-5}
		100%	NA	0.0014
soap[c] (hand washing)	2.6 g	1%	26.8	2.3×10^{-5}
soap[c] (body washing)	2.6	1%	1.4	2.3×10^{-5}
shampoo[c]	16.4 g	0.5%	67.2	9.6×10^{-5}
		1%	67.2	1.9×10^{-6}
conditioner[c]	12.4 g	1%	50.8	3.6×10^{-5}
		3%	50.8	1.1×10^{-5}
sunscreen	3.18 g	2%	3.22	0.0053
		10%	3.22	0.027
lip balm	0.015 g	10%	12.5	0.00047
body milk	5 ml	4%	4.5	0.0084
		10%	4.5	0.021
body milk	10 ml	4%	9.1	0.017
		10%	9.1	0.042
creme (face)	2 ml	5%	27.4	0.0042

Table 4.2.2-2a: Estimated Internal Dose of THC (ug/kg body weight/day) in Adult Male Through Use of Cosmetics and Personal Care Products Containing Industrial Hemp Oil[a]

Product Type	Amount Used	% Hemp Oil in Product	Application Rate g/m^2	Adult Male Internal Dose[b] ug/kg/day
		10%	27.4	0.0084
salve	0.01 g	10%	25	0.00017
		75%	25	0.0013
salve	0.02 g	10%	50	0.00034
		75%	50	0.0025

[a]For details of each exposure scenario refer to Annex I, Section 3.7, Table 3.7-3; detailed calculations of dermal exposure assuming dermal absorption of 33%, 1% and 100% are provided in Annex I - Appendix C.
[b]estimated exposures for intact healthy skin assuming a dermal absorption of 33% and the concentration of THC in hemp oil= 10 ppm; to estimate THC exposure for damaged skin conditions, apply a factor of x2 to these values estimated for exposure of healthy skin.
[c]estimated exposure was adjusted by x10 from values in Annex I - Appendix C based on the observation that dermal permeability was increased 10-fold in the presence of water (see Annex I, Section 3.5 and Annex I -Appendix A, Section A.1.1.1.2).
NA - not applicable.

Table 4.2.2-2b: Estimated Exposure of Male Adult to THC through Combined Daily Use of Cosmetics and Personal Care Products Made with Industrial Hemp Oil

Concentration of THC in Hemp Oil[a] (ug/ml)	Adult Male Estimated Total Daily Intake of THC Related to Combined Use of Cosmetic/Personal Care Products Made with Industrial Hemp (ug/kg body weight/d)	
	Minimum[b] Estimated	Maximum[c] Estimated
10	0.038	0.19

[a] assuming total THC (ug/g) in hemp oil equals Canadian limit for industrial hemp.
[b] Calculated as the sum total of the estimated daily internal dose (ug/kg bw/d) for each product category, corresponding to scenarios on a per product basis of the lesser amount used, lesser % hemp oil in product and a dermal absorption of 33%, to represent the minimum estimated combined exposure related to use for the exposure scenarios assessed.
[c] Calculated as the sum total of the estimated daily internal dose (ug/kg bw/d) for each product category, corresponding to scenarios on a per product basis of the greater amount used, greater % hemp oil in product and a dermal absorption of 33%, to represent the maximum estimated combined exposure related to use for the exposure scenarios assessed.

Table 4.2.2-3a: Estimated Internal Dose of THC (ug/kg body weight/day) in the Child (5 to 11 years) Through Use of Cosmetics and Personal Care Products Containing Industrial Hemp Oil[a]

Product Type	Amount Used	% Hemp Oil in Product	Application Rate g/m^2	Child[b] (5 to 11 years) Internal Dose ug/kg/day
hand lotion, moisturizer	2 ml	4%	42.6	0.016
		10%	42.6	0.04
body moisturizer/ body lotion	3.5 g	4%	6.2	0.026
		10%	6.2	0.064
massage oil	5 ml	6%	5.4	0.0043
		100%	5.4	0.072
massage oil	10 ml	6%	10.7	0.0086
		100%	10.7	0.14
bath oil[c]	15 ml	6%	NA	1.1×10^{-4}
		100%	NA	0.0018
soap[c] (hand washing)	2.6 g	1%	55.3	5.5×10^{-5}
soap[c] (body washing)	2.6	1%	2.6	5.5×10^{-5}
shampoo[c]	16.4 g	0.5%	92.1	2.3×10^{-4}
		1%	92.1	4.6×10^{-4}
conditioner[c]	12.4 g	1%	69.7	8.6×10^{-5}
		3%	69.7	2.6×10^{-4}
sunscreen	3.18 g	2%	6.2	0.013
		10%	6.2	0.064
lip balm	0.015 g	10%	27	0.031
body milk	5 ml	4%	9.7	0.02
		10%	9.7	0.05
body milk	10 ml	4%	19.5	0.04
		10%	19.5	0.1
creme (face)	2 ml	5%	30.8	0.01

Table 4.2.2-3a: Estimated Internal Dose of THC (ug/kg body weight/day) in the Child (5 to 11 years) Through Use of Cosmetics and Personal Care Products Containing Industrial Hemp Oil[a]

Product Type	Amount Used	% Hemp Oil in Product	Application Rate g/m^2	Child[b] (5 to 11 years) Internal Dose ug/kg/day
		10%	30.8	0.02
salve	0.01 g	10%	25	0.0002
		75%	25	0.0015
salve	0.02 g	10%	50	0.0004
		75%	50	0.003

[a]For details of each exposure scenario refer to Annex I, Section 3.7, Table 3.7-3; detailed calculations of dermal exposure assuming dermal absorption of 33%, 1% and 100% are provided in Annex I - Appendix C.
[b]estimated exposures for intact healthy skin assuming a dermal absorption of 33% and the concentration of THC in hemp oil= 10 ppm; to estimate THC exposure for damaged skin conditions, apply a factor of x2 to these values estimated for exposure of healthy skin.
[c]estimated exposure was adjusted by x10 from values in Annex I - Appendix C based on the observation that dermal permeability was increased 10-fold in the presence of water (see Section 3.5 and Annex I -Appendix A, Section A.1.1.1.2).
NA - not applicable.

Table 4.2.2-3b: Estimated Exposure of the Child (5 to 11 years) to THC through Combined Daily Use of Cosmetics and Personal Care Products Made with Industrial Hemp Oil

Concentration of THC in Hemp Oil[a] (ug/ml)	Child (5 to 11 years) Estimated Total Daily Intake of THC Related to Combined Use of Industrial Hemp Cosmetic/Personal Care Products (ug/kg body weight/d)	
	Minimum[b] Estimated	Maximum[c] Estimated
10	0.12	0.47

[a]assuming total THC (ug/g) in hemp oil equals Canadian limit for industrial hemp.
[b] Calculated as the sum total of the estimated daily internal dose (ug/kg bw/d) for each product category, corresponding to scenarios on a per product basis of the lesser amount used, lesser % hemp oil in product and a dermal absorption of 33%, to represent the minimum estimated combined exposure related to use for the exposure scenarios assessed.

[c] Calculated as the sum total of the estimated daily internal dose (ug/kg bw/d) for each product category, corresponding to scenarios on a per product basis of the greater amount used, greater % hemp oil in product and a dermal absorption of 33%, to represent the maximum estimated combined exposure related to use for the exposure scenarios assessed.

Exposure of the infant to THC through the use of personal care products (i.e. body lotions, and soaps) was not estimated as no baby products containing industrial hemp oil were identified. However, exposure (ug THC/kg body weight/day) of the infant through use of the products selected for assessment would be greater than those estimated for the child due to the lower body weight of the infant, 8.2 kg versus 32.9 kg, respectively.[54]

4.2.3 Results - Exposure Assessment - Nutraceuticals Made from Industrial Hemp Oil

The estimated exposures to THC of the female adult, male adult and child (5 to 11 years old) related to nutraceutical use are presented in Table 4.2.3-1 below.

Table 4.2.3-1: Estimated Exposure to THC Related to Use of Nutraceuticals of Industrial Hemp Oil[a]

Consumer	Amount Ingested (ml) per Treatment	Body Weight (kg)	Internal Dose of THC[b] ug/kg bw/day
Adult Female	15 -60	63.1	2.4 - 9.5
Adult Male	15-60	78.8	1.9 - 7.6

[54] see Section 3.2 1 of this report and Annex I, Section 3.4.2, Table 3.4-1.

Child (5 to 11 years)	15-60	32.9	4.6 - 18.2

[a] assumed a THC concentration in industrial hemp oil of 10 ppm (the Canadian limit).
[b] assumed one dose per day.

4.2.4 Results - Exposure Assessment - Adolescent and Teenagers

Teenagers generally consume greater quantities of various foods, particularly snack foods than other age groups (Bull, 1992). As some of the more commercially available hemp foods fall into the category of snack foods, teenagers may be also expected to consume these types of foods. Although the quantity of food consumed by teenagers may be greater than that of children, it is unlikely that the daily intake on a per body weight basis would be greater due to the larger size of the teenager compared to the child. It is noteworthy that teenagers may tend to embrace fads or "new styles" more readily than other ages. Teens empowered with their own ability to select and purchase "trendy foods, treats and products" may thus be attracted to the "cannabis nature" of industrial hemp products and could plausibly consume and use with greater frequency products made with industrial hemp materials than the average child (5 to 11years) and adult.

4.2.5 Results - Exposure Assessment - Exposure of Infant Through Breast Milk

There is evidence, from both human and animal data, that THC is transferred via breast milk to the nursing infant.[55] This consistent with the lipophilic nature of this chemical. No direct study of the relationship between THC consumption and concentrations in breast milk in humans was identified. Infant

[55] See Annex I - Appendix A, Section A.1.3.5.

exposure to THC in breast milk may correspond to breast milk lipid (fat) content which is known to be variable and is dependent on maternal factors including diet (food and liquid intake), metabolism, fat stores, as well as the duration and frequency of nursing.

The available data do not allow quantification of cannabinoid exposure of the infant through breast milk. Although the potential for THC exposure of the infant through maternal use of industrial hemp products containing THC is certain. It should also be noted that due to the capacity of THC and other cannabinoids to be stored in fat, it is possible that exposure to the infant through breast milk could bear little relationship to recent exposures of the mother. Mobilization of cannabinoids that have accumulated over time with repeated exposure could result in much higher concentrations in breast milk than would be predicted based on acute exposure.

5.0 RISK CHARACTERIZATION

5.1 Approach

The traditional risk assessment approach of developing a tolerable daily intake (TDI) based on application of uncertainty factors to the NOEL (or LOEL) from experimental studies and comparing the TDI with the estimated exposure was not used for this assessment. The high degree of uncertainty in the data did not allow the confident assignment of uncertainty factors and development of a TDI (see Section 5.7 for a discussion of sources of uncertainty). It was not considered possible to develop a TDI because of the absence of a threshold in the observed effects in animal and human studies, the lack of data from chronic exposure studies and lack of data on the effects of other cannabinoids.

As a result of the difficulties involved in attempting to develop a TDI for THC and other cannabinoids, the approach taken in this risk characterization was to compare the results of the exposure assessment for cosmetic products, food and nutraceuticals with the LOELs for neuroendocrine disruption in pregnant rat and prepubescent rat and the LOEL for acute neurological impairment (as evidenced by decrements in performance measures) in humans. The exposure estimates (see Section 4.2) were compared with the following:

- LOEL of 70 ug THC /kg for acute neurological impairment (as evidenced by decrements in performance measures) in humans based on single oral dose in adult marihuana users (Chesher et al., 1990); and,

- LOEL of 1 ug THC /kg/d for neuroendocrine changes in pregnant rat (Wenger et al., 1991) and permanent reproductive system changes in rats exposed peripubertally (Wenger et al., 1988).

The direct comparison of exposure results with the LOELs does not give consideration to a number of factors as listed below:

For neurological impairment based on the LOEL from an acute dose-response study in humans:

- no consideration was given to the bioaccumulative potential of THC with repeated dosing;
- no consideration was given to the fact that the NOEL has not been identified;
- no consideration was given to the potential that some individuals may be more sensitive than the adult marihuana users who were the subjects of the study that yielded the LOEL of 70 ug/g; and,
- no consideration was given to the potential for neurological impairment of other cannabinoids that would be present in industrial hemp-based products.

For neuroendocrine disruption based on the LOEL from a subchronic rat study:

- no consideration was given to the bioaccumulation potential of THC under the long term exposure conditions that would exist for humans;
- no consideration was given to the fact that the dose-response relationship has not been adequately characterized and no studies have indicated where the No Observed Effect Level might lie;
- no consideration was made for the possibility that humans could be more sensitive than rats or that some individuals could be more sensitive (see Section 5.5 for a discussion of sensitive populations); and,
- no consideration was given to the potential for neurological impairment of other cannabinoids that would be present in industrial hemp-based products.

Conclusions regarding potential risks based on the direct comparison of the LOELs with the exposure results must be tempered by the uncertainties inherent in such a comparison based on the above.

The impact on other cannabinoids is addressed in a less rigourous approach than was used for THC, since there are no dose-response data and no specific exposure data (see Section 5.6).

5.2 Estimate of Food Consumption Associated With LOEL Values

Data were unavailable to allow estimation of the extent to which industrial hemp-based foods might come to replace traditional foods in Canada. This precluded the estimate of exposure to THC through food consumption expressed as an internal dose (ug/kg body weight/d). In order to avoid using an arbitrary assumption of the amount of foods made from industrial hemp that might be eaten, the approach taken to the exposure assessment through food was to estimate the amount of food from each food category that would need to be consumed in order for an individual to be exposed to the amount of THC at the LOEL. The calculated consumption amounts in grams represent the estimates associated with the Canadian guideline for THC in industrial hemp products of $\leq$ 10 ug/g. This was done for the LOEL of 70 ug/kg for neurological impairment in humans and for the LOEL of 1 ug/kg/d for neuroendocrine disruption in animals.

5.2.1 Food Consumption Associated With Neurological Impairment NOEL

Food consumption estimates associated with the neurological impairment LOEL of 70 ug/kg/d were presented in Section 4.2.1.1, Tables 4.2.1.1-1 to 4.2.1.1-3. The data are shown graphically in Figure 2 for the child consumer only, since children would be able to consume less than adults before reaching the LOEL of 70 ug/kg. The estimated amount of each type of food that would lead to exposure at the LOEL is compared with a standard serving, or mean daily intake.. Based on this analysis it would seem unlikely that an individual could consume sufficient quantities of industrial hemp-based foods to cause neurological impairment. In the case of the child, the data for some foods bears further analysis, since amounts that could reasonably be consumed could exceed the threshold for neurological impairment and psychoactivity (see Table 5.2-1).

Table 5.2-1: Summary of Food Consumption Levels by Children That Would be Equivalent to the LOEL for Neurological Impairment (70 ug/kg) or Psychoactivity (140 ug/kg)

Hemp Food	No. of Servings to Give THC Dose of 70 ug/kg	No. of Servings to Give THC Dose of 140 ug/kg
Yogurt	1.64 175 g hemp yogurt cups[a]	3.2 175 g hemp yogurt cups
Milk	4 glasses of hemp milk	8 glasses of hemp milk
Frozen desserts	2.3 125 ml ice cream- type bars	4.6 125 ml ice cream-type bars
Candy bars	4.5 64g candy bars	9 64g candy bars

[a] Sample calculation: 10 ug THC/g x 80% hemp seed in yogurt x 287 g yogurt consumed/ 32.9 kg bw = 70 ug THC/kg BW

It must be stressed that currently these products are not widely available in Canada and it is not known to what extent food products made with industrial hemp will replace traditional products. The analysis in Table 5.2-1 provides an indication that if THC was present at a concentration of 10 ug/g in such products as yogurt, milk and ice cream, it would be possible that a child could consume enough in one day, or even in one sitting (i.e. yogurt and ice cream bars) to experience exposures sufficient to cause acute neurological impairment or psychoactive effects. A child weighing less than the 32.9 kg used in this assessment could consume proportionately less of these foods. For example a five year old weighing 20 kg could be expected to experience neurological impairment after consuming one 175 ml yogurt cup. These types of foods could also conceivably be fed to infants or toddlers. A comparison of the"serving size" with the 95th percentile daily food intake for children (5 to 11 years)[56] per food group illustrates that some children could be expected to consume quantities of food in excess of the "serving sizes" used in the assessment.

It is concluded on the basis of this assessment that consumption of some food products made with ingredients from industrial hemp, particularly in the case of children, may be associated with a risk of neurological impairment and psychoactivity.

This conclusion does not apply to hemp beer or hemp wine, as discussed in Section 4.2.1.1.

5.2.2 Food Consumption Associated With Neuroendocrine LOEL

Food consumption estimates associated with the neuroendocrine LOEL of 1 ug/kg/d were presented in Section 4.2.1.2, Tables 4.2.1.2-1 to 4.2.1.2-3. The data are shown graphically in Figure 3 for the child consumer only. The estimated amount of each type of food that would lead to exposure at the LOEL is compared with a standard serving, or mean daily intake. These data show that consumption of very low quantities of many of the food types would provide a dose of THC of 1 ug/kg/d or greater. The possibility that an individual could consume food from more than one category of food on a daily basis is not considered, due to uncertainties in estimating combined food intakes. If an individual were to consume more than one type of industrial hemp-

[56] See Annex I, Section 3.6.4, Table 3.6.4-1

based food, then smaller amounts of each would result in a combined exposure to the LOEL of 1 ug/kg/d THC. Since the amounts of the majority of foods made from industrial hemp ingredients that would deliver a dose of THC equal to the NOEL for neuroendocrine disruption are less than the mean daily intake, or"serving size" for these food groups (see Section 4.2.1.2, Table 4.2.1.2-4), it is concluded that these foods could pose a human health risk with respect to neuroendocrine disruption.

Consumption estimates for beer that could be associated with exposure at the LOEL were on the order of 1000-fold greater than likely consumption levels. This estimate was prepared based on the assumption that THC concentration in beer was half the detection limit, since none was detected. It is not expected that THC or other lipophilic cannabinoids would remain in the aqueous phase during beer preparation, so it is likely that this represents an underestimate of consumption that would result in a THC dose at the LOEL. It is considered unlikely that cannabinoids in beer are present at sufficient levels to constitute a risk of adverse health effects in adult males or non-pregnant females. The same may be true for wine, but no data were available on measured concentrations of THC or manufacturing processes.

5.3 Comparison of Exposure Through Cosmetic Use With LOEL Values

Exposure estimates (mean and maximum estimate) for THC are compared with LOELs for neuroendocrine disruption and neurological impairment as discussed in Section 5.0. These comparisons are shown in Figure 4 for cosmetics. The exposure estimates used in these comparisons were extracted from Tables 4.2.2-1a to 4.2.2-3a and 4.2.2-1b to 4.2.2-3b, presented in Section 4.2.2. These data represent the estimates associated with the Canadian guideline for THC in industrial hemp products of $\leq$ 10 ug/g. These exposure estimates for hemp cosmetic and personal care products (with the exception of salves) were based on the assumption of that products would be applied to healthy intact skin. Application of salves to compromised skin (i.e. eczematous, chapped, abraded) was estimated assuming an increased dermal absorption of 2-fold.[57] It was noted in Annex I, Section 3.7.1 that many of the skin care products are advertised for use on very dry skin. The exposure estimates for products other than salves applied to healthy skin (presented in the tables) were based on a dermal absorption of 33%, a value that was based on the best available data, but which could represent an overestimate or underestimate (see Table 5.6-1 for a list of uncertainties). If the dermal absorption was as low as 1% this would result in 33 times lower exposure. If the dermal exposure was as high as 100% then the exposure would be 3 times greater than estimated.

[57] See Section 3.2.3.2 of this report and Annex I, Section 3.5.2 for a discussion of the basis for the statement that absorption is 2-times greater in damaged skin compared to normal skin.

5.3.1 Exposure Through Cosmetics Associated With Neurological Impairment LOEL

The maximum estimated exposure for an adult is within about 350-fold of the acute neurological impairment LOEL for humans (see Figure 4). The maximum estimated exposure for a child is within about 125-fold of the acute neurological impairment LOEL for humans (see Figure 4). Although the estimated exposures to THC are below the LOEL, a definitive conclusion about the likelihood that this suggests a lack of risk of neurological impairment cannot be made because of the uncertainties listed in Section 5.1. It is concluded on the basis of the current assessment that it is unlikely there could be a risk of neurological impairment through the use of cosmetic products made with industrial hemp oil, but that this possibility cannot be excluded with complete confidence, particularly for children and infants due to the limitation of the data at hand.

5.3.2 Exposure Through Cosmetics Associated With Neuroendocrine LOEL

The estimated exposures are all within about 10 times below the LOEL of 1 ug/kg/d THC(see Figure 4). Although the estimated human exposures are below the LOEL for neuroendocrine disruption in animals, this does not support a conclusion that there is no risk to humans at these exposure levels. This is because direct comparison of the human exposure estimates with the animal LOEL does not consider several uncertainties as outlined in Section 5.1. Consideration of these various uncertainties through application of uncertainty factors would result in the conclusion that there would likely be a risk of neuroendocrine disruption associated with the use of industrial hemp-based cosmetics, particularly in children, infants and developing fetus through maternal use.

5.4 Comparison of Exposure Through Nutraceutical Use With LOEL Values

Exposure estimates for THC are compared with LOELs for neuroendocrine disruption and neurological impairment . The exposure estimates used in these comparisons were extracted from Table 4.2.3-1 in Section 4.2.3 and represent the estimates associated with the Canadian guideline for THC in industrial hemp products of $\leq$ 10 ug/g. Comparisons of exposure estimates with the LOELs for the adult and child consumer are shown in Figure 5.

5.4.1 Exposure Through Nutraceuticals Associated With Neurological Impairment LOEL

For a child, the mean and maximum estimated exposures are within 4-15 fold of the LOEL for acute neurological impairment, with exposures in adults being about 50% less (see Figure 5). Although the estimated exposure levels for THC are less than the LOEL for neurological impairment, a definitive conclusion about the likelihood that this suggests a lack of risk of neurological impairment cannot be made because of the uncertainties listed in Section 5.1. It is concluded on the basis of the current assessment that there could be a risk of neurological impairment through the use of industrial hemp-based nutraceuticals, particularly for a child.

5.4.2 Exposure Through Nutraceuticals Associated With Neuroendocrine LOEL

The exposure to THC from the minimum estimated dose exceeded the LOEL for neuroendocrine disruption for both the adult and child consumers (see Figure 5). These results support the conclusion that nutraceuticals at the doses assessed would likely pose a human health risk with respect to neuroendocrine disruption.

figure 2 - food neuroendocrine

figure 3 - food neurological

figure 4 - cosmetics - old fig 2

Figure 5 - nutraceuticals - old fig 3

5.5 Sensitive Populations

Three groups have been identified as being particularly sensitive to the adverse effects of THC. These are pregnant women (because of fetal exposure), nursing infants and children (prepubertal and pubertal). Pregnant women and nursing infants are expected to be more sensitive because of the potential for greater exposure to the developing infant and fetus than can be estimated based on administered dose. The reasons for this expectation that relative sensitivity could be greater in the infant and fetus are as follows:

- The fetus and newborn infant have much less body fat then adults and so less cannabinoid can be sequestered in fat and therefore would remain available in circulation to interact with the target site(s).
- Cannabinoids are extensively bound to lipoprotein (Harvey, 1984; Hunt and Jones, 1980); the fetus and infant have much less blood lipoprotein, so there is less potential for cannabinoid binding and thus more freely available cannabinoid for receptor binding (McNamara et al., 1991; McNamara et al., 1992).
- The hepatic microsomal enzyme system is immature in the infant and fetus, so THC would be metabolized slowly, increasing the effective exposure duration (Asch and Smith, 1986).
- Infants and fetus (human studies) have been reported to have a greater density of brain cannabinoid binding sites so greater disruption could occur at a lower dose (Glass et al., 1997).
- Tissues and biological systems in the fetus and infant are undergoing development and growth, and during this period are most sensitive to perturbations affecting neuroendocrine dependent processes (Crisp, 1997).
- Chronic exposure to an extremely lipophilic substance like THC would be expected to result in accumulation in fat over time with slow release back to circulation. This slow release could affect exposure to the fetus after a long period of prepregnancy dosing in the mother.
- The production of milk would result in mobilization of lipid stores and transfer to milk of THC and other lipophilic cannabinoids that had accumulated over time in fat. Exposure to the infant during lactation could be much higher if the mother had been chronically exposed as opposed to having received only a few doses of THC.

In addition, it has been hypothesized that an increase in dermal absorption of chemicals occurs during pregnancy because of physiologically increased skin hydration and blood flow (Mattison, 1990), which could contribute to greater maternal exposure and subsequent exposure of the developing fetus than indicated by the estimated exposure of the adult female. On the other hand, increased body fat and metabolic changes occurring during pregnancy could mitigate the hypothesized increase in dermal absorption and subsequent fetal exposure

but which would later be transferred to the newborn through breast milk. No data are available to define the effects of pregnancy on cannabinoid storage or metabolism.

In animal studies, the manifestation of perinatal endocrine disruption has been observed to include behaviour changes, reduced sensitivity to morphine and reproductive system disturbances. In the human male, development and regulation of testicular function begins *in utero*, during the earliest stages of pregnancy under the influence of hypothalamus-pituitary function (Hembree et al., 1975). This raises concern about the potential for exposure to the developing fetus to agents that may disturb the hypothalamus-pituitary gonadal axis. In the female, all ova are present at birth and so any damage caused during prenatal exposure will be permanent. Two studies have provided data to indicate that this is an area of potential concern. In one study the ova of exposed mice did not develop normally, possibly as a result of interference of THC with meiosis (Morishima, 1984). In another study there were reduced numbers of ova in rats exposed to THC during the prepubertal period (Wenger et al., 1988). Influences of cannabinoids on the developing opioid system in the brain have led to the suggestion that these changes may lead to a predisposition to drug use in adulthood (Corchero et al., 1998; Rodriguez de Fonseca et al., 1997; Rubio et al., 1998). It is possible that the other effects observed in animals could occur in humans, but no studies have been done. Evidence from studies in animals indicates a need for concern about the potential for the sensitivity of the developing brain and reproductive system to the potential effects of cannabinoids.

Children (prepubertal and pubertal) have also been identified as being potentially more sensitive to adverse reproductive effects by endocrine disruptors, since this is a period of major development of the reproductive system (Crisp et al., 1997). Several authors have suggested that exposure during the pubertal and prepubertal period may be a time of increased sensitivity to the adverse reproductive effects of THC and marihuana (Kolansky and Moore, 1972; Maykut, 1985; Nahas, 1979; Wenger et al., 1992). This is consistent with the suggestion, based on a review of the literature, that the peripubertal period in rats appears to be a period of greater sensitivity than younger or older ages (Scallet, 1991). In rats, it has been reported that the density of cannabinoid receptors in the brain is higher during puberty that at other ages (Rodríguez de Fonseca et al., 1993). It is also possible that adolescents may seek out hemp foods if they become fashionable, thus increasing their potential exposure to cannabinoids.

5.6 Other Cannabinoids

The available data do not allow a rigourous assessment of exposure or hazard from other cannabinoids. It is not known how the mixture of chemicals acts together. Studies on the impact of the other cannabinoids on the effects of THC have given inconsistent results and there are insufficient data available to allow consideration to be given to the potential interaction between the various cannabinoids.

No analytical data were available to allow the estimation of exposure to other cannabinoids, since only THC concentrations have been measured in raw materials from industrial hemp, with the exception of one study of birdseed. Based on the content of the various cannabinoids in plant material of *Cannabis sativa* and that reported for birdseed of industrial hemp it has been estimated that the ratio of CBN:THC in industrial hemp products could be as low as 0.1:1 or as high as 1.3:1., and the ratio of CBD:THC could range from 10:1 to 30:1.[58]

No data are available on the potential contribution to the risk of the other of the 60 or so cannabinoids known to be present in natural hemp. The inability to consider the influence of the other cannabinoids is considered to be a major shortcoming of this risk assessment.

5.6.1 Other Cannabinoids - Risk of Neurological Impairment

CBN and CBD are generally considered to be non-psychoactive. No data were reviewed that would allow a determination of whether they may contribute to neurological impairment as evidenced by deficits in performance measurements. It is recognized that THC is not the only component of marihuana that contributes to psychoactive and pharmacological effects, and it is possible that the other components of marihuana that contribute to psychoactivity are also present in industrial hemp. These may also contribute to the risk of neurological impairment. It is stressed that there are no data on the content of other cannabinoids in industrial hemp products for human use, nor is the potential for these to cause neurological impairment known. The possibility exists that they may contribute to the risk, and information on their effects in humans and measurements of their concentration in industrial hemp-based products is required to address this issue.

[58] The basis for the estimated ratios of THC to other cannabinoids is noteded in Section 3.2.1, and is discussed in Annex I, Section 3.2.1, Tables 3.2-1 and 3.2-2)

5.6.2 Other Cannabinoids - Risk of Neuroendocrine Disruption

The contribution to risk from CBN could be an additional 10%-130% over that predicted from THC alone based on the ratios shown above, since CBN could be as potent as THC in causing neuroendocrine disruption. In the case of CBD exposure could exceed the THC exposure by 10 to 30 times, but since it is has less capacity for disruption of the neuroendocrine system, its contribution to the total risk may not exceed that of THC. The interactive effect of these and other cannabinoids with THC are not well understood; interactions may be antagonistic, additive, potentiative or synergistic. Data on the relative potencies of CBN, CBD and THC are not sufficient to allow the contribution of these other cannabinoids to the total risk to be definitively determined.

5.7 Uncertainties in the Hazard and Exposure Assessments and Influence of Uncertainties on Interpreting Health Risks

There are a number of uncertainties associated with the hazard and exposure assessments which form the basis of this risk assessment. These are summarized in Table 5.7-1. The direction in which the uncertainty is thought to have influenced the assessment is indicated (*i.e.*, leads to overestimate or underestimate of risk) as is the possible magnitude of the influence (small, moderate or large). The assessment could be made more definitive through the reduction of uncertainty associated with any of these parameters. The development of data relating to those uncertainties for which the magnitude of the influence is considered to be large would have the greatest impact in reducing the overall uncertainty of the assessment.

Based on the crude evaluation of the uncertainties shown in Table 5.6-1, it seems possible that the risks could have been underestimated in this assessment, especially for situations of repeated consumption or product use. The best available data were used in this assessment and there was no scientific basis to make modifications to increase the degree of conservatism in the assessment. Refinement of the risk assessment based on additional data would allow for greater confidence in the results of the assessment. Critical data gaps leading to the most significant uncertainties in the risk assessment are outlined in Section 6.0.

Table 5.7-1: Summary of Uncertainties

Source of Uncertainty	Leads to Over- or Underestimate of Risk	Magnitude of Influence on Overall Uncertainty
Hazard Assessment		
no adequate toxicology data on other cannabinoids; or data on industrial hemp oil	under	large
chemicals other than THC in industrial hemp not considered	under	small?
no NOEL for neuroendocrine disruption; LOEL based on i.p studies not repeated in a second laboratory	under	large?
no NOEL for acute neurological disruption	under	?
no studies on effects of chronic parental exposure on F1 generation; only single dose or short-term dosing studies	under	moderate? (depends on extent to which cannabinoids accumulate over time)
Exposure Assessment		
potential bioaccumulation of THC in fatty tissues due to repeated exposure was not calculated; accumulated THC and other cannabinoids in tissues would act as a reservoir for subsequent release to circulation	under	large

Table 5.7-1: Summary of Uncertainties

Source of Uncertainty	Leads to Over- or Underestimate of Risk	Magnitude of Influence on Overall Uncertainty
Dietary Intake Surveys- 24-hour recall studies tend to overestimate daily intake as surveys conducted over longer periods have found (CanTox, personal communication; R.Breecher, Global Tox, personal communication) use of these types of studies may overestimate exposure of the population; Assessment on an Individual basis - generally people tend to over-report consumption of healthy foods and under-report consumption of un-healthy foods (i.e. fat-rich foods and sweets by dieters); also snack foods are difficult to estimate actual amounts and tend to be under-reported (see Annex I, Section 3.6).	Over estimate exposure of population but may under estimate exposure of an individual through intake of certain food types	large Dietary Surveys Not Used - directly due to large uncertainty
relative percent of total food group intake comprised of hemp food consumption by Canadians - unknown to what extent this will occur	?	The greater quantities and frequency of hemp food consumption the greater the potential health risks
consumption of more than one food/food group per sitting or day (i.e total industrial hemp food consumption per day) was not determined.	Under	large? (would depend on types of foods; food with greater hemp content (i.e. 80%) would increase exposure.
assumed 33% dermal absorption based on *in vitro* study using human skin (Touitou et al., 1988). QSAR calculated Kow and dermal absorption of THC suggest dermal absorption may be as great as 100% (in which case dermal exposure estimates may be up to 3-fold greater than those used in the dermal exposure assessment); data for some highly lipophilic chemicals indicate that such chemicals may not be as well absorbed based on parabolic correlations with Kp and Log Kow reported in the literatur; a dermal absorption of 1% was also considered.	over or under estimate dermal exposure	large

Table 5.7-1: Summary of Uncertainties

Source of Uncertainty	Leads to Over- or Underestimate of Risk	Magnitude of Influence on Overall Uncertainty
Touitou et al (1988) is the only published study on dermal permeability of THC using animal and human skin; used tritiated-labelled THC in oleic acid formulation, may have over-estimated dermal permeability due to dissociation of H3 from parent molecule; full thickness of human skin was used which may underestimate permeability of lipophiles; delta-8-THC was used not delta-9-THC; skin was previously frozen which may compromise permeability; did not consider chemical binding to serum proteins; also the study design may not have been the most suitable for a lipophilic chemical such as THC	over or under estimate dermal exposure	large
Touitou and Fabin (1988) did not add the % THC left in the skin depot to the total reported % dermal absorption ; also the study design may not have been the most suitable for a lipophilic chemical such as THC	under	none- this study not used to derive % dermal absorption in human skin
equations used to calculate dermal absorption and dermal exposure for directly applied products assume steady-state conditions	over	?
use of physical-chemical properties were considered to calculate kp, but as these equations are for aqueous solutions and would not account for increased penetration of skin by chemicals when applied with a carrier, such as oleic acid.	under	?
no consideration of potentially greater skin permeability in pregnancy	under or over estimation due to increases fat stores of pregnant woman and greater sequestration of THC	?
use of hemp oil products in presence of water and soap, propylene glycol and other constituents of cosmetics and personal care products would be expected to increase dermal absorption; may also form an emulsion in bath water leaving an oil residue on exposed skin	under	?
an *in vitro* study with mouse skin (Touitou and Fabin, 1988) indicated that the lag time of THC was shorter by 2-fold in the presence of water (lag time decreased from 4.45 to 2.15 h); thus the lag time for THC exposure using bath products and water may be less than the lag time of 8.5 h for human skin (Touitou et al., 1988).	under	small

Table 5.7-1: Summary of Uncertainties

Source of Uncertainty	Leads to Over- or Underestimate of Risk	Magnitude of Influence on Overall Uncertainty
greater dermal absorption occurs surrounding hair follicles; thus dermal absorption of shampoos and products applied to "hairy" skin may be greater than predicted using a dermal absorption of 33%	under	?
no consideration of greater internal exposure to fetus and infant because of lower fat and metabolic capability and greater density of brain cannabinoid receptors	under	large
no analytical data on other cannabinoids in industrial hemp products; no absorption data for other cannabinoids	under	large
small analytical data set for industrial hemp products (n=1 per manufacturer; participating manufactures = 4) - should have at least 3 samples from every batch of hemp oil, hemp seed, hemp seed meal, hemp nut, from each manufacturer.	?	large
THC concentrations in industrial hemp materials harvested in 1998 were near or less than analytical detection limit (d.l.= 4 ppm) (Industrial Hemp Manufacturers, personal communication); how much less than 4 ppm is unknown; improved analytical techniques for THC and other cannabinoids in industrial hemp oil, seed, meal, nut matrices and finished product formulations is needed.	over estimate of exposures using 10 ppm	? Uncertain as THC concentrations may be just less than d.l. or orders of magnitude less; this remains to be determined.
little analytical data on THC content in finished cosmetic, food and nutriceutical products	published data supports calculated concentrations of THC in foods and cosmetics	small- for products made with industrial hemp materials containing $\leq$10 ppm; large- for those products from uncleaned or poorly cleaned industrial hemp seeds (i.e seeds from China and other countries imported pre 1999 or from varieties of *C. sativa* with

Table 5.7-1: Summary of Uncertainties

Source of Uncertainty	Leads to Over- or Underestimate of Risk	Magnitude of Influence on Overall Uncertainty
		greater THC content that those used in Canada)
non-users were included in industry estimates of daily use of cosmetics and personal care products	may under estimate exposure on an individual basis, especially high-users;	small

6.0 CRITICAL DATA GAPS

The availability of critical data would help to reduce some of the uncertainties described in the previous section and would facilitate the development of more definitive conclusions with respect to the existence and/or magnitude of human health risks associated with the use of foods, cosmetics and nutraceuticals made from industrial hemp.

6.1 Critical Data Gaps for Hazard Assessment

- Lack of multiple generation, multiple dose level feeding studies with industrial hemp products, THC and/or other cannabinoids, in animals with a focus on neuroendocrine, reproductive and behavioural outcomes.

- Lack of multiple generation, multiple dose level dermal studies in animals with industrial hemp products, THC and/or other cannabinoids with a focus on neuroendocrine, reproductive and behavioural outcomes.

- Lack of data on the validation of animal models for the prediction of the potential for neuroendocrine disruption in humans.

- Lack of data on steady-state kinetics and tissue accumulation of THC and other cannabinoids in humans or animals after long term (e.g. lifetime) exposure.

- Lack of data on the potential for human neurological impairment (adults, child and infants) after short and long term use of industrial hemp products.

6.2 Critical Data Gaps for Exposure Assessment

- Paucity of data on concentrations of THC in raw materials made from industrial hemp and in finished products - available industry data indicates that THC concentrations in raw materials produced under stringent methods are near the limits of the analytical methods proposed in the Canadian Industrial Hemp Regulations.

- Lack of a suitable analytical method for detection of THC at ppb or lower concentrations in industrial hemp raw materials and finished products

- Lack of data on concentrations of cannabinoids other than THC in raw materials made from industrial hemp and in finished products.

- Insufficient data on the metabolism, distribution and accumulation of THC and other cannabinoids in humans to enable predictive modelling of tissue levels following longterm exposure to low levels of these chemicals.

- Lack of data on accumulation of THC and other cannabinoids in human breast milk after long term low level exposure and correlation to oral/dermal exposure.

- Lack of *in vivo* data for human skin on dermal absorption of THC and other cannabinoids in industrial hemp oil and cosmetic and personal care product matrices, determined under conditions representative of intended use (includes dermal use on chapped, dry and otherwise damaged skin).

- Lack of data on absorption from the g.i. tract after ingestion of foods or nutraceuticals made from industrial hemp.

- Lack of information on daily intake of foods made with industrial hemp by the consumer groups selected for assessment.

7.0 CONCLUSIONS

The potential hazards associated with exposure to THC and other cannabinoids through the use of food, cosmetic and nutraceutical products made from industrial hemp include acute neurological impairment and neuroendocrine disruption. Exposure to cannabinoids during the perinatal period in animals has been found to cause neuroendocrine disruption leading to permanent effects on adult offspring, including decreased sensitivity to morphine, behavioural changes and adverse effects of reproductive parameters. Good concordance between observed effects of THC and marihuana in humans and animals and similarities in pharmacokinetics, metabolism and cannabinoid binding site distribution in the brain among species provides a sound scientific basis for the extrapolation of hazard data from animals to humans. The available data did not support the development of a TDI for THC or other cannabinoids. This is because there was no NOEL identified for neuroendocrine disruption and the studies showing permanent effects on the brain and reproductive system in animals exposed *in utero* and/or during lactation were conducted using short term dosing schedules. As a result of this inability to determine a TDI for THC, the estimated exposures were compared with the LOEL for neuroendocrine disruption of in rat of 1 ug/kg/d and with the single dose LOEL of 70 ug/kg for acute neurological impairment due to in adult humans. The latter comparison was made because of the attention which has been focused on psychoactivity and the need to maintain exposure below a dose that could cause acute neurological impairment.

The direct comparison of exposure results with the LOELs does not give consideration to a number of factors as listed below:

- bioaccumulative potential of THC with repeated dosing;
- the No Observed Effect Level (NOEL) has not been identified for neuroendocrine disruption or neurological impairment;
- the potential that some individuals may be more sensitive than the adults with a history of marihuana use who were the subjects of the study that yielded the LOEL of 70 ug/g for neurological impairment;
- the potential for neuroendocrine disruption or neurological impairment by other cannabinoids that would be present in industrial hemp-based products;
- the possibility that humans could be more sensitive than the rats in the study used to derive the LOEL of 1 ug/kg for neuroendocrine disruption; and

- the potential that some individuals could be particularly sensitive to the adverse effects of cannabinoids.

In consideration of the uncertainties inherent in the direct comparison of the LOELs with the exposure results as listed above, the conclusions from the risk characterization were as follows:

Food: The majority of foods considered in this assessment could pose a human health risk with respect to neuroendocrine disruption. With respect to neurological impairment, the amount of each food type that would need to be consumed to deliver a dose of THC equal to the LOEL exceeded the mean daily intake and "serving size"which may suggest an absence of risk. In the case of the child; however, there are some foods (dairy substitutes and candy) that could potentially be consumed in sufficient quantities on occasion in a single day or a single sitting to cause neurological impairment, or even psychoactive effects. For example 2.3 ice cream bars could deliver a dose of THC of 70 ug/kg (the LOEL for neurological impairment) and 4.6 ice cream bars could deliver a dose of 140 ug/kg (the LOEL for psychoactivity) for a 33.9 kg child. It was concluded that consumption of some food products made with ingredients from industrial hemp may be associated with a risk of neurological impairment and psychoactivity, particularly for children.

Cosmetics: The use of cosmetics made with ingredients from industrial hemp could be associated with a risk of neuroendocrine disruption, but are unlikely to be associated with a risk of neurological impairment. The risk of neurological impairment cannot be excluded entirely, particularly in the case of children without further information on the relative sensitivities of children vs adults, the relative sensitivities of marihuana users vs non users, the effects of repeated exposure over a long time period, the effects and concentrations of cannabinoids other than THC and the extent of dermal penetration and systemic exposure of topically applied cannabinoids under conditions of actual product use.

Nutraceuticals: The use of nutraceuticals made from industrial hemp oil would likely be associated with a risk of neuroendocrine effects and could be associated with a risk of neurological impairment, particularly in children.

Major shortcomings related to key data gaps identified in the assessment that preclude the development of definitive conclusions regarding the degree of potential risk are:

- the inability to consider the potential contribution of cannabinoids other than THC (limited toxicity data indicate the ability of other cannabinoids to cause neuroendocrine disruption) to the overall health risks;

- the inability to consider the long term effects of bioaccumulation of THC over time from repeated low dose exposure due to lack of chronic low level toxicity studies lack of data on the steady-state pharmacokinetics of THC;

- the inability to consider the effects of THC and other cannabinoids after multi-generation long term exposure;

- the inability to determine the degree of exposure to the developing fetus and nursing infant; and

- the lack of analytical data for THC and other cannabinoid concentrations, at detectable levels, in raw materials and finished products made from industrial hemp.

At greatest risk of long term effects of neuroendocrine disruption are the developing fetus, nursing infant and prepubertal/pubertal child. This conclusion is based on animal data that document adverse and permanent effects on brain function and the reproductive system caused by cannabinoid induced neuroendocrine disruption during development. In addition, the peripubertal period in children is a period of major development of the brain and reproductive system which is controlled by neuroendocrine signals. In rats, the density of cannabinoid receptors was found to be greatest during the pubertal period, suggesting a underlying basis for the increased sensitivity to the adverse effects of cannabinoids during this period. Concern is warranted for THC exposure of the developing fetus and nursing infant through maternal use of industrial hemp products based on the knowledge that THC is rapidly transferred from the mother to the fetus crossing both the placental and blood brain barriers within in minutes of maternal exposure, and that THC accumulates and is transferred via human breast milk to the infant.

On the basis of currently available data it is concluded that the present Canadian limit of 10 ug/g THC in raw materials and products made from industrial hemp (*Cannabis sativa* cultivars with <0.3% THC) would likely not protect the Canadian consumer using industrial hemp-based food, cosmetic and personal care, and nutraceutical products from potential health risks of neurological

impairment and neuroendocrine disruption associated with low level exposure to THC and other cannabinoids.

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