ASSESSMENT OF EXPOSURE TO AND HUMAN HEALTH RISK FROM THC AND OTHER CANNABINOIDS IN HEMP FOODS

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by

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

EXECUTIVE SUMMARY

In recent years, the presence of trace residual delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient of marijuana, in food products incorporating hemp seed and seed derivatives (whole and hulled seeds (also called hemp nuts), oil, flour, meal, and protein isolate) has raised concerns over THC's potentially adverse impacts on human health. To assess whether THC intake from the consumption of currently available hemp foods may pose an unacceptable health risk, a study was conducted on behalf of several North American growers and processors of hemp seeds, manufacturers and distributors of hemp food and cosmetics items, and their trade associations.

The study's main objectives were to:

- Prepare a *hazard assessment* for the intake of THC via hemp foods, including the establishment of Lowest Observed Adverse Effects Level (LOAEL) and No Observed Adverse Effect Levels (NOAEL) for oral ingestion of THC, derivation of safety factors, and estimation of the corresponding acceptable daily intake (ADI).
- Develop an *exposure assessment* for the intake of THC via hemp foods, assuming their extensive daily consumption with trace residual THC levels now commonly achieved by Canadian suppliers in hemp seed and seed derivatives (less than: 2 μg/g for whole seeds, meal and flour; 1.5 μg/g for hulled seeds and protein powder; 5 μg/g for hemp oil).
- Assess whether THC intake may, under highly conservative assumption of consumption patterns, present the potential for adverse health effects.
- Comment on the acceptability of currently achieved THC levels in hemp seed and seed derivatives as health-based THC limits.

The ***hazard assessment*** for oral THC uptake was based on a current, critical review of the original scientific literature on the subject, including several recent studies and previous reviews, such as the Health Risk Assessment conducted by Health Canada in 1998/99.

The ***exposure assessment*** used statistical data on food consumption by North Americans. Daily food intakes by food group were estimated based on the most recent U.S. Department of Agriculture's (USDA) *Continuing Survey of Food Intakes by Individuals (CSFII) 1996*. The potential for substitution of conventional foods by hemp foods and the typical THC content in hemp seed derivatives was established based on previous Canadian reports, industry sources and analytical data. Several food intake scenarios were evaluated. Scenario 1 assumed an average recommended daily caloric intake with complete replacement of protein by hemp protein, without further differentiation of hemp products. Scenario 2 assumed a typical North American diet in which all food items, except meat, were completely replaced by technically feasible hemp foods. Scenario 3, the "reasonable worst-

case", assumed a high caloric intake by a vegetarian with complete replacement of animal protein by hemp protein.

The ***hazard assessment*** provided the following major findings and conclusions:

- The lowest single oral THC dose, at which acute adverse neurological effects, *i.e.* slightly reduced psychomotoric performance, have been observed, is 5 mg (for a body weight of 70 kg). This dose represents the LOAEL for acute effects caused by THC.
- The same single dose of 5 mg also did not cause a difference to a placebo with respect to psychotropic effects and thus constitutes the NOAEL for this effect.
- Adverse chronic effects, such as cognitive changes, structural brain changes, mutagenicity, carcinogenicity, significant changes to hormone levels in males and females, congenital effects, and adverse impact on child development were either not found in humans or were found only at doses significantly higher than the equivalent of oral doses of 10 mg/day, in which cases observed effects were moderate.
- The relevance of animal studies, which found increased risk of stillbirth and other adverse effects on the fetus following peritoneal injection of THC, to humans, is highly questionable. No such effects had been found with humans after oral or inhalative administration of much higher doses. The same applies to the reported impact of low THC doses on hormone levels in pregnant rats. These studies had been the basis for the conclusion by Health Canada's 1999 draft risk assessment that inadequate margins of safety exist to protect the population from the assumed neuroendocrine disruption caused by THC.
- Since chronic and subchronic adverse effects require doses higher than those for acute neurological effects, determination of an acceptable daily intake should be based on the LOAEL for reduced psychomotoric performance of 5 mg for a single dose, or 2×5 mg, taken orally over the course of a day. Considering that the observed psychomotoric effects are not severe and according to scientific practice, selection of a safety factor of 20 provides a sufficient margin of safety from acute adverse neurological effects.
- Based on the above, an acceptable daily intake (ADI) for orally ingested THC of 500 µg/day was assumed to provide protection from both acute and chronic adverse effects to humans.
- Less efficient transfer to the fetus and suckling infant of THC orally ingested by the mother—compared to inhaled THC—provides additional protection to both by limiting THC uptake. Children also appear to be less susceptible to THC compared to adults. Thus, the proposed ADI appears to provide sufficient protection to both fetuses and children of mothers who routinely consume hemp foods.
- The accumulation of THC in body tissue represents a source of THC to the plasma even after cessation of THC uptake. The establishment of a dynamic equilibrium between

accumulation and remobilization and the slow rediffusion process indicate that corresponding THC levels in body tissue will be insufficient to supply THC to the plasma at rates that could result in or contribute to adverse effects.

- Other cannabinoids present in industrial hemp in relevant quantities appear to be effective either at much higher concentrations than THC, *e.g.*, cannabinol (CBN), or may act as an antagonist to the neurological effects of THC, as with cannabidiol (CBD). Regulating the THC level in hemp raw seed and seed derivatives (whole and hulled seeds, oil, flour, meal, and protein isolate) thus would provide comprehensive protection from potentially adverse health effects caused by ingestion of hemp food products.

The ***exposure assessment*** for THC intake via hemp foods generated the following major conclusions:

- Complete replacement of conventional food items in a "typical American diet", including meat products, by currently available hemp food items containing common levels of THC will, even under **"**reasonable worst-case" Scenario 3 assumptions, not cause a daily THC uptake via hemp food in excess of 500 µg. This reasonable worst-case scenario makes the following assumptions:
  - Complete substitution of all meat and non-meat food items by hemp foods, wherever technically feasible;
  - A high daily caloric intake at the 95th percentile of the U.S. population (3182 kcal/day),
  - The use of the maximum technically conceivable hemp content in all food products, irrespective of the higher relative cost of hemp seed ingredients.
- The more realistic typical daily THC uptake by individuals who consume hemp food items regularly and extensively will rarely exceed the lower level of Scenario 2, *i.e.* 100 µg/day. This implicitly assumes increased future commercial availability of these items and the maintenance of the current THC levels.
- The corresponding range of daily intake of cannabidiol (CBD) in Scenarios 2 and 3 is estimated at 1 to 5 mg, respectively.
- Consequently, the daily THC ingestion even by extensive users of hemp foods will remain consistently and, in general, significantly, below the proposed ADI for oral THC, and thus will not cause any acute or chronic adverse health impacts. Specifically, the highest conceivable intake of THC via hemp foods is far below the psychoactive threshold for THC.

Generally achieved THC levels in hemp seed derivatives thus represent a conservative choice for achievable and enforceable THC limits in these materials.

The estimated 10–20% contribution by the two non-psychoactive THC acids A and B to total THC in hemp seed derivatives, predominantly measured by gas chromatography/mass spectrometry (GC/MS), provides an additional small margin of safety from potentially adverse effects of THC.

THC uptake from the use of hemp oil cosmetics is still lower than from hemp food ingestion. A recent study estimated that exclusive and extensive use of hemp oil cosmetics containing high amounts of hemp oil, or pure hemp oil, on compromised skin will not contribute more than 10 µg/day to total THC uptake. Typical THC uptake from the extensive application of commercially available hemp oil cosmetics to healthy skin is typically less than 1 µg/day. Thus, compared to hemp foods, hemp cosmetics do not contribute significantly to total THC intake.

Extensive hemp food consumption also no longer appears to have the potential for causing confirmed positive urine tests for marijuana. A recent study showed that daily THC ingestion with hemp oil, in single doses of up to 600 µg/day and over a 40-day period, failed to cause confirmed positive urine test according to the protocol used by most public and private employers in the U.S. Positive screening tests at a lower cutoff level are conceivable but unlikely.

Little representative information on the content in hemp seed derivatives of cannabinoids other than THC, notably cannabidiol (CBD) and cannabinol (CBN), is currently available. It is estimated that CBD intake is typically 10 times that for THC. CBD is considerably less pharmacologically active than THC. Studies suggest that typical CBD intake via food is far too low to cause measurable effects on humans. Findings of low-dose adverse effects of CBN on the hormone secretion of male rats are contradicted by human studies at higher doses. Thus, uptake via hemp foods of other relevant cannabinoids does not appear to pose the risk of adverse health effects. However, this subject requires further study.

The findings and conclusion from this present study support the following recommendations:

- Generally achieved THC levels in hemp seed derivatives—*i.e.* less than: 2 µg/g for whole seeds, meal and flour; 1.5 µg/g for hulled seeds and protein powder; 5 µg/g for hemp oil—should be considered by regulatory agencies as a conservative and enforceable choice of THC limits in hemp seed derivatives.
- The apparently safe use of hemp foods relative to the presence of generally achieved THC residues and the lack of evidence of other adverse health effects supports the industry's position that hemp seed derivatives and foods should be recognized as safe and not be subjected to regulations for "novel foods".

Two controversial issues regarding the toxicity of THC and other cannabinoids require clarification by future studies. These issues are:

- The reported effects via intraperitoneal dosing (direct injection through the peritoneum into the abdominal cavity) of very low THC doses on the rodent fetus and the outcome of pregnancies observed in animal studies with intraperitoneal dosing (versus no observed effects in human mother/fetus studies with much higher orally ingested doses of THC by the mother), and an analysis of their relevance to humans; and
- The importance of other cannabinoids to the pharmacological activity of hemp food products.

ACRONYMS AND ABBREVIATIONS

ACTH	Adrenocorticotropin
ADI	Acceptable daily intake
AF_{THC}	Oral absorption factor for THC
BgVV	Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin
BW	Average body weight (70 kg)
C_i^{THC}	Concentration of THC in hemp food item i (µg/g)
CB1	Cannabinoid receptor 1
CB2	Cannabinoid receptor 2
CBD	Cannabidiol
CBN	Cannabinol
CSFII	(USDA) Continuing Survey of Food Intake by Individuals
C_{THC}	Concentration of THC in hemp food
DEA	(U.S.) Drug Enforcement Agency
EDI	Estimated daily intake
EFA	Essential fatty acid
EU	European Union
f_j^i	Fraction of hemp seed derivative j in product i (g/100 g)
FDA	(U.S.) Food and Drug Administration
FSH	Follicle-stimulating hormone
GI	Gastrointestinal (tract)
GLA	Gamma-linolenic acid
GnRH	Gonadotropin-releasing hormone
GC/MS	Gas chromatography/mass spectrometry
HC	Health Canada
i.p.	Intraperitoneal
kcal	Kilocalories
LD_{50}	Median lethal dose
LH	Luteinizing hormone
LOAEL	Lowest observed adverse effect level
mRNA	Messenger ribonucleic acid
NIDA	National Institute on Drug Abuse
NOAEL	No observable adverse effect level

OPPS	Ottawa Prenatal Prospective Study
p_j^{THC}	THC concentration in hemp seed derivative j (µg/g)
ppb	Parts per billion
ppm	Parts per million
PUFA	Polyunsaturated fatty acid
Q_i^{HF}	Daily ingestion rate for hemp food product/product category i (g/day)
Q^{THC}	Daily THC ingestion rate (µg/day)
Q_{BW}^{THC}	Daily specific THC ingestion rate (µg/(kg body weight * day))
RDA	Recommended daily allowance
RH	Releasing hormones
SCE	Sister-chromatid exchange (test)
SIDS	Sudden infant death syndrome
SKLM	German Senate Commission for The Assessment of Food Safety
STH	Somatotropin
TDI	Tolerable daily intake
THC	Delta-9-tetrahydrocannabinol
THC_{int}	Average absorbed daily THC dose
TSH	Thyrotropin
U.S. EPA	U.S. Environmental Protection Agency
UF	Uncertainty factor
USDA	U.S. Department of Agriculture

1. INTRODUCTION

1.1 Background

Increasing use of hemp foods in North America

Since the mid 1990's, seeds of the hemp plant (*Cannabis sativa* L.) and seed derivatives (whole and hulled seeds, oil, flour, meal, and protein isolate) have increasingly been used in food products—mainly those distributed in the growing market for natural foods in the U.S. and Canada.

The seed meat protein contains the essential amino acids in easily digestible form with a high protein efficiency ratio. Hemp oil provides high concentrations of the two essential fatty acids (EFA's) in a balanced ratio of the omega-3/omega-6 acids and smaller quantities of other physiologically relevant polyunsaturated fatty acids (PUFAs) such as gamma-linolenic acid (GLA) and stearidonic acid. Because of this nutritional profile, hemp seed and seed derivatives have been incorporated into a wide range of functional foods. Hulled hemp seed in particular is used in many natural food products, such as corn chips, nutrition bars, hummus, breads and cereals, while the oil is commonly used as an omega-3/6 EFA supplement like fish and flax oils. The high EFA content of hemp oil also explains its use as a topical ingredient in body care products. Reviews of the nutritional benefits of hemp seed products are provided in the literature (Leson *et al.* 2001, Scheifele 2000a, Leson & Pless 1999, Przybylski *et al.* 1997, Deferne & Pate 1996).

THC residues in hemp foods: recent developments and regulatory considerations

The gradual expansion of hemp foods into the natural products market now faces a significant obstacle, particularly in the U.S. Hemp seeds and their derivatives contain small quantities of cannabinoids, including ^{9}-tetrahydrocannabinol (THC), the pharmacologically most active cannabinoid in marijuana (in this study, the term "THC" refers to "total THC" as determined by GC/MS, and includes both free phenolic ^{9}-tetrahydrocannabinol and THC acids A and B). Both industrial hemp and marijuana, varieties of the same species, *Cannabis sativa* L., produce cannabinoids as constituents of resins secreted by gland cells on leaves and bracts of the mature cannabis plant. Industrial hemp and marijuana are generally distinguished by their THC content. Marijuana contains, in its female flowers, typically 2–5% THC (per dry weight), but THC levels of 15–20% have been reported (ElSohly *et al.* 2000, Grotenhermen & Huppertz 1997, Avico *et al.* 1985). In comparison, "industrial" hemp varieties grown for fiber and seeds and licensed for farming in the European Union (EU) and Canada must legally be bred to maintain a THC content of less than 0.3% (Bócsa & Karus 1998, Health Canada 1998). Hemp and marijuana also differ in their cannabinoid

composition. In marijuana, the ratio of THC to cannabidiol (CBD) is greater than two; in industrial hemp it ranges from 0.06–0.5 (see Table 2.7).

The production of industrial hemp has been prohibited in the U.S. since the 1970's and was banned in Canada prior to 1998. Thus, hemp foods were initially produced from imported seeds. Until 1998, virtually all hemp seeds originated in China, where they had been grown for birdseed. Anedoctal evidence and several reports in the literature suggest that these seeds and the resulting products often contained considerable concentrations of THC (Wirtshafter 1997–2001). Consequently, there had been mounting evidence that THC residues are in fact found in hemp seed and seed derivatives in measurable quantities. For example, a 1997 survey of hemp oils in the U.S. found THC levels between 11 and 117 µg/g (equals parts per million or ppm) (Bosy & Cole 2000).

Presence of THC in hemp seed products is predominantly caused by external contact of the seed hull with cannabinoid-containing resins in bracts and leaves during maturation, harvesting, and processing. Thus, these elevated THC levels were likely due primarily to a lack of attention to proper seed cleaning after harvesting and possibly the seeds' origin from cultivars containing higher amounts of THC than is legal in Canada and the EU.

Since 1998, when commercial hemp farming was permitted in Canada, the majority of hemp seed products used in the U.S. originates from that country, with smaller quantities being imported from countries in the European Union (EU). Their exclusive use of low-THC varieties and thorough seed drying and cleaning by hemp seed processors has significantly reduced THC levels in seeds and oil available in North America. Canadian processors now routinely achieve THC levels in whole seeds, hulled seeds, oil and seed cake below 2 microgram/gram (µg/g) or parts per million (ppm). Oils containing 5 (µg/g), sometimes up to 10 µg/g are found occasionally. The increasingly common hulled seeds generally achieve THC levels below 1.5 ppm and routinely less than 1 ppm (Laprise 2001, Moravcik 2001, Webster 2001, Crew 2000/2001).

Hemp foods are now becoming increasingly available to the general public through mail order businesses and retail stores in both Canada and the U.S. Thus, the presence of THC residues in hemp foods has raised concerns among health and drug officials. In most Western countries, these concerns relate primarily to the known pharmacodynamic and other, potentially adverse, effects of THC when ingested. In the U.S., concern has also been raised over the demonstrated potential of hemp foods to cause positive test results under workplace drug-testing programs instituted by many public and private institutions.

Health risk and THC limits for food

Two comprehensive assessments of the exposure to and potential adverse health effects caused by THC and other cannabinoids in hemp foods have been conducted since 1998 (Health Canada 2001, Grotenhermen 1998). Primarily due to differences in their assessment of the applicability of findings from animal studies and their choice of appropriate safety factors, their assessment of the health risk posed by cannabinoid residues in hemp foods has

considerably different results. Moreover, these studies did not address the need to avoid undesirable impacts on the outcome of workplace drug testing.

To date, only few countries have established policies, binding limits or guidelines for the maximum acceptable THC content in hemp products. Switzerland established THC limits for hemp foods in 1998 (Swiss Federal Office for Public Health 1998 and 1996, cited in Grotenhermen *et al.* 1998). The respective limits are shown in Table 1.1.

Canada was the second country to pass regulatory limits on THC. The original Canadian limit of <10 mg THC per kg (ppm) represents a de-facto limit for handling of hemp food and applies to hempen raw and semi-finished products, such as hemp fibers, hemp seeds, and hemp oil. This limit of <10 mg THC per kg is not based on the protection of human health. Subsequently, in 2000, Health Canada adopted an interim policy, which classified all hemp foods as "novel foods" and subjected them to the Novel Food Regulations. Pending the completion of its evaluation of the safety of hemp foods, Health Canada currently requests that manufacturers of hemp food products purchase exclusively hemp seed derivatives containing less than 2 µg/g of THC (Driscoll 2001).

In March 2000, the German Federal Institute for Consumer Health Protection and Veterinary Medicine (BgVV) and the German Senate Commission for The Assessment of Food Safety (SKLM) adopted guidelines for the maximum permissible THC content in hemp foods. These limits represent non-enforceable guidelines for manufacturers and were characterized by the BgVV as precautionary, pending a more extensive evaluation (Dusemund 2000).

Limits for THC in hemp foods had also been suggested in a report prepared by the nova Institute (Grotenhermen *et al.* 1998). The THC limits for food recommended by the nova Institute are: 20 mg/kg edible hemp oil, 1.5 mg/kg finished hemp products, hemp breads and pastries, and pasta, 0.7 mg/kg alcoholic drinks, 0.3 mg/kg nonalcoholic drinks. These limits were based on protecting consumers from psychoactive effects.

The following Table 1.1 summarizes these proposed and adopted limits. Note that European limits focus on limits for consumer products while Health Canada to date has opted to limit THC levels in the raw and semi-finished products used as ingredients in the production of hemp foods.

Table 1.1 THC limits for hemp foods

		Health Canada Interim Policy	Switzerland 1996/98	nova Institute 1998	BgVV* 2000
Whole and hulled seeds	µg/g	2	20		
Food-grade oil	µg/g	2	50	20	5
Alcoholic beverages	µg/g**	–	0.2	0.7	0.005
Non-alcoholic beverages	µg/g	–	0.2	0.3	0.005
All other food items	µg/g	–	2–20	1.5	0.15

* Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin

** µg/g = microgram per gram of product, equals parts per million (ppm) by weight

Regulatory status in the U.S.

Federal law in the U.S. currently prohibits commercial farming of any variety of *Cannabis sativa,* including low-THC varieties, but allows for the importation and use of non-viable hemp seeds, requiring sterilization prior to entry. Concerns over inadvertent exposure of hemp food consumers to THC and previous reports of positive results in workplace drug tests have since 1998 caused several U.S. federal agencies to oppose importation from Canada of hemp seeds and oil, as well as their use in consumer products. Since federal law currently exempts sterilized hemp seeds and their products, hemp foods and cosmetics remain, despite attempts to prohibit their use, unregulated. No limits for THC in foods have been adopted by the Federal Food and Drug Administration. More recently, the U.S. Drug Enforcement Administration (DEA) has announced its intent to propose three rules by October 2001, which would in effect make illegal the use of any "hemp products that result in THC entering the human body" (Federal Register 2001). These measures would set a de-facto THC limit of "zero" without specification of a finite limit of detection. No rationale for their proposed position has been offered by the DEA.

Pending the release of the DEA's rationale for the proposed policy, such a "zero THC" limit appears neither justified without further evaluation of the health impacts of concern, nor is such a standard acceptable to hemp seed processors and suppliers of hemp food products. Failure to achieve modification of the DEA's proposed "zero THC" standard will eliminate the potential for economic expansion of hemp foods in U.S. markets and have strongly detrimental impacts on the economic viability of Canadian growers and processors.

1.2 Objectives

LEC was commissioned by Dr. Bronner's Magic Soaps, Escondido, CA, and the North American Industrial Hemp Council (NAIHC), Madison, WI, to conduct a re-evaluation of the health risk potentially caused by the ingestion of THC via hemp foods currently available in the North American market. The goal of this desktop study was to assess whether current levels of cannabinoids, primarily THC, in hemp foods are sufficiently low to prevent adverse health effects and interference with workplace drug tests with a sufficient margin of safety.

Specific objectives of the study included the following:

- To conduct a critical review of the scientific literature and compile current information relevant to the generation of acute and chronic adverse health impacts from ingestion of THC via hemp foods;
- To establish the NOAEL (no observable adverse effect level) and the LOAEL (lowest observable adverse effect level) for various known impacts of THC;
- To derive safety or uncertainty factors (UF), which will provide a wide margin of protection from any such effects and develop a corresponding acceptable daily intake (ADI) for THC.
- To critically review and possibly modify existing exposure scenarios for the ingestion of hemp foods. Most importantly, this included revision of previous assumptions of hemp food intake and the amount of hemp seed derivatives commonly found in hemp foods.
- To develop typical and reasonable worst-case scenarios for daily intake of hemp seeds and oil.
- Based on commonly achieved levels of THC in hemp seed derivatives, to derive estimated daily intake (EDI) for THC under these scenarios and compare them to the proposed ADI;
- Evaluate whether the proposed ADI would also provide protection from undesirable impacts on the outcome of work place drug tests;
- Comment on the sufficiency of the currently achieved THC levels in hemp seed derivatives and the need for potential further reductions.

1.3 Approach and sources of information

The main objective of this study was the development of a risk assessment regarding the potential health risks posed by THC residues in hemp foods. Elements of a health risk assessment include a dose-response assessment, exposure assessment, and risk characterization. The following activities were carried out to achieve this objective:

- An extensive evaluation of the current scientific literature on the pharmacology and pharmacokinetics of THC was conducted, including critical analyses of previous reviews.

Specific attention was given to factors relevant to the oral intake of THC via food and potential impacts on the fetus and child development. NOAEL and LOAEL for documented adverse effects were derived. Potential effects caused by the concurrent intake of other cannabinoids were evaluated. Safety factors for each such adverse effect and the corresponding ADI for THC were derived.

– Representative levels of hemp seeds and seed derivatives in hemp foods and THC levels in the hemp seed and seed derivatives were established based on information obtained from manufacturers, researchers, and commercial laboratories in North America and Europe. Nutritional, technical, and economic limitations to the use of hemp seed derivatives were discussed with industry members.

– Several scenarios for the daily intake of various macronutrients and food categories were developed. Scenarios were based on data from food surveys and disappearance studies conducted by the U.S. Department of Agriculture (USDA), as well as other literature sources and personal experience. Results were compared to a previous survey by Health Canada. Typical and reasonable worst-case scenarios for the consumption of hemp foods and the respective intake of hemp seed derivatives were developed.

– Based on commonly achieved levels of THC residues in hemp seed derivatives, daily THC intake for each food consumption scenario was estimated and compared to the proposed ADI. These EDIs were also compared to THC estimated uptake rates from the use of hemp cosmetics and to oral intake rates which had previously been found not to cause confirmed positive urine tests for marijuana.

1.4 Structure of this report

The hazard assessment (Section 2) and exposure assessment (Section 3) portions of this study were designed as independent modules for reference by the reader.

Section 2, the hazard assessment for orally ingested THC, focuses on a quantitative assessment of potential adverse health effects caused by THC and other cannabinoids consumed via food products. It proposes NOAEL and LOAEL for various effects, discusses the appropriate selection of safety factors, and derives ADI levels for oral uptake of THC.

Section 3 focuses on the development of an exposure assessment for THC in hemp foods. It estimates the potential intake of hemp seed derivatives under various scenarios. These scenarios were developed to include typical and extreme, yet conceivable, food consumption patterns by individuals living in North America. Development of the exposure assessment involves a critical assessment of the substitution potential for hemp seed derivatives in food products and a review of currently achieved THC levels in hemp seed derivatives. The obtained information is used to estimate daily oral intake of THC via hemp foods under the various scenarios.

Section 4 summarizes the findings of the previous sections and provides an assessment of the potential health risk caused by THC in hemp foods. It compares the EDI under various scenarios with the previously derived ADI for THC and provides an assessment of whether even extensive use of hemp foods may cause adverse health effects. The relevance of THC uptake from hemp cosmetics is discussed, as is the potential interference of THC from hemp foods with drug testing programs. Recommendations for further action and research are provided.

2. HAZARD ASSESSMENT FOR THC INGESTION

The potential adverse health impacts caused by the oral intake of THC and other cannabinoids via hemp foods have been the subject of two previous reviews (Health Canada 2001, Grotenhermen *et al.* 1998). These studies also recommended guidelines for the maximum acceptable THC content in hemp foods. Each study has been subject to criticism. Particularly the Draft Health Risk Assessment by Health Canada (Health Canada 2001), which has not been officially released, has been criticized for basing its conclusions that existent margins of safety are inadequate to protect the population from neuroendocrine disruption on controversial animal studies, which contradict findings from human studies that applied considerably higher doses.

The following hazard assessment for THC represents an up-to-date reevaluation of potential adverse effects caused by the ingestion of THC and other cannabinoids via hemp foods. Particularly, it will address several of the concerns raised in the Draft Health Risk Assessment prepared by Health Canada.

Its main objectives were to develop "lowest observed adverse effect levels" (LOAEL) and "no observed adverse effect levels" (NOAEL) for those health effects of THC that have been demonstrated credibly to occur in humans or animals, to select safety factors that will provide a sufficient level of protection from the observed effects, and to derive corresponding acceptable daily intake (ADI) levels for THC.

2.1 Pharmacodynamics and pharmacokinetics of THC

Most specific THC-effects on humans and other mammals are mediated through cannabinoid-receptors. Reviews on the mode of action of THC have been conducted by Matsuda (1997), Howlett (1995), and Pertwee (1995). At very high doses, also non-specific effects on membrane fluidity and other non-specific effects may become relevant (Martin 1986). Two types of cannabinoid receptors, CB1 and CB2, each with additional subtypes, have been identified and cloned. The CB1 receptor is predominantly found in brain cells, with a particularly high receptor density in motoric, limbic, associative, cognitive, sensory and autonomic brain structures (basal ganglia, cerebellum, limbic system, hypothalamus, and cerebral cortex). In addition, the CB1 receptor was also found in the testes and other peripheral tissues.

The CB2 receptor has so far only been found outside the brain of any species investigated, particularly in cells of the immune system, such as in the spleen, the tonsils, thymus, mast cells, and blood cells. Presumably it is involved in the modulation of the operation of immune cells. Often CB1 and CB2 receptors are expressed from the same immune cells.

Endogenous ligands for the cannabinoid receptors, so-called endocannabinoids or endogenous cannabinoids, differ strongly from plant cannabinoids in their molecular structure (Stella *et al.* 1997, Devane 1992).

THC's receptor-mediated mode of action appears to provide an additional margin of safety from undesirable health effects, particularly for children, for two reasons:

As a rule, for most harmful chemicals the severity of a toxic effect is a function of cumulative exposure, *i.e.* its exposure concentration and its duration time (Gaylor 2000). Thus, the NOAEL correspondingly decreases with the duration of exposure. In the case of THC, the opposite applies since the effect of a given exposure level decreases with time. This is due to the development of tolerance to THC by its receptors.

Children are considered particularly sensitive to many harmful chemicals. Consequently, higher safety factors are chosen to provide adequate protection. However, several clinical studies have indicated that children are less sensitive to the effects of THC effects (Abrahamov *et al.* 1995, Dalzell *et al.* 1986). However this point appears to be controversial. One study on cannabinoid receptor density (Glass *et al.* 1997) found a higher receptor density in the fetus and children compared to adults. Other researchers have found that cannabinoid receptor density increases fivefold from birth to adulthood (Belue *et al.* 1995).

There are also some non-specific actions of cannabinoids, *e.g.*, some antioxidative activity in doses possibly relevant for the situation of a cannabis consumer, but so far there seem to be no relevant harmful non-specific actions in this dose-range.

The pharmacokinetics of a substance relate to the kinetics of its absorption, distribution in the body, metabolism, and excretion. For THC and other cannabinoids, pharmacokinetics vary significantly as function of the route of administration. Recent reviews of the subject can be found in the literature (Brenneisen 2001, Grotenhermen 1999).

Human users of drug cannabis products (marijuana, hashish) generally prefer administration by inhalation (cigarettes, pipes). Less common is oral ingestion of tea, pastries, and tincture. In animal studies, intravenous injection into the blood vessel, subcutaneous injection under the skin) and intraperitoneal injection into the abdominal region are widely used routes. This present study focuses on the impacts of THC which has been ingested orally with food.

Inhalative administration: Following inhalation, THC is quickly absorbed and the time course of its plasma concentration is similar to that following intravenous administration. Bioavailability of inhaled THC, as measured by its plasma concentration, is only 10–30%. Consequently, typically five times the dose of intravenous administration is required to achieve the same effects. About 0.05 mg/kg of THC, corresponding to 3.5 mg for a person weighing 70 kg, are required to produce minimum psychotropic effects. Generating the intoxication level desired by cannabis consumers requires at least 10–20 mg THC in a cigarette. This dose produces a maximum plasma concentration of 100 ng/ml after about 5 minutes. It decreases rapidly and only little THC is detected 2–3 hours after exposure (Figure 2.1).

Oral administration: The systemic bioavailability of THC reaches 6–20% after oral administration in a lipophilic vehicle, such as vegetable oil, which enhances the absorption of the lipophilic THC. Bioavailability usually remains below 10%. To achieve minimum psychotropic effects, humans require a single dose of 0.2–0.3 mg/kg, typically 10–20 mg, depending on the body weight. This is 10–15 times the intravenous dose required for minimum psychotropic effects. The maximum plasma level after oral administration of this dose is of the order of 5 ng/ml and is reached after 1–4 hours. Psychotropic effects set in 30–60 minutes after ingestion, peak after 1–3 hours, and last for 6–8 hours. The average maximum plasma concentration of THC in 6 cancer patients after oral ingestion of 15 mg THC was 3.9 ng/ml and was typically attained after 2 hours (Frytak *et al.* 1984). With the exception of one patient, the plasma levels of THC in all cancer patients had dropped below 1 ng/ml after 6 hours. Three patients received three doses of 15 mg THC a day. The maximum plasma level ranged between 3.6 and 6.3 ng/ml and did not increase significantly from that caused by a single dose. Ohlsson *et al.* (1980) observed a maximum THC-concentration of 5 to 6 ng/ml, occurring between 1 and 1.5 h after experienced marijuana smokers had ingested a chocolate cookie containing 20 mg THC.

2.1.1 Distribution to tissues, accumulation, and redistribution

Hunt & Jones (1980) estimated that 70% of THC initially leaving the central compartment is taken up by tissue and 30% is metabolized. THC rapidly penetrates highly vascularized tissues, among them liver, heart, fat tissue, lung, jejunum, kidney, spleen, mammary gland, placenta, adrenal cortex, muscle, thyroid, and pituitary gland, resulting in a quick decrease in plasma concentration.

Subsequently, intensive accumulation occurs in less vascularized tissues and finally in the body fat, the major long-term storage site. Studies with tritium-labeled THC determined maximal levels of radioactivity in kidneys and lungs after 2 hours, whereas after 72 hours, the highest levels were found in the spleen and body fat (Agurell *et al.* 1970), and levels in body fat were still increasing after 28 days of chronic administration (Kreuz & Axelrod 1973). The exact composition of the material accumulated in fat is unknown (Harvey 1991), among them unaltered THC and its hydroxy metabolites. A substantial proportion of the deposit in fat seems to consist of fatty acid conjugates of 11-OH-THC. Rediffusion from fat into plasma is slow.

Metabolism: More than 100 metabolites of THC have been identified. Within several minutes, 11-hydroxy-THC (11-OH-THC, the primary product for further metabolism to THC acids and similar to THC with respect to its pharmacological activity and toxicity) along with other hydroxy metabolites are formed. The predominant acid metabolite, 11-nor-9-carboxy-delta-9-THC (THC-COOH) (Wall *et al.* 1983) is commonly used to identify prior use of marijuana in urine tests. Following oral intake, higher amounts of THC-COOH are formed more rapidly compared to inhalation or intravenous administration (Wall *et al.* 1983). This is attributed to the first-pass effect of orally ingested THC, *i.e.* its initial metabolism by the

liver. The time course of plasma levels of THC and its metabolites 11-OH-THC and THC-COOH following oral application shows large variations among individuals (see Table 2.4, page 38) and often deviates strongly from the theoretical model in Figure 2.2. As it affects the rate of THC absorption from the digestive system, the composition and timing of meals ingested prior to an oral THC dose is one of the factors that influences the time course of plasma level of THC and subjective response.

Elimination from plasma: THC concentrations in plasma usually drop below 2 ng/ml within 6 hours after inhalation of a marijuana cigarette, than more slowly with increasing time from use (Huestis 1992). After smoking a low dose cannabis cigarette (1.75% THC, about 13 mg), the detection limit of 0.5 ng/ml THC in plasma was reached after 7.2 hours (range: 3–12 h); following a high dose cigarette (3.55% THC, about 27 mg), a plasma concentration of 0.5 ng/ml THC was reached within 12.5 hours (range: 6–27 hours) (Huestis 1992). Metabolites disappear more slowly.

The major reason for the slow elimination of THC from the plasma is the slow rediffusion of THC from body fat and other tissues into the blood (Leuschner *et al.* 1986). The true elimination half-life of THC from the plasma is difficult to calculate, as the concentration equilibrium ratio plasma/fatty tissue is only slowly reached, resulting in very low plasma levels that are difficult to analyze. In a study by Wall *et al.* (1983), the terminal phase ranged from 25–36 hours for THC, from 12–36 hours for 11-OH-THC and from 25–55 hours for THC-COOH after oral or intravenous dosing. The elimination half-life for THC metabolites from plasma is longer than the elimination half-life of the parent molecule. In a study by Hunt and Jones (1980), the terminal half-life of THC for chronic users was 18.7±4.2 hours and of the overall metabolites 52.9±3.7 hours.

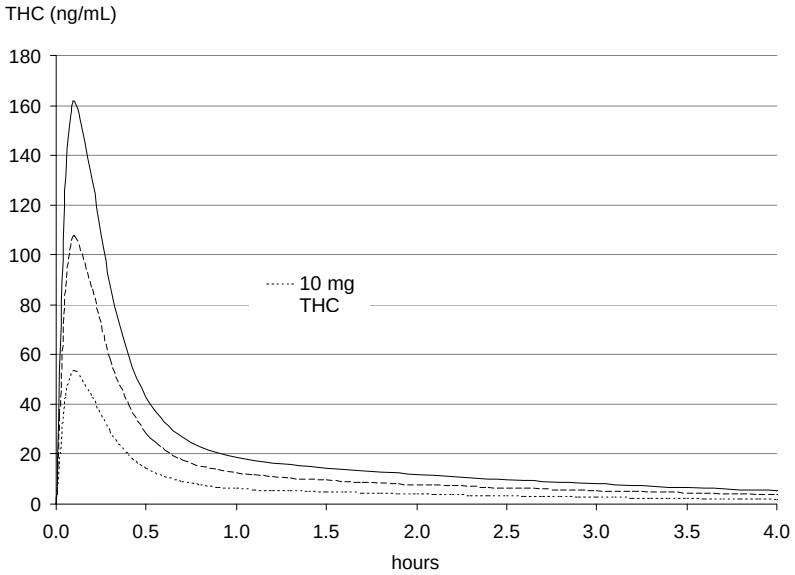


Figure 2.1 Course of THC plasma concentration following inhalation according to a mathematical model (Sticht & Käferstein 1998) for three different THC doses, assuming a 20% bioavailability

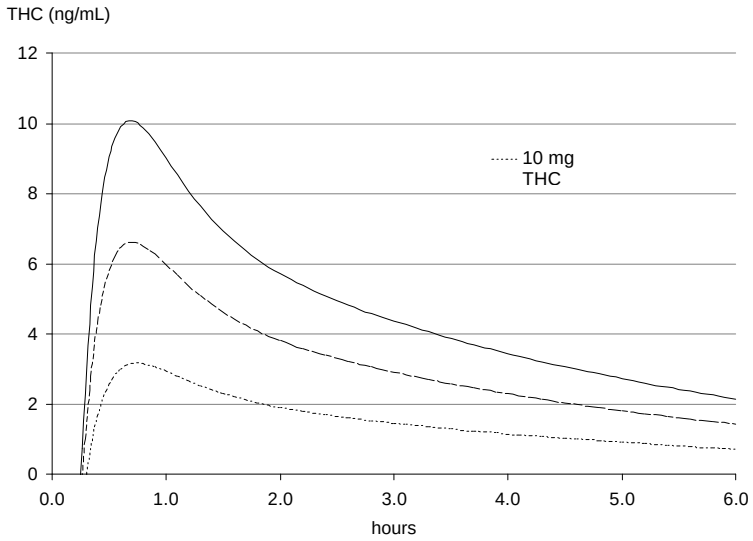


Figure 2.2 Course of THC plasma concentration with oral use according to Sticht & Käferstein (1998) for four different THC doses of THC, assuming a systemic bioavailability of 6%

2.2 Pharmacological effects of THC

THC is a pharmacologically highly active substance with dose-dependent effects on several organ systems and body functions. Reviews of the pharmacology of THC have been published by Grotenhermen (1999), Hall *et al.* (1994), Dewey (1986), and Hollister (1986). The most conspicuous effects are those on the central nervous and the cardiovascular systems.

The physical toxicity of THC is low. Tests to establish a lethal THC dose for monkeys were unsuccessful because the maximum administered dose of 9000 mg/kg body weight did not result in the death of the monkeys (Thompson *et al.* 1973).

2.2.1 Overview of toxicity

With regard to physiological effects, THC produces an increased heart rate, reddened eyes, and a dry mouth. As for psychotropic effects, a mild euphoria, an enhanced sensory perception, fatigue, and eventually dysphoria together with anxiety have been observed.

The following dose dependent effects were observed in clinical studies, both in vivo (*i.e.* in living organisms) and in vitro (*i.e.* in laboratory dishes):

Psyche and perception: fatigue, euphoria, enhanced well-being, dysphoria, anxiety, disturbed orientation, increased sensory perception and enhanced sexual experience, hallucinations, psychotic states.

Cognition and psychomotoric performance: fragmented thinking, enhanced creativity, disturbed memory, unsteady walk, slurred speech.

Nervous system: attenuation of pain, muscle relaxation, appetite enhancement, decrease in body temperature, vomiting, anti-emetic effects, neuroprotective effects in brain ischemia.

Cardiovascular system: increased heart rate, enhanced heart activity and increase in oxygen demand, vasodilation, reduced blood pressure, collapse.

Eye: reddened conjunctivae, reduced tear flow, reduced intraocular pressure.

Respiratory system: bronchodilation, dry mouth.

Gastrointestinal tract: reduced bowel movements.

Hormonal system: effects on luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, prolactine, somatotropin, TSH, reduced sperm count and sperm mobility and quality, suppressed ovulation and suppressed menstruation.

Immune system: impairment of cell-mediated and humoral immunity, anti-inflammatory and immune stimulating effects.

Fetal development: fetal malformations, fetal growth retardation, impairment to fetal and postnatal cerebral development, improved postnatal development.

Even a long-term high-dosing regimen of THC is tolerated relatively well by animals, *i.e.* does not result in the development of any serious deterioration in general health. This was suggested by a study of rats, which ingested 50 mg/kg THC per day over a period of two years (Chan *et al.* 1996). After two years, 45% of the controls and 70% of the dosed animals had survived. The higher survival in the THC-group was primarily due to a decreased incidence of cancer.

2.2.2 Acute effects

Acute psychotropic effects caused by the consumption of marijuana and hashish include mood changes and changes in sensory perception, the sense of time, etc. Acute physical effects include the acceleration of heart rate and dry mouth.

Several clinical studies have been conducted which allowed determination of a NOAEL for these effects. Lucas & Laszlo (1980) found pronounced psychotropic reactions (anxiety, marked visual distortions) in patients undergoing cancer chemotherapy that had received oral doses of 15 mg THC/m^2 (square meter of body surface) corresponding to 25 mg THC for an average adult (body surface: 1.7 m^2). A reduction to 5 mg THC/m^2, about 8–10 mg THC, produced only mild reactions. In a study by Frytak *et al.* (1984), oral administration of 15 mg THC to 38 cancer patients caused psychotropic effects in 58% while 42 % experienced no

effects. Brenneisen *et al.* (1996) administered single oral doses of 10 or 15 mg THC to two patients. Physiologic parameters (heart rate) and psychological parameters (concentration, mood) were not modified by the administration.

In a study by Chesher *et al.* (1990) of a healthy population dosed orally with 5 mg of THC following a light breakfast, no difference in the subjective level of intoxication was found relative to placebo controls. Doses of 10 and 15 mg THC respectively caused slight differences relative to a placebo. An oral dose of 20 mg caused marked differences in subjective perception. In several clinical studies, psychotropic reactions were also observed following a single dose of 5 mg THC (Petro & Ellenberger 1981). However, these were indistinguishable from effects observed after the administration of placebos.

At the lowest administered oral dose of 5 mg, Chesher *et al.* (1990) observed a decrease in several psychomotoric performance scores, primarily related to standing steadiness, reaction time, and arithmetic performance. It should be noted that the observed effects were small. Findings by other researchers suggest that even doses of 10 or 15 mg of orally administered THC generally result in minor psychomotoric effects (Brenneisen *et al.* 1996).

Several other physical effects, which are relevant to the therapeutic uses of cannabis were reported to occur in some individuals at oral doses of 5 mg or even 2.5 mg. For example, Maurer *et al.* (1990) noted a decrease in muscle spasticity in a patient suffering from spinal cord injury after a 5 mg dose, while Ungerleider *et al.* (1987) noted that a "7.5 mg dose is required to achieve significant spasticity reduction." Single doses of 5 mg THC or higher were used in several clinical studies with all indications (pain, spasticity, nausea and vomiting, glaucoma, etc.) except appetite loss and weight loss (Grotenhermen 2001). In appetite loss and wasting due to HIV/AIDS, doses of 2.5 mg once or twice daily have been shown to be effective (Beal *et al.* 1997). Oral dosing of THC causes tachycardia, *i.e.* an increase in heart rate (Karniol *et al.* 1974). Impacts are not expected to occur at single oral doses of less than 10 mg.

These findings relative to the production of effects by THC indicate that the psychotropic threshold of THC is in the range of 0.2–0.3 mg THC per kg body weight for a single oral dose taken in a lipophilic carrier, corresponding to an administration of 10–20 mg THC to an adult person. A single dose of 5 mg THC can be regarded as a placebo dose or the NOAEL for psychotropic effects and certain physical effects. The same single dose of 5 mg can be considered as the LOAEL for reduction in psychomotoric performance and some other physical effects. The LOAL for increase of appetite is 2.5 mg oral THC.

The effects of a single dose of THC typically last for 4 and 6 hours, with a maximum duration of up to 12 hours at higher doses. Thus, the ingestion of an oral dose of 5 mg of THC twice per day in a lipophilic carrier, equivalent to 10 mg taken over the course of a day, represents the NOAEL for psychotropic effects and the LOAEL for the reduction in psychomotoric performance.

2.2.3 Chronic effects

Several studies have suggested the potential damage to the respiratory system, caused by the smoking of marijuana or hashish, and impacts on the human psyche, as the major detrimental effects from chronic consumption of cannabis for intoxication. These effects are of no importance when THC is taken orally in sub-psychotropic doses.

Thus, limiting the daily ingestion of THC with food to well below the NOAEL and LOAEL for psychotropic and other nervous system impacts will provide ample protection from these effects. However, the question of whether non-perceptible and chronic physical health impairment may occur below the psychotropic threshold must also be addressed.

Based on the effects observed in animal studies, five major areas of potential adverse impacts on humans must be considered. They include effects on cognition and brain function, genotoxicity, teratogenicity, *i.e.* the creation of abnormalities in the developing fetus, impacts on the hormonal system and fertility, and effects on the immune system. The available literature suggests the following evidence with respect to these effects:

Cognition and brain function

Several of the detrimental impacts of chronic cannabis use are attributed to psychological effects, among them social behavioral problems, addiction and induction of psychosis. These effects are not relevant for sub-psychotropic doses. Instead, these effects were observed with long-term, often extensive consumption of cannabis products, representing typical oral equivalent daily THC doses in excess of 100 mg.

There is no evidence from human studies of any structural brain damage following prolonged exposure to cannabinoids (Solowij & Grenyer 2001). Several studies indicated that chronic use of the drug might adversely affect memory function and contribute to other lasting cognitive impairments (Solowij 1998). The long-term use of cannabis does not result in gross cognitive deficits, but there is evidence that it leads to a more subtle and selective impairment of higher cognitive functions (Solowij 1998). It has been reported that chronic cannabis use was associated with unique quantitative EEG features, which were also present in the non-intoxicated state (Struve *et al.* 1999).

While several studies found indications of minor cognitive changes from cannabis use (Solowij 1998, Fletcher *et al.* 1996), some studies of heavy users failed to detect any differences relative to controls. A study with long-term heavy marijuana users revealed many abnormal health features that distinguished them from the population as a whole (Gruber *et al.* 1997), but minor changes may have been overlooked because of the insensitivity of the methods used to quantify impairment of cognitive skills. In a study by Bowman and Phil (1973), cognitive performance was investigated in 24 heavy cannabis users who consumed cannabis on average for 19.2 years with a daily THC intake of about 500–1000 mg. No

differences were found in cognitive functioning, psychomotoric function, and reaction time in a multitude of sensitive tests.

Apparently, cognitive changes require long and heavy use. Thus, Fletcher *et al.* (1996) compared heavy younger and older users of cannabis with controls of similar age. The older cohort had consumed cannabis for an average of 34 years, the younger cohort for an average of 8 years. Short-term memory, working memory, and concentration skills were measured. Older long-term users performed worse than older non-users on 2 short-term memory tests involving the memorizing of lists of words. In addition, older long-term users performed worse than older non-users on selective and divided attention tasks associated with the working memory. No notable differences were apparent between younger users and nonusers.

In conclusion, chronic heavy cannabis use may slightly impair cognitive and psychomotoric performance. Such changes seem to require heavy and long-term use of cannabis with daily THC doses routinely exceeding 100 mg.

Genotoxicity

Several studies with cannabis users found no any increase in chromosomal breaks related to cannabis consumption (Matsuyama & Fu 1981, Cohen 1976, Cruickshank 1976, Matsuyama *et al.* 1976).

Joergensen *et al.* (1991) evaluated the genotoxicity of cannabis smoking by application of the sister-chromatid exchange (SCE) test, a sensitive tool for the discovery of genotoxic agents. They compared 22 tobacco smokers and 22 persons that smoked tobacco and marijuana. The smoking of tobacco in itself enhanced the SCE level significantly by 18.5% compared to non-smoking controls. The addition of marijuana did not further affect this level. Based on this observation, the authors concluded that cannabis smoke could not be considered genotoxic.

Several animal studies have found some evidence that THC might interfere with cell division (mitosis or meiosis) at doses that far exceed the doses relevant for the human consumption of cannabis (Desoize *et al.* 1981). Two studies in male mice investigated effects of perinatal exposure with THC on permanent genetic damage in germ cells, one giving negative results (Generoso *et al.* 1985), the other positive results, both conducted with high doses not relevant for this risk assessment.

Consequently, when consumed in doses typical for marijuana users, THC appears to be neither mutagenic nor carcinogenic. It also does not affect cell metabolism. The NOAEL is above concentrations relevant for the human consumption.

Teratogenicity

Birth defects

Several early animal studies found congenital malformations subsequent to the administration of high doses of THC (review by Abel 1980). Abel emphasizes the fact that findings of malformations were consistent only following exposure to relatively high doses using intraperitoneal administration (Abel 1985).

The findings from virtually all studies with humans did not find an increase in congenital malformations following marijuana use during gestation. The only exception is an early study by Hingson *et al.* (1982). They examined 1690 mother/child pairs for the effects of alcohol- and marijuana-use on embryonic development and fetal growth. Marijuana use was associated with the increase of a fetal syndrome known as alcohol embryopathy, or fetal alcohol syndrome.

All other epidemiological studies involving thousands of children have failed to show a relationship between marijuana use by pregnant women and fetal malformations (Grotenhermen *et al.* 1998).

Weight at birth

In a study with 1,226 women of whom 27 percent either had positive urine assays for THC or reported using marijuana during pregnancy, Zuckerman *et al.* (1989) found a significant mean reduction in neonatal weight by 79 grams and a decrease in size by a mean of half a centimeter. The study of Hingson *et al.* (1982) also associated marijuana use during gestation with a lower birth weight. Another study found the elevated risk of a low birth weight only among white regular marijuana users whereas nonwhites (of Hispanic or African-American descent) were generally not at an increased risk (Hatch & Bracken 1986).

In most studies, no correlation between marijuana use and fetal growth was found (Knight *et al.* 1994, Day *et al.* 1991, Shiono *et al.* 1985, Tennes *et al.* 1985, Fried *et al.* 1984, Gibson *et al.* 1983, Linn *et al.* 1983).

Other studies also evaluated the further development of the children of mothers who had used cannabis during pregnancy. According to a study by Fried and O´Connell (1987), the children of cannabis users were, on the average, heavier and taller than non-exposed children. In contrast to these results, another research group found that maternal use of marijuana was significantly and inversely related to infant size at eight months, but not to weight and head circumference (Barr *et al.* 1984). Yet another study did not find any growth retardation at the age of one year (Tennes *et al.* 1985).

Brain development

A study by Fried *et al.* (1987) observed increased tremors and startles on days 9 and 30 postnatal in children whose mothers had regularly used marijuana during gestation, compared

to non-exposed controls. In a sleep study, marijuana use was found to be associated with alterations in the sleep cycle of neonatals (Scher *et al.* 1988). A different group of children, aged three years, showed a disturbance in their nocturnal sleep, waking up more often during the night (Dahl *et al.* 1995). Children exposed to marijuana during pregnancy, aged 9 months, achieved slightly lower mental test scores compared to non-exposed controls (Richardson *et al.* 1995). However, no difference was found in the same group at the age of 19 months. In another study, children aged one year did not show any significant differences in their sleeping or eating habits, their mental functions or their psychomotoric abilities (Tennes at al. 1985). The gestational exposure to marijuana was concluded not to increase the rate of SIDS (sudden infant death syndrome) (Ostrea *et al.* 1997). Dreher *et al.* on day 3 postnatal could not detect any differences between neonatals of marijuana users and those of non-consuming mothers in neuro-behavior assessments (Dreher 1997, Dreher *et al.* 1994). After one month, the differences became apparent in favor of the marijuana population: in the prenatally exposed children, this was manifested in a greater liveliness, less irritability, and less tremors; these children were more easily quieted and scored higher in their reaction to different stimuli (sound, light, and touch).

Since 1978, an ongoing longitudinal study, the Ottawa Prenatal Prospective Study (OPPS) by Fried and colleagues, has been investigating the effects of marihuana and cigarettes inhaled during pregnancy. In a review, Fried (2001) summarized his findings as follows: “The consequences of prenatal exposure to cannabis are subtle. The impact during the course of pregnancy and upon the neonate appear to be considerably moderated by other risk factors with evidence from a number of cohorts suggesting mild effects upon fetal growth and central nervous system functioning. During the toddler stage, there is little evidence for a prenatal cannabis effect either upon growth or behavior. However, beyond the age of three, there are suggestive findings indicating a putative association between prenatal marihuana exposure and aspects of cognitive behavior that fall under the rubric of executive function.”

The Institute of Medicine Report (Joy *et al.* 1999) points out that it is unclear whether the slight cognitive impairment observed in children born to marijuana using mothers are cannabinoid effects or effects of smoking. They refer to the study conducted with Jamaican women (Dreher *et al.* 1994) that found no differences in fetal outcome depending on cannabinoid exposure: “For most of these studies, much of the harms associated with marijuana use are consistent with those associated with tobacco use, and smoking is a significant factor, so the contribution of cannabinoids cannot be confirmed. However, Jamaican women who use marijuana rarely smoke it, but instead prepare it as tea (Dreher 1987). In a study of neonates born to Jamaican women who either did or did not ingest marijuana during pregnancy, there was no difference in neurobehavioral assessments made at 3 days after birth and at one month” (Dreher *et al.* 1994).

In summary, scientific evidence regarding the development of the human fetus and child supports the assumption that marijuana use by women during pregnancy does not cause malformations. Various epidemiological studies stated inconsistent effects of cannabis use on

length of gestation, birth weight, and infant size. The majority of those studies, however, could not provide any evidence that the outcome of pregnancy was affected. Furthermore, there is no reference to an influence on postnatal growth development. The early neurological symptoms found in neonates by some researchers can be interpreted as withdrawal symptoms. There is indication that subtle impairment of cognitive functioning could appear during the course of development. However, it is unclear whether these effects are related to smoking or to cannabinoid exposure.

Controversial issue: In several studies on rats, Wenger and colleagues had found relevant effects on fetal outcome at very low doses (Wenger *et al.* 1999, Wenger *et al.* 1989). These studies used intraperitoneal injections of 0.001 mg/kg THC per day, resulting in significant effects on hormone levels, an increase in stillbirths, and other adverse effects. Wenger's findings obviously contradict the above-cited studies on human females who received significantly higher THC doses during pregnancy. The coordinator of Health Canada's THC health risk assessment (Davis 2001), who had based some of its conclusions on the potential risk from neuroendocrine disruption in offspring on work by Wenger and his colleagues, acknowledged that the applicability of his findings to humans require further confirmation by a two-generation study. We agree with this conclusion and have opted to dismiss findings by Wenger and his colleagues until confirmed in a study designed to more appropriately evaluate potential impacts on humans.

Hormonal system and fertility

Marijuana acts on the hypothalamo-hypophyseal axis. The hypophysis secretes the sex hormones LH, FSA, and prolactin, the thyroid hormone TSH (thyrotropin), ACTH (adrenocorticotropin) and somatotropin (STH). These hormones respond to releasing hormones (RH) of the hypothalamus. LH regulates the testosterone production in the testes. Testosterone and FSH are vital for the sperm production (sperm count, sperm motility and sperm function). The impact of using marijuana or administering THC on hormone levels in humans has been the subject of numerous studies.

Studies on males

Testosterone: Dax *et al.* (1989) investigated the effects of oral administration of three times 10 mg THC per day, or three times 18 mg THC in a marijuana cigarette, over a three-day period on male chronic marijuana users, following at least two weeks of abstinence. They did not find any alterations in the plasma testosterone concentration. Cone *et al.* (1986) did not find any decrease in testosterone after the smoking of two marijuana cigarettes (2.8% THC). Mendelson *et al.* (1978) could not detect any influence on the testosterone level in 27 marijuana users that had consumed a mean of 54 marijuana cigarettes (moderate users) or 120 marijuana cigarettes (heavy users) over a period of 21 days.

FSH: Acute THC-exposure (two marijuana cigarettes of 2.8% THC) did not result in an alteration of the FSH-level (Cone *et al.* 1986). Chronic administrations also did not have any

significant impact (Vescovi *et al.* 1992, Block *et al.* 1991, Hembree *et al.* 1976, Cushman 1975).

LH: In a study by Cone *et al.* (1986), a decrease in the LH-level after acute THC-exposure (approximately 50 mg inhalative) was noted. In a study of 10 chronic marijuana users, a reduction in their basal and GnRH (gonadotropin-releasing hormone) stimulated levels of LH was found (Vescovi *et al.* 1992). However, in other studies using a different experimental design, the LH-concentration was not affected by THC-exposure or cannabis consumption (Cushman 1975, Hembree *et al.* 1976, Kolodny *et al.* 1974, Mendelson *et al.* 1978, Block 1991).

Prolactin: After three days of abstinence, a slight elevation of prolactin-concentration was observed in six chronic cannabis users (Markianos & Stefanis 1982). Dax *et al.* (1989) investigated the effect of three times 10 mg oral THC per day or 18 mg THC in a marijuana cigarette three times per day for three days on male chronic marijuana users after two weeks of abstinence. Though no difference was found in plasma concentrations of LH and testosterone, they found the plasma prolactin level to be altered. The authors attributed this last finding to the heavy marijuana use. However, Cone *et al.* (1986) did not find any decrease in prolactin level after smoking two marijuana cigarettes (2.8% THC). Chronic cannabis users do not show any significant alteration in their prolactin levels (Vescovi *et al.* 1992, Cohen 1976, Kolodny *et al.* 1974).

Puberty: Copeland *et al.* (1980) observed pubertal arrest in a boy aged 16 years, who had consumed at least 5 marijuana cigarettes per day since he was 11 years old. Three months after cessation of consumption a normal entry into puberty was observed. This is the only observation of this kind so far.

The assumption of a causal connection between the observed gynecomastia of strong marijuana smokers and their use of marijuana does not appear to be conclusive, all the more so as no associations between marijuana consumption with prolactin levels or other relevant parameters were found in later studies. Considering the widespread use of marijuana, one would expect that more observations of this kind would have been reported in the literature. Relative to the possible impact of THC on puberty, only a single case has been described to date. In animal studies, high doses produced a slightly higher incidence of abnormal sperm. In human males, following daily consumption of 8–10 marijuana cigarettes (100–300 mg THC) over a period of several weeks, a slight reduction in sperm count was found, yet no increase in abnormal sperms or any impairment of function, primarily mobility, was observed. Neither acute nor heavy chronic cannabis usage was found to cause any consistent effects on the serum level of FSH, LH, prolactin, or testosterone in male subjects.

Studies on females

Menstrual cycle: Kolodny *et al.* (1979) reported an abnormal cycle length in marijuana smokers of an average of 26.8 days as compared to 28.8 days in controls. Moreover the cycle often was anovulatory (12.5% vs 38.3%). Dornbush *et al.* (1978) also found a reduced cycle length but did not state an increase in THC-induced anovulation. Other researchers did not find any significant influence on cycle length (Mendelson & Mello 1984).

Estrogen and progesterone: The hormonal profile of estrogen and progesterone did not differentiate chronic marijuana users from controls (Kolodny *et al.* 1979). Dornbush *et al.* (1978) did not find any significant influence on estrogen and estradiol. No correlation was found between acute marijuana smoking (18 mg THC) and the course of estrogen and progesterone concentrations during the menstrual cycle (Mendelson *et al.* 1986).

Testosterone: 26 female chronic cannabis users showed an increased testosterone level when compared to 16 controls (Dornbush *et al.* 1978). In the most extensive study to date, Block *et al.* (1991) did not discover any significantly elevated serum testosterone concentrations in comparison to controls and no significant association with their being grouped in occasional, intermittent, or heavy users.

Prolactin: The smoking of one marijuana cigarette (1.83% delta-9-THC) did not produce any significant changes in plasma prolactin levels during the follicular phase (between menstruation and ovulation) of the menstrual cycle. However, when smoked during the luteal phase (between ovulation and menstruation) this was reflected by a transient small suppression of the plasma prolactin levels that occurred 1 to 3 hours after consumption. (Mendelson *et al.* 1985b). Chronic users did not show any change in prolactin levels (Block *et al.* 1991).

LH: Mendelson *et al.* (1985a) did not find any change in the LH-level in 10 women after the smoking of a single marijuana cigarette. However, a small, but statistically significant decrement ($p < 0.02$) was observed when the marijuana was consumed during the luteal phase. Chronic users presented a normal LH-level (Block *et al.* 1991, Dornbush *et al.* 1978, Kolodny *et al.* 1979).

FSH: Mendelson *et al.* (1986) did not observe any change in FSH-level following acute exposure to 18 mg THC. Chronic female marijuana users also showed equally normal FSH-levels (Block *et al.* 1991, Dornbush *et al.* 1978, Kolodny *et al.* 1979).

Much less research of the impact of THC on female sex hormones has been conducted compared to that on the male sex hormone system. The results are inconsistent. There are no conclusive indications of any THC-associated impacts on the menstrual cycle length, the number of cycles without ovulation or on the plasma concentrations of estrogens, progesterone, testosterone, prolactin, LH or FSH in female marijuana users. The transient THC-induced suppression of prolactin and LH levels during the luteal phase of the menstrual cycle should be further investigated. However, this effect occurred only following the inhalative route which, in comparison to oral administration, is associated with a faster absorption of

the drug and higher plasma THC-levels. Chronic marijuana users did not show any significantly altered hormone levels.

Controversial issues: Again, Wenger and his colleagues reported significant alterations following very low doses of intraperitoneally administered THC, including a reduced LH concentration after i.p. injection of 0.001 mg/kg THC over the 1st, 2nd or 3rd week of pregnancy in rats (Wenger *et al.* 1988). In contrast, Tyrey (1980) administered intravenous THC in doses of 0.0312 to 0.5 mg/kg to female ovariectomized rats and found no effects on LH secretion at the lowest dose of 0.0312 mg/kg and significant effects at 0.0625 mg/kg and higher. It is unclear why an intravenous dose of 0.0312 mg/kg (corresponding to about 0.3 mg/kg oral THC with regard to bioavailabilty) should cause no effects while a 0.001 mg/kg THC dose should cause effects. Considering this contradiction in findings, we again opted to dismiss the findings by Wenger and his colleagues until confirmed independently.

Note that for both male and female subjects, the THC doses not producing a conclusive impact on hormone levels were those typically administered by marijuana users, *i.e.* above the psychotropic threshold of typically 10-20 mg of oral THC equivalent.

Immune system

The immune system is a complex functional system for the protection against noxious foreign material, for example bacteria and viruses, or for the elimination of anomalous structures (such as tumor cells). The organs of the lymphatic system (spleen, lymph nodes), the production sites of lymphocytes and other immune cells (thymus, bone marrow), a multitude of cells (lymphocytes, macrophages) and different molecules (immunoglobulines, cytokines, etc.) contribute to the immune system.

Immunity is either unspecific or specific (acquired). Unspecific immunity does not require sensitization through previous exposure. The ingestion of bacteria by macrophages and the destruction of tumor cells by natural killer cells fall in this category. In contrast, acquired immunity is based on selective responses of antibodies specifically sensitized to certain substances (antigens) or of specifically sensitized cells (T-lymphocytes, macrophages). The B-lymphocytes produce antibodies and regulate the humoral (mediated by specific antibodies) acquired immunity, whereas the activity of T-lymphocytes controls the cell-mediated immunity.

THC alters some immune parameters of humoral and cell-mediated immunity in a dose-related manner, acting either in an immunosuppressive or immunostimulating manner, depending on its specific effect on the system. At high THC-concentrations, unspecific effects on the cell membrane seem to play an important role, whereas at a lower dosage, THC-effects on the immune system appear to at least partly be mediated by a cannabinoid receptor-dependent pathway (Sanchez *et al.* 1997, Burnette-Curley 1995, Kaminsky *et al.* 1994). The CB2-receptor was found to be of particular relevance to these processes (Patrini *et al.* 1997).

Potential effects of THC on the immune system have been reviewed in detail by Grotenhermen *et al.* (1998). The analysis concluded that "…cell experiments and animal studies demonstrate that THC has suppressive effects on the humoral and cell-mediated immunity. However, the majority of those can be attributed to toxic unspecific effects. Many of the parameters analyzed required extremely high doses before exhibiting any significant effect. These effects were dose-dependent with the threshold concentration being precisely determinable. When applying lower doses one often observed differentially immunostimulating effects or no effects at all. Thus, for many immune system related parameters, the NOAEL falls within a range which is too high to be relevant to human consumption of marijuana or hemp food. In studies on humans or on the cells of marijuana users the effects observed were often contradictory. If such effects were found at all, they were weak, even in cases of heavy cannabis use, and of questionable relevance to health. The World Health Organization summarized in its most recent cannabis-report regarding the impact of cannabinoids on the immune system: 'Many of their effects appear to be relatively small, totally reversible after removal of the cannabinoids, and produced only at concentrations or doses higher than those required for psychoactivity (more than 10 µM in vitro, or more than 5 mg/kg in vivo)' (WHO 1997, p. 27)."

Consequently, the Health Canada risk assessment (2001) concluded: "The available data on the effects of cannabinoids on the immune system do not allow characterization of the dose-response for these actions. Since these effects are likely to be secondary to endocrine disruption, it is assumed that exposures below those not causing neuroendocrine disruption would not elicit adverse effects on the immune system."

2.3 Special aspects

2.3.1 Extrapolation of animal data to humans

One advantage of animal studies is that they allow for accurate control of the conditions of exposure to THC, such as dose and duration, and for the control of confounding factors. Thus, animal studies are an indispensable element of toxicological research. However, for several reasons, caution is required when using "data produced by those that continue to extrapolate animal data to humans without some attempt to discuss in detail the validity of their assumptions" (Campbell 1996).

Extrapolation from animal to human data is usually performed on the basis of body weight (BW), body surface, pharmacokinetics or of precise toxicological data (see Tables 2.1 and 2.2).

Table 2.1: Extrapolation of a dose of 1 mg/kg in a mouse and other animal species to humans on the basis of body weight and body surface (after Ings 1990)

Species	Weight (g)	Surface (cm^2)	Extrapolation Based on weight	Extrapolation Based on surface
Mouse	20	45	0.02	0.02
Rat	200	313	0.2	0.14
Monkey	4,000	3,057	4.0	1.36
Man	69,000	18,200	69	8.1

Table 2.2: Dosage conversion factors based on equal body surface (after Voisin 1990)

	To				
	Mouse	*Rat*	*Monkey*	*Dog*	*Man*
Weight (kg)	0.020	0.150	3	8	60
Surface (m^2)	0.0066	0.025	0.24	0.40	1.6
From					
Mouse	1	½	1/4	1/6	1/12
Rat	2	1	1/2	¼	1/7
Monkey	4	2	1	3/5	1/3
Dog	6	4	5/3	1	½
Man	12	7	3	2	1

Results from several studies suggest that extrapolation of animal data to humans is hampered by several conflicting factors. This aspect has already been addressed in connection with the findings from animal studies by Wenger and his colleagues. Several other examples shall illustrate this problem.

The Health Canada risk assessment (2001) cited the review by Scallet (1991) of chronic neurotoxicity studies in animals that led to the conclusion that neurotoxic effects, similar to those observed in humans after chronic marihuana exposure, require a period of three months to develop in rodents and that monkeys appear to be less sensitive. The risk assessment argues that this apparently lower sensitivity in monkeys may be due to the shorter relative time period of exposure in the longer-lived species.

However, other studies have demonstrated that rodents are also more sensitive to acute effects. Thus, the median lethal dose (LD_{50}) was established to range between 800 and 1,900 mg/kg oral THC for rats, depending on sex and strain (Thompson *et al.* 1973). When this dose is extrapolated on the basis of body surface, the oral LD_{50} in monkeys would be a half of this dose (400–950 mg/kg) per kg BW. However, experimental studies showed that none of the monkeys receiving up to 9,000 mg/kg of THC orally died as a result of exposure to

THC (Thompson *et al.* 1973). Instead of being 50% more sensitive, as predicted based on body surface, primates were at least five to ten times more resistant to THC.

Similar contradictory results have been observed relative to hormonal disruptive effects and impacts on the human fetus, relative to fetal rats. An example is the previously mentioned animal research by Wenger and his colleagues at the Medical School of Budapest (Hungary), who observed effects at very low doses of 0.001 mg/kg THC in rats injected intraperitoneally. Other researchers have also observed effects on animals at high doses, which could not be reproduced in studies of humans (see Table 2.3).

There are several indications that the effects observed by Wenger and his colleagues should not be extrapolated to humans. *E.g.*, in one of their studies (1989), i.p. injection of 0.001 mg/kg THC during the 3rd week of pregnancy in rats caused a significant prolongation of pregnancy and 42% of stillbirths. This contrasts strongly to studies in humans. There are many studies of pregnancy outcome in users of marijuana. None of them reported any increase of stillbirths relative to controls who did not consume marijuana.

Steger *et al.* (1990) found a significant decrease of plasma-LH and testosterone levels following doses of 0.1, 1.0 and 10 mg/kg THC in male rats. There was no dose-response relationship; all doses were equally effective. However much higher THC doses had no effect on testosterone level in humans. *E.g.*, Dax *et al.* (1989) investigated the effects on male chronic marijuana users of administering orally three times per day 10 mg of THC or inhaling three times per day 18 mg of THC for three days, following at least two weeks of abstinence. These conditions simulate routine cannabis drug use. The researchers did not find any alterations in the plasma testosterone concentration. Mendelson *et al.* (1978) could not detect any influence on the testosterone level in 27 marijuana users that had consumed a mean of 54 marijuana cigarettes or 120 marijuana cigarettes over a period of 21 days.

In a National Institute on Drug Abuse (NIDA) Research Monograph, Mendelson *et al.* (1984) stated with regard to the effect of THC on female hormones: “It is clear from the foregoing that THC consistently produces significant changes in pituitary gonadal hormones, which are essential for normal reproductive function in experimental animal models. The major unanswered question is: what is the relevance of these data for human females? There are often marked species differences even within animal models and the degree to which THC induced disruption of pituitary gonadal hormones in animals can be extrapolated to humans is an empirical question. Despite the predictive values (and relative economy) of studying drug effects in animals, the ultimate significance of these findings can only be determined in human studies” (page 105).

Table 2.3: Selected discrepancies between animal and human data on THC. These data had been used as the basis for selecting NOAEL/LOAEL in Health Canada's risk assessment (Health Canada 2001).

Target effect	Animal study	Human study
Male plasma testosterone hormone concentration	– 0.1 mg/kg oral THC resulted in decrease in male rats (Steger *et al.* 1991).	– 0.15 mg/kg oral THC three times daily did not cause an effect (Dax *et al.* 1989). – 0.25 mg/kg inhaled THC three times daily did not cause an effect (Dax *et al.* 1989).
Male prolactin level in plasma	– Increase following 0.04 mg/kg THC intraperitoneally in rats (Daley *et al.* 1974). – Decrease after 0.5 mg/kg oral THC in rats (Rodriguez De Fonseca *et al.* 1992).	– No change following about 0.6 mg/kg inhaled THC (Cone *et al.* 1986). – Chronic cannabis users do not show any significant alteration in their prolactin levels (Vescovi *et al.* 1992, Cohen 1976).
Female luteinizing hormone (LH) concentration	– 0.0625 mg/kg intravenous THC caused a profound decrease in rats (Tyrey 1980).	– No change in LH level following about 0.3 mg/kg inhaled THC (Mendelson *et al.* 1985a). – However, a light significant decrement ($p < 0.02$) was observed when the marijuana was consumed during the luteal phase. Chronic users present a normal LH-level (Block *et al.* 1991, Dornbush *et al.* 1978, Kolodny *et al.* 1979).
Stillbirths	– 0.001 mg/kg intraperitoneally THC resulted in 42% stillbirths (Wenger *et al.* 1989).	– No increased rate of stillbirths in any human study of female marijuana users.
Duration of pregnancy	– 0.001 mg/kg intraperitoneally THC resulted in an increase of duration of pregnancy (Wenger *et al.* 1989).	– Most human studies did not find any effect of cannabis use on duration of pregnancy (*e.g.*, Shiono *et al.* 1995, Day *et al.* 1991, Zuckerman *et al.* 1989. Hatch and Bracken 1986). – Some found a decreased length of gestation or a higher rate of premature births (Sherwood *et al.* 1999, Fried *et al.* 1984, Gibson *et al.* 1983).
Birth weight	– 0.001 mg/kg intraperitoneally THC reduced birth weight in rats (Wenger *et al.* 1991)	– Chronic marijuana use (about 0.1 to 2.0 mg/kg inhaled THC) did not cause reduced birth weight (Shiono *et al.* 1995, Dreher *et al.* 1994, several other studies).

Conclusion: Toxicological data from animal studies can help to elucidate the toxicity of cannabinoids in humans. However, comparison of the data from studies on humans and animals reveals often considerable inconsistencies. These may result from not only interspecies differences, but also different routes of administration. Particularly, the suitability of the intraperitoneal route for extrapolation to oral and inhalative exposure has previously been questioned (Abel 1985). The findings by Wenger and his colleagues, which contradict findings from human studies applying much higher doses and using the more

representative oral or inhalative routes, are a case in point. Thus, wherever possible, a quantitative risk assessment should be based on data from human studies. Furthermore, effects observed in other mammals may not occur in humans even at much higher doses.

2.3.2 Extrapolation of different routes of administration to oral ingestion

A large portion of the data on the toxicology of THC for humans and animals was not obtained following oral administration but from studies employing inhalative or parenteral (intravenous, subcutaneous, intraperitoneal) application. As discussed above, different routes of administration result in a different bioavailability and in different pharmacokinetics (surveys: Harvey 1991, Agurell *et al.* 1986, Wall *et al.* 1983). This must be taken into account when dosage and plasma concentrations for example from inhalative studies are translated to the situation of an oral administration, *i.e.* the only relevant exposure route for hemp foods.

Table 2.4: Comparison of the effectiveness of THC application to man via relevant routes (Harvey 1991, Agurell et al. 1986, Frytak et al. 1984, Stefanis 1978)

Parameter	Intravenous	Inhalative	Oral (lipophilic vehicle)
Systemic bioavailability	100%	10–30 (–50)%	6–20%
Psychotropic threshold per kg body weight	0.02 mg/kg	0.06–0.1 mg/kg	0.2–0.3 mg/kg
Psychotropic threshold per person	1 mg	2–6 mg	10–20 mg
Maximum plasma concentration at the psychotropic threshold	20–50 ng/ml	20–50 ng/ml	5 ng/ml
Dose for a marked intoxication	2–4 mg	10–20 (–50) mg	30–40 (–90) mg

The comparison in Table 2.4 suggests that extrapolation of data from studies using intravenous or inhalative administration to the oral route requires the use of different conversion factors for the acute single application and effects of chronic use. The systematic bioavailability is relevant primarily to chronic effects, whereas other aspects are relevant to acute effects. These include the faster re-absorption and the considerably higher peak plasma concentrations of THC after smoking and intravenous intake, compared to those caused by oral administration. For example, the only relevant effect in several acute studies, which evaluated the impact of THC on hormone levels (estrogen, progesterone, LH, testosterone, prolactin, FSH) in women, was a transient small decrement ($p < 0.02$) observed between 60 and 120 minutes after the smoking of one marijuana cigarette in a study by Mendelson *et al.* (1985a). If such effects are strongly dependent upon THC levels in the plasma, they may not have been caused by oral intake of a comparable dose, due to a much less pronounced effect on THC levels in the plasma.

Conclusion: The oral ingestion of THC shows distinct differences to parenteral application (intravenous, intraperitoneal) and inhalation with regard to metabolism and time course of plasma level. Compared to inhalation, oral ingestion of the same dose will cause less toxicity because of the lower systemic bioavailability. Ingestion may also result in less toxicity compared to inhalation of a dose producing the same bioavailability, due to a less pronounced THC plasma peak.

2.3.3 Transfer of THC to the fetus

In both humans and animals, transfer of delta-9-THC to the vascular system of the fetus occurs across the placenta. The time course of THC-concentration in fetal blood is strongly correlated to that in maternal blood, though fetal plasma concentrations were found to be lower compared to the maternal level in rats (Hutchings *et al.* 1989), in sheep (Abrams *et al.* 1985–1986), in dogs (Martin *et al.* 1977), and in monkeys (Bailey *et al.* 1987).

According to a study in monkeys, the major THC metabolite THC-COOH (11-nor-9-carboxy-THC) does not appear to cross the placenta and the fetus does not seem to produce much of this metabolite (Bailey *et al.* 1987). While maternal plasma THC-COOH levels peaked at 1 hr (44 ng/ml), almost no THC-COOH was detected in fetal plasma.

Following oral intake of THC by the mother, the ratio between fetal and maternal THC levels in plasma appear to be much lower—about one to ten—compared to intravenous and inhalative THC intake, where fetal THC levels are about one third of the mother's. This is likely attributable to the difference in metabolic pathways between oral, inhalative (smoking), and intravenous administration. In a study on dogs, the brain of the fetus showed a THC concentration of one third of the mother's concentration half an hour after intravenous administration (Martin *et al.* 1977). This relation was also maintained with multiple administrations, indicating that the maternal plasma THC and not the fetal tissue is the actual source for the fetal plasma THC.

The only conclusive study on THC transfer following oral administration was carried out with rats (Hutchings *et al.* 1989). Two multiple-dose groups were administered either 15 or 50 mg/kg THC once daily during the last two weeks of gestation. Two single dose groups were given the same dose as above but only once on the last day of gestation. Sixty minutes after receiving the last dose, plasma THC levels of all dams and their fetuses were analyzed. Among the dams, plasma concentrations co-varied with dose, and multiple dosing produced higher concentrations than acute dosing, especially at the high dose. Among the fetuses, both in the acute and the chronic dosing group, plasma concentrations were approximately 10% of those found in the dams.

An additional difference between inhalative and oral intake is the much lower maximal peak concentrations of THC following the oral route. Inhalation of a single dose of 10–20 mg THC will result in THC peak plasma concentration in the order of about 50–100 ng/ml, whereas the same oral dose will result in a broader, less pronounced peak with maximum

concentrations of typically 5 ng/ml (see Figures 1 and 2). This will also result in a lower broader THC peak in the fetal plasma. Since higher peak concentrations result in stronger effects for the same route of administration, it can be assumed that the fetus is less affected following oral ingestion, since oral and inhalative route of administration of the mother result in the same supply route for the fetus, *i.e.* the blood vessels of the umbilical cord.

This indicates that the absence of cognitive effects in the children of mothers who used oral cannabis in the Jamaican study (Dreher *et al.* 1996) may be due in part to the inefficient transfer, thus low fetal toxicity, of THC ingested by pregnant women.

Conclusion: Fetuses experience significant exposure to THC following maternal cannabis ingestion. However, due to different metabolic routes for oral and inhalative THC, fetal exposure after oral THC intake by the mother, *e.g.*, with hemp foods, will be lower compared to inhalative THC intake by the mother, *e.g.*, by smoking cannabis cigarettes, even after correction for the lower bioavailability to the mother of oral THC. Assuming a systemic bioavailability of oral THC of about half that of inhaled THC (10 vs. 20%) and a fetus/mother plasma level ratio of 1:10, compared to 1:3 for inhaled THC, fetal exposure to THC ingested by the mother is about one-sixth of the exposure caused by the inhalation of the same dose (see Table 2.5). In addition, oral ingestion by the mother results in a much lower maximum peak concentration compared to inhalation of the same dose, further reducing possible impacts from THC. These differences in the transfer to the fetus between oral and inhalative uptake of THC thus provide an additional margin of safety from potential teratogenic effects, as discussed in Section 2.2.3.

Table 2.5: Comparison of dose-specific fetal toxicity caused by maternal ingestion vs. inhalation of THC.

	Inhalation (smoking a marihuana cigarette)	**Oral intake in a lipophilic carrier** (hemp oil)
Systemic bioavailability	20 %	10 %
Ratio of ingested THC to THC systemically available	1/5	1/10
Ratio of THC concentration in fetal and maternal plasma	1/3	1/10
Overall ratio	1/15	1/100

2.3.4 Exposure of infants through milk of nursing mothers

Small quantities of THC also pass into the milk of the mothers. In a study on monkeys, 0.2% of the THC ingested by the mother appeared in the milk (Chao *et al.* 1976). Chronic administration leads to a THC accumulation in the milk (Perez-Reyes & Wall 1982). Milk of cannabis-using mothers may show higher concentrations of THC compared to their plasma. In a cannabis-using mother, the concentration of THC in milk was 8.4 times higher than in

plasma (Perez-Reyes & Wall 1982). It should be noted, however, that even the highest concentrations of THC in milk do not exceed the ng/ml range. Assuming a concentration of 5 ng/ml THC in plasma after oral ingestion of 15 mg THC and a ten-fold higher concentration in the milk (50 ng/ml), this would result in the daily uptake by an infant of 0.035 mg THC in 700 ml milk (700 ml × 50 ng/ml), a medium daily milk intake of an infant (Köhler *et al.* 1984). Note that daily oral intake of 3 × 15 mg of THC will not result in higher maximal plasma concentrations (see Table 2.4, page 38).

Thus, 1 mg THC taken orally every 12 hours via hemp foods is expected to produce THC concentrations in mothers milk in the low ng/ml range, even if regular consumption of hemp products has caused some accumulation of THC. The corresponding worst-case daily doses ingested by infants is in the low µg-range

Conclusion: Small quantities of THC also pass into the milk of mothers who use marijuana or consume hemp foods. Typical daily THC intake by mothers consuming even extensive amounts of hemp foods (see Section 3, pages 53ff.), *i.e.* less than 1 mg of THC, will cause THC uptake by the suckling infant in the low microgram range.

2.3.5 Susceptibility of fetuses and children to THC

It has been argued that fetuses and children are more susceptible to the effects of THC than is suggested by the administered dose when compared on the basis of body weight or surface. Several reasons are given: a) a lower proportion of body fat in children and correspondingly lower potential for THC sequestration, resulting in a higher fraction remaining in circulation; b) a lower proportion of blood lipoprotein and correspondingly lower potential for cannabinoid binding, resulting in a larger proportion of THC available for receptor binding; c) immaturity of the hepatic microsomal enzyme system, and thus, THC is metabolized more slowly, increasing the effective duration of exposure; d) infants and fetuses (human studies) have been reported to have a greater density of brain cannabinoid-binding sites so greater disruption could occur at a lower dose (Health Canada 2001).

Since all relevant effects of THC on humans caused at lower doses are receptor mediated, the relative receptor density in fetuses, infants, and adults will critically affect relative susceptibility to adverse effects.

Glass *et al.* (1997) found that the fetal and neonatal human brains show patterns of receptor distribution similar to those observed in the adult human brain. They found a similar density of CB receptors in several parts of the brain (neocortex, cerebellum) and a greater density in children in other parts (midbrain, basal ganglia). The authors admit some limitations of their study: “Due to the small numbers of cases available for the study, it is not possible to draw any definitive conclusions on the precise levels of cannabinoid receptors binding within the developing brain. Also, since the fetal/neonatal and adult tissue was not processed together, considerable care must be taken in comparing the results of the fetal/neonatal studies with the results in the adult brains” (Glass *et al.* 1997).

These observations contrast to the results of a study by Belue *et al.* (1995), who found that cannabinoid receptor density in rats increases fivefold from birth to adulthood. Also, Rodriguez de Fonseca *et al.* (1993) found an increase in CB binding in rats between birth and day 30, followed by a slight decrease until adulthood (day 60 and later). Another group (McLaughlin *et al.* 1994) found that cannabinoid receptor mRNA (messenger ribonucleic acid) is present at adult levels as early as postnatal day 3, while CB binding increased almost 50% with increasing age. The last study may resolve some of the contradictions between the different studies since receptor density may be high in infants and children while receptor activity may be low.

In contrast to the theoretical assumption of a higher susceptibility of fetuses and children in the Health Canada draft risk assessment (2001), clinical studies have shown that children tolerate much higher doses of THC than adults before psychotropic side effects become significant (Abrahamov *et al.* 1995, Dalzell *et al.* 1986).

In one study, eight children, aged 3 to 10, who underwent chemotherapy, orally received 18 mg delta-8-THC per square meter of body surface, four times daily. Each child received an average of 60 doses, which caused only mild psychotropic side effects in two children and none in the other six. Thus, children with a body surface of 1.0 m^2 received 18 mg THC four times daily (see Table 2.6). Assuming a body surface of 1.8 m^2 for an adult, this corresponds to single doses of 30 mg and a daily dose of about 120 mg THC. Delta-8-THC is assumed to be somewhat less psychotropic than delta-9-THC, with a relative potency of approximately 75%. Thus, a single 30 mg delta-8-THC dose corresponds to about 23 mg of delta-9-THC, a dose at which adults usually experience considerable psychotropic effects.

Table 2.6: Body weight and body surface according to Richardson & O'Connor Associates Environmental Inc. (1997) and U.S. EPA (1996).

Parameter	Adult female	Adult male	Child (5–11 years)
Body weight (kg)	63.1	78.8	32.9
Body surface (m^2)	1.675	1.872	1.0

Dalzell *et al.* (1986) conducted a study of 23 children (age: 10 months to 17 years) receiving the THC derivative Nabilone for treatment of the side-effects of chemotherapy. Children weighing less than 18 kg received 0.5 mg Nabilone twice daily, children weighing between 18 and 36 kg received 1.0 mg Nabilone twice daily, and children >36 kg received 1.0 mg Nabilone three times per day. The dose typically administered to adults is 2.0 mg twice daily (*e.g.,* Niiranen & Mattson 1985). 1 mg Nabilone corresponds to about 10 mg THC. Side effects among children were similar in frequency and severity to those observed in adults, and only one child with pronounced psychic effects found them intolerable. This study also demonstrated that even very small children tolerate comparatively high doses of psychotropic cannabinoids, *i.e.* ligands of the CB1 receptor. However, in the Nabilone study there was no relevant difference in response between adults and children, if one considers the applied dose corrected for body surface.

This leaves open the question whether fetuses and infants, less than 10 months in age, might show a higher susceptibility due to more free THC in the plasma (because of less body fat and less blood lipoprotein) and a lower capacity to metabolize THC by the liver. We concede this possibility, but due to the experience from clinical studies in children we assume that the theory of continuing increased receptor density and/or receptor activity from fetus to adult is more in line with observations in real life than the assumption of a higher receptor activity in fetuses and infants.

Conclusion: With respect to psychotropic side effects, infants and children show a lower susceptibility to THC and the THC derivative Nabilone in clinical studies compared to adults. The findings contradict the assumption of a higher susceptibility of children to THC, caused by the higher availability of free THC in the plasma and a lower metabolic capacity of the liver. It is conceivable that the lower metabolic capacity of the immature liver in fetuses results in increased THC levels as a result of cumulative dosing, for example, from extended consumption of hemp foods. However, multiple dosing studies provide no indication that plasma levels in the fetus in fact increase (see section 2.3.3). Even with chronic administration, THC levels in the plasma of fetuses are much lower compared to that of the mother.

2.3.6 Accumulation of THC in body tissue

Because of its high lipophilicity, an estimated 70% of THC administered to the body is initially absorbed by and accumulated in body tissue (Hunt & Jones 1980). The accumulation of THC in tissue is driven primarily by its concentration in the plasma. As plasma levels fall off, some of the accumulated THC rediffuses into the plasma. Following extended THC uptake via hemp foods or drug cannabis, a dynamic equilibrium between THC accumulation in tissue and its remobilization and rediffusion into the plasma is attained. Rediffusion of THC into plasma is slow and its low rate appears to be the main reason for the comparatively slow THC elimination from the plasma (Leuschner *et al.* 1986).

No studies have been conducted to assess the impact of THC rediffusion from tissue, which has previously accumulated THC following extended ingestion of hemp foods, into the plasma. Such studies would provide a more accurate assessment of the contribution of accumulated THC to THC plasma levels. However, the low daily doses ingested with hemp foods, the very low resulting peak THC levels in the plasma (typically below 1 ng/ml) and the documented slow rediffusion of THC indicate that rediffusion rates will be too low to raise plasma concentration to levels which could result in or contribute to adverse effects.

Concern has been raised by Health Canada (2001) that extended consumption of hemp foods may cause significantly increased THC levels in mother's milk. The discussion in Section 2.3.4 shows that THC concentrations in the milk of drug cannabis using mothers in fact exceed those in the plasma. However, the resulting concentrations in milk, even following repeated cannabis use by the mother, are in the ng/ml range. As a concentration-driven process, the redistribution of THC accumulated from extended use of hemp foods

will, as was discussed previously, result in THC levels in milk in the low ng/ml-range, corresponding to daily doses significantly below 100 µg/day.

Conclusion: The accumulation of THC in body tissue represents a source of THC to the plasma even after cessation of THC uptake. The establishment of a dynamic equilibrium between accumulation and remobilization and the slow rediffusion process indicate that corresponding THC levels in plasma will be insufficient to supply THC at rates which could result in or contribute to adverse effects.

2.3.7 Other cannabinoids

Cannabis plants and hemp foods contain cannabinoids other than THC in significant proportions, primarily cannabinol (CBN) and cannabidiol (CBD). Compared to THC, there are much less data available on the toxicology of non-psychotropic cannabinoids. Cannabidiol was usually well tolerated in several clinical studies, when taken in daily doses of 100–1,500 mg (Zuardi *et al.* 2001), *i.e.* apart from the sedative effect no side effects were observed. In a study by Zuardi *et al.* (1993), which investigated the effects of cannabidiol (CBD) on plasma prolactin, growth hormone, and cortisol in normal volunteers, oral doses of 300 mg and 600 mg significantly influenced the normal circadian rhythm of cortisol attenuating the normal decrease in cortisol level. There were no effects on plasma prolactin and growth hormone.

An oral dose of 50 mg cannabinol (CBN) did not cause any measurable effects (psychotropic effects, pain threshold, skin sensitivity, heart rate, electrocardiogram, blood pressure, body temperature) but appeared to increase slightly the effect of THC on some aspects of physiological and psychological processes (Karniol *et al.* 1975).

There are no toxicological data available on the effects of low doses of CBN in humans. Animal studies suggest that CBN is as effective as THC in influencing gonadotropin and testosterone secretion. The LOAEL for this effect was 0.1 mg oral CBN (the same as for THC) in a study by Steger *et al.* (1990) with male rats. However, much higher THC doses had been found to have no effect on testosterone level in humans (Dax *et al.* 1989, Mendelson *et al.* 1978). In our opinion, it can thus be safely assumed that CBN will have no effect either.

Conclusion: When present in complex mixtures, other cannabinoids may add to the toxicity of THC. However, the cannabinoids relevant in hemp seed products seem to have measurable adverse effects on humans only at doses too high to be relevant to this evaluation of the impacts of hemp foods on humans.

2.3.8 Impact of cannabidiol on THC effects

It has recently been demonstrated that CBD acts as a weak antagonist to all agonists at the CB1 cannabinoid receptor, including THC (Petitet *et al.* 1998). CBD has been shown to

antagonize in humans the psychotropic, other subjective, and several physical effects of THC, mediated by the CB1 receptor (Karniol *et al.* 1974). CBD is found in industrial hemp at much higher concentrations than THC. While in cannabis of the drug type, the THC/CBD ratio typically ranges from 2:1 to 7:1, industrial hemp varieties show THC/CBD ratios ranging from 0.06:1 to 0.5:1. Thus, CBD is by far the dominant cannabinoid in industrial hemp varieties (de Meijer *et al.* 1992). Typical THC/CBD ratios in various cannabis types are shown in Table 2.7.

Table 2.7: Ratio of THC and CBD in cannabis types (after de Meijer 1992)

Chemotype	**THC content**	**THC/CBD ratio**	**CBD/THC ratio**
drug type	>1–20%	2.3–7.4	0.14–0.4
intermediate type	0.3–1.0%	0.5–2.0	0.5–2.0
fiber type	<0.3%	0.06–0.5	2–17

High doses of THC can induce anxiety, panic reactions, and functional psychotic states. Zuardi *et al.* (2001) found that a dose of 300 mg of CBD caused a significant reduction in anxiety in a model of speech simulation, comparable to the effect from 10 mg of the sedative diazepam. The same research group treated a young man with bipolar disorder, who had been admitted to a hospital because of aggressive behavior, self-injury, incoherent thoughts, and hallucinations, for four weeks with doses up to 1,500 mg CBD daily (Zuardi *et al.* 2001). All symptoms improved impressively following treatment with CBD, suggesting that the improvement could not solely be attributed to an anxiolytic effect.

It has been demonstrated in several studies that simultaneous administration of CBD antagonized the characteristic psychotropic effects of THC (Zuardi *et al.* 1982, Dalton *et al.* 1976, Karniol *et al.* 1974). In a study by Zuardi *et al.* (1982), eight volunteers received, in a double-blind design, either a high single oral dose of THC (0.5 mg THC per kg body weight, *i.e.* between 25 and 40 mg), or the same THC dose combined with twice that amount of CBD. The study demonstrated that CBD blocked the anxiety produced by THC. This antagonistic effect was also found with other symptoms caused by THC, among them difficulty concentrating and disconnected thoughts. Cannabidiol also blocks several physical effects of THC, among them tachycardia, *i.e.* an increase in heart rate (Karniol *et al.* 1974). 30 mg of oral THC caused, 50 minutes after ingestion, a maximum increase in pulse rate of 135 beats per minute, on the average; in comparison, a placebo caused only 98 beats/min, while simultaneous ingestion of 30 mg of THC and 60 mg of CBD caused a maximum pulse rate of 106 beats/min (Karniol *et al.* 1974). Human volunteers were also asked to estimate the subjective duration of a time period of 60 seconds. After ingestion of a placebo, 30 mg THC, and a combination of 30 mg THC and 60 mg CBD, respectively, average estimates were 58 seconds (placebo), 34 seconds (THC), and 50 seconds (THC + CBD) (Karniol *et al.* 1974).

Conclusion: CBD acts as a weak antagonist at the CB1 receptor and significantly reduces certain THC effects exerted at this receptor in animals and humans. The CBD/THC ratio in industrial hemp used for the production of hemp seeds is 2 or higher. This ratio was shown to be sufficiently high for CBD to antagonize subjective and physical effects of THC in humans. CBD appears to increase the threshold above which THC is expected to cause acute psychotropic, cognitive and physical effects. It can be assumed that other effects of THC exerted at the CB1 receptor, *e.g.*, effects on the hormonal system and on brain development in the fetus, will be antagonized as well. A lack of data on the combined impacts of THC and CBD at the low doses characteristic of hemp food consumption currently precludes an assessment of the relevance of these antagonistic effects.

2.4 Determination of acceptable daily intake for THC

The effective protection of the general population from the adverse health effects of a non-carcinogenic toxic food ingredient or food additive routinely involves determination of a "safe dose", *i.e.* a dose of the substance of concern at which occurrence of any of its known toxic effects can be excluded with an ample margin of safety. This safe or sub-threshold dose is commonly referred to as acceptable daily intake (ADI) or tolerable daily intake (TDI). Regulatory agencies responsible for the safety of the domestic food supply, such as the U.S. Food and Drug Administration (FDA), routinely follow a two-step process when determining the ADI for a substance under review.

Few chemicals have been adequately studied in humans for accurate identification of a sub-threshold dose. Thus, agencies generally rely on human epidemiological and animal laboratory data to estimate sub-threshold doses for humans. First, scientists review all toxicity data and determine which of the observed effects caused by the substance can be considered adverse. Not all produced effects are adverse effects, and the judgment of what constitutes an adverse effect is often difficult. Subsequently, scientists determine the appropriate safety or uncertainty factors (UF) to apply to the No-Observed-Adverse-Effect Level (NOAEL) or Lowest-Observed-Adverse-Effect Level (LOAEL) for the critical effects. The NOAEL is the highest dose that causes no observed adverse effects in the animal species tested, while the LOAEL represents the lowest dose at which a specific effect has been observed. Critical overviews of the methodology of developing ADI as well as scientific and legal aspects involved in the process have been provided by Hattan *et al.* (1999) and Dourson *et al.* (1996).

The need to develop UFs is based on the lack of data on the effects of sub-threshold doses and the uncertainty involved in the extrapolation of the response observed for a small cohort to the general population and the extrapolation from other animal species to humans. UFs are generally chosen based on toxicity, pharmacodynamic, and pharmacokinetic data.

2.4.1 NOAEL and LOAEL

The above review of studies on the toxicology of THC suggests that much of the toxicological data for adverse effects caused by THC are derived from animal studies in which high doses were applied as well as from cell-experimental studies. For most of the potential health effects of THC, the NOAEL was found at doses higher than those relevant for hemp food uses. For the effects of interest in this study, human data are generally available and should be used to develop an ADI for THC, considering the mentioned systematic problems and uncertainties involved in interspecies extrapolation. Several studies in the literature have reported adverse effects of THC on rodent species at very low doses. Since these results contradict findings from human studies, their relevance to humans has been questioned.

Table 2.8 summarizes relevant LOAEL and NOAEL levels for effects caused by THC (tabulated for THC dose per body weight and total THC dose). It suggests that the LOAEL for oral dosing of THC refers to a slight impairment in psychomotoric functions at a single dose of 5 mg of oral THC. Since the effects of such low doses of THC persist generally for 4–6 hours, with a maximum of up to 12 hours, the ingestion of three equal doses per day do not significantly raise THC levels in the plasma, compared to a single dose. Consequently, daily intake of $2 \times 5 = 10$ mg of THC, taken over the course of the day, will not result in impacts exceeding those observed for a single 5 mg dose. Oral THC intake via hemp food is comparable to the repeated intake of smaller doses over the course of a day. This ingestion pattern causes broader and lower THC levels in plasma over time, compared to higher single or multiple doses. Thus, the ingestion of 10 mg/day of THC with food represents a conservative choice for the LOAEL for slight impairment in psychomotor functions.

The NOAEL for psychotropic effects caused by the oral ingestion of THC has also been established at 5 mg/day. As for the above LOAEL, a daily dose of $2 \times 5 = 10$ mg of THC does not produce cumulative effects. Thus, ingestion of 10 mg of THC per day with food represents the NOAEL for psychotropic effects caused by orally taken THC.

There is no conclusive evidence as to whether repeated oral dosing of THC causes minor reversible cognitive effects on the fetus or transient effects on the hormonal level of humans. It appears that for such effects to occur at all, the inhalative dose routinely consumed by the subjects would have to be in the range of 5–10 mg of inhaled THC, corresponding to 10–20 mg of oral THC. Again, the findings of an embryo-toxic effect may have been confounded by the increased blood levels of carbon monoxide with smoking (Joy *et al.* 1999).

Table 2.8: Ranges of THC doses and selected effects on humans and animals (Health Canada 2001, BgVV 2000, Grotenhermen et al. 1998)

THC Dose		Effect
Per body weight	**Total dose**	
0.001 µg/kg/day	0.07 µg/day	Tolerable daily intake, based on neuroendocrine disruption in female rats, intraperitoneal injection, suggested by Health Canada (2001)
0.001 mg/kg/day	0.07 mg/day	LOEL for neuroendocrine disruption (see above)
0.007 mg/kg	0.5 mg	Acceptable daily intake (ADI) proposed in this study for THC ingestion via hemp foods
0.07 mg/kg	5 mg	LOAEL for acute neurological effects in humans (single oral dose) NOAEL for psychotropic effects in humans (single oral dose)
0.14 mg/kg/d	10 mg/day	LOAEL for acute neurological effects in humans (2 x 5 mg/day oral) NOAEL for psychotropic effects in humans (2 x 5 mg/day oral)
0.2–0.3 mg	10–20 mg	Minimum psychotropic effects (single oral dose)
1–2 mg/kg	50–100 mg	Heavy cannabis consumption
10–20 mg/kg	–	Medium dose in animal studies
100–200 mg/kg	–	High dose in animal studies

* *Health Canada (2001) stated that available data do not allow a tolerable daily intake (TDI) due to the degree of uncertainty in the identification of a NOEL. The authors discuss a LOEL of 0.001 mg/kg observed in the studies by Wenger et al. (1991, 1989, 1988) and recommend a safety margin of 10 for intra-individual variability, another 10 for interspecies variability, another 10 because there is no NOEL, and another 10 for the protection of the child/fetus. This results in a TDI of below 0.0000001 mg/kg THC.*

2.4.2 Choice of uncertainty factor

Over the last decades, health organizations and regulatory agencies have developed generally accepted methods for addressing the uncertainty involved in determining the sub-threshold dose for a known toxic substance. Estimation of the sub-threshold level which provides protection for the general population from any adverse effects involves the selection of three independent UFs, which are multiplied to form a composite UF.

Default uncertainty factors of 10 are commonly used for extrapolation of an average human NOAEL to the NOAEL for the most sensitive human. A factor of 10 is also used for extrapolating data from animal studies to human data. It accounts for interspecies variation and assumes implicitly that humans are significantly more sensitive to an observed effect than the animal used in a test. As discussed in Section 2.3.1, this seems to represent an unreasonably conservative assumption for the extrapolation of toxicity data for THC obtained from studies with rats.

If a LOAEL exists for a specific effect but no NOAEL has been established, the uncertainty in the to-be-derived NOAEL must be addressed. Generally, a factor of 10 or lower appears to be adequate. When using a LOAEL for determination of the sub-threshold dose, the severity

of the effect at the LOAEL level is to be considered. Mild effects that may represent an adverse impact will require lower UFs. Previous reviews of LOAEL/NOAEL for a range of toxic chemicals indicate that corresponding uncertainty factors mostly range between 1 and 6 (Dourson *et al.* 1996).

The effect observed at the LOAEL for THC represents a rather mild adverse impact. In accordance with the above guidelines we conclude that an uncertainty factor of 2 is adequate for extrapolation of the LOAEL to the NOAEL for this effect.

Consequently, a UF of $10 \times 2 = 20$ appears to provide an ample margin of protection from acute adverse effects caused by oral intake of THC.

2.4.3 Acceptable daily intake

Based on this selection of a daily dose of 10 mg of THC ingested with food by a person of average weight (70 kg) as LOAEL and applying a composite uncertainty factor of 20, we propose an acceptable daily intake for oral THC with hemp food of:

ADI = 10 mg/day THC ÷ 20 = 500 µg/day

As discussed above, additional margins of protection are provided to the consumer of hemp foods and their offspring by the oral ingestion route and cannabinoid ratio, relative to the injection or inhalation of pure THC which represent the routes of administration and cannabinoid ratio of many of the studies used in the determination of this ADI.

2.5 Summary conclusions and recommendations

Acute effects: The lowest observed adverse effect level (LOAEL) for the ingestion of THC, representing a slight impairment in psychomotoric functions, is represented by a single dose of 5 mg of oral THC. Daily intake of 10 mg of THC, taken over the course of the day, will not result in impacts exceeding those observed for a single 5 mg dose. Consequently, the ingestion of 10 mg/day of THC with food is equivalent to the LOAEL for slight impairment in psychomotor functions.

The NOAEL for psychotropic effects caused by the oral ingestion of THC has been established at 5 mg/day. As for the above LOAEL, a daily dose of 10 mg of THC does not produce cumulative effects. Thus, ingestion of 10 mg of THC per day with food represents the NOAEL for psychotropic effects caused by oral THC.

Fetal development: Various epidemiological studies on humans report inconsistent effects attributable to the use of drug cannabis by pregnant women on the duration of gestation, weight at birth, and infant size, with the majority of those studies not providing evidence of any impact on pregnancy. There are indications that subtle impairment of cognitive functions during early development stages may occur in children of mothers who smoked marijuana during pregnancy. However, it is being debated whether these effects are caused by smoking

or the fetus' exposure to THC. The maternal use of drug cannabis implies the repeated uptake of THC at doses corresponding to more than 10–20 mg taken orally.

A highly elevated risk of stillbirths and other teratogenic effects produced by administration of very low intraperitoneal doses of THC to rats has been reported by Wenger and his colleagues. An increased rate of stillbirths has not been observed with human females who used marijuana during pregnancy, corresponding to a much higher THC uptake. Thus, we recommend dismissal of these findings, pending independent confirmation of their relevance to humans.

Hormonal system: Low dose chronic or acute marijuana use was not observed to be associated with hormonal or other reproductive changes in males. In females, the only conclusive hormonal effect reported was a transient THC-induced suppression of prolactin and LH levels during the luteal phase of the menstrual cycle after smoking one cannabis cigarette. Again, Wenger and his colleagues found significant effects on the levels in female sex hormones, following intraperitoneal administration to rats of very low doses of THC. For the same reasons as above, we recommend dismissal of these findings.

Extrapolation from animal data to humans: Animal studies offer distinct advantages over studies on humans, notably the accurate dose control. However, considerable inconsistencies between human and animal data have been observed for studies on THC. Compared to humans, specifically rats appear to be much more sensitive to the acute effects of THC, especially if it is administered by intraperitoneal injection. Thus, wherever possible, a risk assessment for humans should be based on data obtained from studies on humans.

Different routes of administration: THC in hemp foods is ingested orally, while much of the toxicological data on THC was obtained from other routes of administration, including inhalation and parenteral application. Compared to inhalation and intravenous administration, THC shows a lower specific toxicity from the oral ingestion. This is due to a lower systemic bioavailability and, depending on the effect under consideration, to a less pronounced peak in plasma level.

Distribution of THC to the fetus: Fetal exposition following oral ingestion by the mother is lower compared to inhalative THC intake by the mother. After oral intake, THC plasma levels in fetuses were approximately 10% of those found in the mother's plasma, compared to about 30% after inhalation. This difference is likely caused by the difference in metabolic routes. In addition, oral ingestion by the mother results in much lower peak concentrations in fetal blood when compared to maternal inhalation of THC, further reducing possible toxic effects to the fetus. These impacts of oral administration on THC uptake by the fetus provide an additional margin of safety from potential effects caused by maternal inhalation of THC.

Transfer of THC to the infant via mother's milk: Small quantities of THC pass into the milk of mothers who consume drug cannabis. The estimated daily THC intake via milk by suckling infants, whose mothers consume hemp foods extensively (maximum conceivable daily intake of 0.5 mg of THC, see Section 3), will be in the low microgram range.

Susceptibility of fetuses and children to THC: In clinical studies, children from 10 months to 17 years of age showed a lower susceptibility to THC and tolerated higher doses with less psychotropic side effects than adults, when compared on the basis of body surface. This contrasts to the theoretical assumption of a higher susceptibility caused by comparatively higher levels of THC in the plasma and a lower metabolic capacity of the liver. It is conceivable that the lower metabolic capacity of the immature liver in fetuses may result in increased THC levels following cumulative dosing. However, there is no indication from multiple dosing studies that plasma levels in the fetus in fact increase.

Accumulation of THC: The accumulation of THC in body tissue represents a source of THC to the plasma even after cessation of THC uptake. The establishment of a dynamic equilibrium between accumulation and remobilization and the slow rediffusion process indicate that corresponding THC levels in plasma will be insufficient to supply THC at rates which could result in or contribute to adverse effects.

Toxicity of other cannabinoids: When present in complex mixtures, other cannabinoids may add to the toxicity of THC. However, they seem to have measurable effects on humans only at doses too high to be relevant to the consumption of hemp foods by humans.

Antagonistic effects of CBD: CBD acts as a weak antagonist at the CB1 receptor and is capable of counteracting THC effects exerted at this receptor in both humans and animals. Unlike in drug cannabis, the CBD/THC ratio in industrial hemp varieties used for the production of hemp seeds exceeds 2:1. This ratio was shown to be sufficiently high to cause antagonistic effects of CBD to subjective and physical effects of THC on humans. It thus tends to increase the lowest THC threshold expected to cause acute psychotropic, cognitive, and physical effects. It can be assumed that other effects of THC exerted at the CB1 receptor, *e.g.*, effects on the hormonal system and on brain development in the fetus, will be antagonized as well. CBD's antagonism to THC would tend to provide an additional margin of protection from the effects of THC. Assessing the relevance of this effect at the low doses of THC and CBD ingested with hemp foods will require further study.

Recommended safety factor and acceptable daily intake for oral THC: This hazard assessment for THC suggests that daily doses of 10 mg of THC, taken orally with food, will not result in adverse acute or chronic effects to the consumer and her/his offspring. The only documented potentially adverse effect experienced by humans at this dose level appears to be a slight reduction in psychomotoric performance and a possible increase in intraocular pressure. There is contradictory evidence on whether this dose may cause minor reversible cognitive effects on the fetus or transient effects on the hormonal level. The choice of a safety factor of 20 (10, to account for variations in the sensitivity among individuals; 2, for extrapolation from the LOAEL for the slight observed effects to the respective NOAEL) provides a sufficient margin of safety from any such effects.

Assuming a LOAEL of 10 mg of THC per day and a safety factor of 20, we suggest that an oral THC dose of 500 microgram/day, ingested via hemp foods, provides an ample margin of

safety from adverse health effects and represents the acceptable daily intake (ADI) level for THC.

Additional margins of protection from potential adverse effects, particularly to the fetus, may, depending on the impact, be provided by the overall lower pharmacological effectiveness of orally ingested THC, the presence of some THC in its inactive form, and the antagonistic effects caused by CBD as the dominant cannabinoid in food products from hemp seeds.

Two controversial issues regarding the toxicity of THC and other cannabinoids require clarification by future studies. These are the reported effects of very low THC doses on the fetus and the outcome of pregnancies observed in animal studies with intraperitoneal dosing and an analysis of their relevance to humans, and the importance of other cannabinoids to the overall toxicity of hemp food products.

3. EXPOSURE ASSESSMENT FOR UPTAKE OF THC FROM HEMP FOODS

As discussed in Section 2, the extent of any adverse health effects from THC intake via hemp foods is strongly dependent on daily THC intake. The latter in turn depends on several factors. They include the technical and nutritional feasibility of food products involving hemp, the corresponding typical hemp seed content in food items, the THC levels in hemp seed derivatives, and the market availability of hemp food products to consumers. Most importantly, actual intake of hemp seed derivatives and THC residues will depend crucially on dietary habits of the exposed population and the extent to which commonly eaten foods can be replaced by hemp foods.

In summary, the following exposure assessment develops and analyzes several dietary scenarios, including a reasonable worst-case diet and estimates corresponding daily THC intake. Section 3.1 summarizes and critiques previous exposure estimates; Section 3.2 establishes typical values for the composition of hemp foods and their respective THC content. Sections 3.3–3.5 evaluate three dietary scenarios for the consumption of hemp foods by exposed individuals in North America, and present and discuss estimates of the corresponding daily THC intakes.

3.1 Review of previous health risk and exposure assessment studies

Two studies have previously provided assessments of the exposure to and potential adverse health effects caused by THC and other cannabinoids in hemp foods (Health Canada 2001, Grotenhermen 1998). Their findings relative to the potential exposure of humans to THC in hemp foods are briefly summarized and critiqued in the following. Both studies provided valuable information to this current study. However, our review suggests that neither study offers a sufficiently detailed, realistic and current representation of THC uptake by North Americans under various plausible dietary scenarios. Among their most obvious shortcomings were their assumptions made on food consumption patterns and the content of hemp seed derivatives in hemp foods. A brief review of these studies follows.

Health Canada study

The Health Canada study (Health Canada 2001) represents a detailed analysis of the potential THC intake from consumption of hemp foods and cosmetics by adult females and males (>20 years) and children (5–11 years). Food consumption patterns of adults were based on unpublished Nutrition Canada data (Bob Hill, personal communication 1999, in Health Canada, 2001); no distinction was made between consumption patterns and quantity of female and male adults. Food consumption data for children were based on U.S. Department of Agriculture data from the 1996 *Continuing Survey of Food Intakes by Individuals* (CSFII) (USDA 1997). Two consumption scenarios were evaluated. They differed by the extent to

which conventional foods were replaced by similar commercial or home-cooked items containing hemp seed derivatives. In the worst-case scenario, representative of individuals that "promote the use of hemp products", all foods, *i.e.* 100%, were replaced with hemp foods. A replacement of 10% of all foods with hemp foods was assumed to produce a more realistic, yet conservative, value, representative of a typical Canadian consumer.

Our review identified several apparently inaccurate or outdated assumptions, including the following:

– The assumed THC levels in hemp seed derivatives under various scenarios, compiled in 1997/98, are higher than those now commonly found. Assumed concentrations were 4, 10, and 15 µg/ml for hemp oil, and 4 and 10 µg/g for meal and whole and hulled hemp seed,, respectively

– Several of the average dietary intakes used in this study for adults appear to be unrealistically high. *E.g.*, the study cited an average consumption of 215 g pasta per day for either males or females, corresponding to about 800 kcal, in addition to a consumption of 333 g of baked goods, 99 g of minced meat products, 372 g of dairy products, and 81 g of snack foods. These figures are considerably higher than those determined by the USDA's 1996 CSFII. Unfortunately, the underlying consumption data were not available and it remains unclear whether some food groups, in the exposure scenario chosen by HC, *e.g.*, rice or meat products, were replaced with other foods. The HC study also does not indicate whether the quantities of foods were given as prepared foods or dry foods.

– Average consumption of beverages also seems to be unrealistically high for an average diet. The total fluid intake, excluding water and milk, added up to 2034 g/day: beer (890 g/day), coffee (537 g/day), fruit drinks (317 g/day), wine (251 g/day), and energy drinks (40 g/day). In comparison, the CSFII from 1996 (USDA 1997) indicates about half to two-thirds of this value for the mean daily consumption of all beverages excluding water, fruit juices, and milk (913 g for female adults, 1302 for male adults).

– Several of the values of hemp seed derivative ingredients' content in hemp foods seem unrealistically high. One example is the assumed content of 47.7 percent weight of hemp flour in pasta. As mentioned in Section 3.1, the bitter taste of hemp flour, the lack of gluten, and the high oil content prohibit such a high content of hemp flour. Rather, a maximum hemp flour content of 20% yields a more realistic, conservative estimate.

Because of these observed inaccuracies and the use of outdated information, the Health Canada study did not appear to provide a reliable basis for a current exposure assessment.

nova Institute study

The evaluation by the nova Institute represented the first published comprehensive risk assessment for THC in hemp foods (Grotenhermen *et al.* 1998). Its objectives were to

establish, based on a review of the literature, ADI levels for THC and other cannabinoids and to derive THC limits for food items reflective of food consumption patterns in Germany.

Based on the NOAEL for psychotropic effects (10 mg/day of oral THC) and applying a safety factor of 10, an ADI of 1 mg of THC for an individual of average weight (70 kg) was derived. Recent average food consumption patterns for a German population were obtained from the German Federal Office of Statistics. Foods were attributed to one of four categories (oil, finished products, alcoholic drinks, non-alcoholic drinks). Total daily consumption for each group was calculated from governmental statistics. Consumption for each category was multiplied with a safety factor to account for potentially higher consumption by individuals. Safety factors ranged from 1.5 for edible oil to 5 for non-alcoholic drinks. The ADI for THC was attributed to the four categories and THC limits were calculated for each category. They are shown in Table 1.1, page 14.

Data and approach used in the study by the nova Institute are not applicable to the current situation in North America for several reasons. Food consumption patterns in Germany and North America are likely to differ considerably. More importantly, the study did not, within each category consider the substitution potential for specific hemp foods. Also, the derived composite THC limits for each category do not account for the fact that the content of hemp derivatives may vary considerably from product to product. For these reasons, we did not utilize the study's findings regarding THC exposure as the basis for this current study.

For reasons of effectiveness and enforceability, we suggest that Health Canada's practice to limit THC uptake via hemp foods by controlling the THC content of hemp seed derivatives is preferable over the alternative of limiting THC levels in the final product. As discussed above, limiting THC levels in the final products had been proposed by the nova Institute's study and used as the basis of the more recent German THC guidelines (see Table 1.1, page 14). Regulating THC content in final products requires considerably more sensitive analytical methods for verification of compliance with the generally lower THC limits in final products. In our opinion, this would increase the cost of compliance, divert attention from controlling the actual source of THC, and may impose unjustified de-facto limits on the content of hemp seed derivatives in final products.

Consequently, our following exposure assessment focuses on developing a detailed analysis of the potential hemp seed derivative content of a multitude of food products and their respective THC levels. In our opinion, this approach provides a better understanding of the most relevant sources of current THC exposure via food and provides a rational basis for efforts to regulate exposure to THC.

3.2 Composition and THC content of hemp foods

3.2.1 Nutritional analysis of hemp seed derivatives

Table 3.1 summarizes typical nutritional analyses of hemp seed derivatives for food uses. In addition to these seed derivatives, essential cannabis oils extracted from the flowers by steam distillation are finding limited use for the flavoring of beverages and candies.

Table 3.1 Typical nutritional characteristics of whole hemp seeds, hulled hemp seeds, and hemp seed flour (from Leson & Pless 1999, Union Deutsche Lebensmittelwerke GmbH 1983).

	Whole hemp seeds /100 g	**Hulled hemp seeds*** /100 g	**Hemp seed flour** /100 g	**Hemp oil** /100 g
Energy	500 kcal	560 kcal	**	835 kcal***
Protein	23 g	33 g	31 g	
Total fat	31 g	44 g	8 g	100 g
Saturated	3 g	5 g		9–11 g
Unsaturated	28 g	39 g		9–91 g
Carbohydrates	34 g	12 g	45 g	
Dietary fiber	30 g	7 g		
Sugars	2 g	3 g		
Ash	6 g	6 g	8 g	
Moisture	6 g	5 g	8 g	

* Composition of hulled hemp seeds varies with residual hull level.

** No values for the energy content of hemp seed flour were found in the literature.

*** Typical value for vegetable oils (Union Deutsche Lebensmittelwerke GmbH 1983).

Since the late 1990's, various food products containing hemp seed derivatives have become commercially available in the U.S. and Canada through retail stores and mail order. Consumers may also encounter hemp foods in restaurants or in home cooking. In most of these products, hemp seed derivatives replace other common ingredients on the basis of their oil or protein content. The content of hemp seed derivatives in hemp foods varies widely. The resulting THC content in food will also vary both as a function of food composition and the THC concentration in the respective derivative. Our approach and findings relative to these two items are presented in the following.

For quantification of the typical and maximum hemp ingredient content in food products available in North America and THC levels now commonly achieved in hemp seed derivatives, this study relied on several sources. They included an Internet survey of available hemp foods, interviews and discussions with practitioners in the areas of natural foods, hemp foods and THC analysis, cookbooks and recipes for hemp foods, and a previous

compilation in the Health Canada risk assessment (Health Canada 2001). Remaining data gaps, particularly for products, which are developmental but not yet commercially available, were completed with estimates based on expert input, professional judgment, and personal experience. Sources of information used for our survey are listed in the "Resources and References" section of this report (p. 79ff.)

3.2.2 THC content in hemp seed derivatives

A review of the literature and discussions with researchers, analytical laboratories and hemp seed suppliers suggest that the THC content in seeds varies considerably with hemp variety, location and growing conditions, timing of harvest, and seed cleaning method employed (Crew 2000/2001, Laprise 20001, Moravcik 2001, Webster 2001, Scheifele 2000b).

Overall, THC levels in hemp seed derivatives have decreased considerably since the early to mid-1990's, when hemp oil and seeds first appeared in the North American market. This decrease is largely attributable to the exclusive cultivation of low- and very-low THC varieties in Canada and the EU and the employment of thorough seed drying and cleaning techniques by seed producers in these countries. Our discussions with practitioners and regulatory agencies, results from the mandatory THC analysis of seeds and oil produced in Canada, and a study evaluating the effectiveness of various dry and wet cleaning methods suggest that Canadian processors now generally achieve THC levels in hulled seeds of less than 1.5 µg/g. "Cold pressed" hemp oil usually contains less than 2 µg/g but concentrations of 5 µg/g and sometimes up to 10 µg/g are found occasionally. Whole seeds and hemp flour, *i.e.* the ground seed cake remaining after oil extraction, typically contain less than 2 µg/g, respectively. Hemp protein powders and isolates, which have not yet entered the North American market, are projected to contain THC levels of usually significantly less than 1.5 µg/g (Crew 2000/2001, Laprise 2001, Moravcik 2001, Webster 2001).

The typical THC content of hemp seed derivatives used in the three following exposure scenarios is listed in Table 3.2. Actual THC levels, particularly in hulled seeds, generally appear to be lower. Thus, the THC ingestion rates in this exposure assessment represent conservatively high estimates for the overall population.

Table 3.2 Typical assumed THC concentration in hemp seed derivatives

Hemp seed derivatives	**THC concentration** (µg/g)
Whole seeds	2.0
Hulled seeds (nuts)	1.5
Hemp seed oil	5.0
Seedcake/flour	2.0
Protein powder/isolate	1.5

Due to the lack of regulatory drivers and the currently higher cost of measuring THC levels reliably at levels below 1 µg/g, little reliable data on the THC content in final products is available. Thus, this study estimated the THC levels in final product based on the more extensively available information on THC levels in hemp seed derivatives and on the hemp seed derivative content in the final product.

When assessing the relevance of THC levels in hemp seed derivatives, one must consider that the THC measured in hemp foods refers to "total THC" as determined by GC/MS. It includes both the psychoactive free (phenolic) ^{9}-tetrahydrocannabinol and the two non-psychoactive acid forms of THC, THC acids A and B. Although limited data suggest that in processed hemp foods, such as oil, their contribution to total THC is low, typically 10-20% (Leson *et al.* 2001), their contribution to the measured total THC provides an additional small margin of safety from the adverse effects of phenolic THC.

3.2.3 Hemp seed derivative content in foods

Table 3.3 lists the typical and maximum likely content of hemp seed derivatives in various food items. Sources of information, primarily seed processors, food manufacturers and distributors are listed in the "Resources and References" section, pages 79ff. As high hemp content is generally considered a competitive advantage, these sources are more likely to present overestimates of the true hemp derivative content. This will result in higher, more conservative exposure estimates.

"Typical hemp content" refers to the upper range of levels commonly found in products now commercially available or close to market introduction. Future increases in these levels are conceivable but limited by one or several product specific factors. They include:

– The high oil content of hemp seeds and the high proportion of triple-unsaturated fatty acids with their sensitivity to oxidation and rancidification;

– The lack of gluten, which renders flours from grains, such as wheat and rye, suitable for baking. This and the characteristic bitter taste of hemp flour limit its maximum reasonable content in baked goods and pasta to about 20%;

– The lack of casein, lactose, and other fermentable sugars, which largely account for the characteristics of dairy products and cereal seeds;

– The amino acid spectrum of hemp protein which appears to be less complete than for meat and soy derived protein and does not render hemp protein suitable as an exclusive source of protein;

– The currently high price of whole and hulled hemp seeds and oil compared to materials derived from other oil seeds.

"Maximum hemp content" refers to hemp seed derivative levels which are conceivable assuming cost constraints are irrelevant, such as in home cooking, and assuming further research and development in improving the areas of food stabilization and separation of

desirable ingredients. For products currently not commercially available, only "maximum" values are listed. Certain listed products, particularly dairy and meat substitutes, are not likely to be produced at all but are nonetheless included for use in the "reasonable worst-case" scenario of a diet, which avoids any source of animal protein. Finally, whole hemp seeds were not included in our analysis. Because of their unappealing shell, they are now found only in a small number of products, mostly snacks, and there only in small proportions. Furthermore, since THC levels in well-cleaned whole seeds now are routinely below 2 parts per million (ppm), even a conceivable increase in their future use would not cause a significant increase in THC uptake compared to the use of hulled seeds.

Hemp foods flavored with hemp flower essential oil extracts, *e.g.*, lemonades or teas, have not been relevant in the North American market. However, such products are available in some European countries and may become more popular in North America in the future. Limited THC analyses of essential oils, obtained through steam distillation of flowers and leaves of industrial hemp plants, suggest that their THC content varies with hemp cultivar and time of harvest. Concentrations in the range of 50–100 ppm appear to be common (Karus 2001, Mediavilla & Steinemann 1997). Because of its distinct flavor, the amount of essential oil used in beverages is kept low. Limited analyses of cannabis-flavored soft drinks indicate that these beverages contain less than 5 µg/kg or parts per billion (ppb) of THC (Karus 2001). Beers containing small quantities of hemp seeds or that are flavored with essential cannabis oil are also becoming increasingly available in both North America and Europe. Again, limited THC analyses indicate that these products generally contain less than 3 µg/kg of THC. For the following exposure estimate we assumed maximum THC concentrations in hemp content beer and soft drinks of 3 and 5 µg/kg, respectively.

Table 3.3 summarizes the typical and maximum hemp content for relevant food products assumed for this exposure assessment. It also lists respective THC levels, assuming THC levels in hemp seed derivatives shown in Table 3.2, p. 57.

Table 3.3 Typical content of hemp seed derivatives in hemp foods, maximum content (in parentheses), and corresponding THC level (from various industry sources, see "Reference and Resources" section and other references from Section 3.2.2)

	Typical hemp seed derivative content in food products			**THC content in product**	
	Hulled seeds	Hemp seed flour	Hemp seed oil	ppm	Note
Assumed THC content (ppm)	1.5	2	5		
Grain products					
Bread, rolls, pizza crust	(10%)	5% (10%)		0.25 (0.35)	
Cereal, muesli, grits, etc.	5% (10%)			0.08 (0.15)	
Quick breads, pancakes, French toast	10% (15%)	(12%)	(5%)	0.39 (0.72)	
Pasta		10% (20%)		0.2 (0.4)	
Mixtures mainly grain	2% (5%)	2% (5%)	(1%)	0.12 (0.23)	[1]

	Typical hemp seed derivative content in food products			THC content in product	
	Hulled seeds	Hemp seed flour	Hemp seed oil	ppm	Note
Assumed THC content (ppm)	1.5	2	5		
Dairy product substitutes					
Butter, margarine			(20%)	(1)	[2]
Cheese	15% (30%)			0.23 (0.45)	[3]
Whole milk	(7%)			0 (0.11)	[4]
Low-fat milk	(5%)			0 (0.08)	[4]
Skim milk	(4%)			0 (0.06)	[4]
Milk drinks, flavored milk, meal replacements with milk	(7%)			0 (0.11)	[4]
Yogurt	(6%)			0 (0.09)	[5]
Fluid and whipped cream, half-and-half, sour cream, milk sauces, gravies	(2%)		(20%)	0 (1.03)	[6]
Spreads, sauces, and dressings					
Mayonnaise			30% (80%)	1.50 (4)	
Salad dressing	(5%)		15% (25%)	0.83 (1.33)	
Sauce (pasta or meat)	(20%)		(5%)	0.30 (0.55)	
Hummus	5% (10%)		5% (10%)	0.33 (0.65)	
Nut butter	(95%)		(5%)	1.68 (0.68)	
Meat substitutes					
Meat loaf, veggie burger	5% (15%)			0.08 (0.23)	[7]
Tofu	30% (35%)			0.45 (0.53)	
Snack foods					
Cookies, cakes, muffins, pastries, pies	5% (20%)	10% (12%)	2% (5%)	0.38 (0.79)	
Candy, other toppings,	5% (15%)			0.08 (0.23)	
Ice cream	10% (20%)			0.15 (0.3)	
Nuts, seeds	(100%)			(1.50)	
Chips, crackers, pretzels, corn chips	5% (12%)	5% (10%)		0.18 (0.38)	
Snack bar	10% (20%)			0.15 (0.3)	
Trail mix	10% (20%)			0.15 (0.3)	
Beverages					
Beer				(0.003)	[8]
Coffee				0.025 (0.04)	
Energy drinks			2% (3%)	0.1 (0.15)	
Lemonade, teas				0.005 (0.005)	[8]
Supplements					
Oil / capsules			(100%)	(5)	

Notes:

1 Includes processed food mixtures and meals (pizzas, tacos, pasta dishes, noodle and rice soups). Estimated hemp content averaged over entire product category, including non-grain raw materials

2 Assumes only replacement in margarine, maximum estimated hemp oil content 20%

3 Theoretical maximum assuming complete protein replacement is 75 g nuts/100 g cheese; technical/economical maximum is 30%

4 Assumes substitutions on protein basis using protein isolate for adjustment of protein content.

5 Hulled seeds used as additive, not to replace milk protein

6 Assumes replacement of fat by hemp oil and addition of protein isolate to adjust protein content

7 Complete replacement of protein, does not consider technical or economic feasibility

8 Assumes maximum THC content in soft drinks and beer of 5 and 3 ng/g (ppb), respectively

3.3 Exposure assessment methodology

The following exposure assessment for THC uptake from hemp foods was conducted in analogy to exposure assessment guidelines published by the U.S. Environmental Protection Agency (1992) and commonly used to assess exposure to potentially toxic food contaminants. The hazard assessment in Section 2 indicates that the acceptable daily intake (ADI) for THC via foods should be based on acute rather than chronic effects. Since these effects are a function of short-term doses, rather than long-term average uptake rates, all scenarios estimate the daily intake rate for hemp foods and the associated THC.

3.3.1 Summary of dietary scenarios

The following three scenarios were developed to estimate daily intake of hemp seed derivatives and THC by North Americans of all ages and average weight, without gender differentiation.

Our initial review of food intake surveys suggested that food consumption patterns and average weight varies somewhat between age groups and gender. However, we determined that the use of population-averaged per capita THC exposure as a function of major variables in food composition and consumption patterns would provide for a meaningful quantification of the potential range of daily exposure. Deviations in food consumption patterns by individuals or population sub-groups, which may result in significantly higher uptake of hemp foods and THC, would best be addressed through the selection of conservative assumptions in the "reasonable worst-case scenario". Furthermore, the findings obtained from the hazard assessment in Section 2 suggest that this approach does not unduly ignore a conceivable higher sensitivity to THC of those groups that are commonly given specific considerations in a risk assessment, *i.e.* females, children, the elderly, and the ill. While food consumption estimates are based on nutritional data for U.S. residents, we have assumed implicitly that, possibly with the exception of ethnic minorities, food consumption patterns in Canada will be comparable to those for the U.S.

The three nutritional scenarios used as the basis for our exposure estimate are described in the following. Figure 3.1 summarizes their main assumptions.

Scenario 1: Exposure screening (macronutrient case)

This scenario was intended to establish a first, conservatively high estimate of the daily intake of hemp seed derivatives and associated THC. It was based on the recommended dietary allowance (RDA) for caloric intake (National Academy of Sciences 1989) and estimated a population-weighted average over all age groups (including infants and children) of 2257 kcal/day. According to RDA recommendations to limit the contribution of fat to caloric intake to 30%, with a minimum contribution by carbohydrates of 50%, macronutrients, *i.e.* protein, fat, and carbohydrates, were assumed to contribute 15%, 30%, and 55%, respectively, to daily energy uptake. The entire daily protein uptake of 85 grams

was assumed to be provided by hemp seed protein in the form of hulled seeds with a THC content of 1.5 ppm. The corresponding estimated daily THC intake is 380 µg. The assumptions and results of this scenario are summarized in Table 3.4.

Table 3.4 Summary of Scenario 1 (exposure screening/macronutrient case)

Daily energy intake (base)	2,257 kcal	
Recommended % from protein	15%	= **85 g** (1g = 4 kcal)
Recommended % from fat	30%	= 75 g (1g = 9 kcal)
Amount of hemp nut (protein equivalent)	255 g	@ 1.5 ppm THC
Protein (33%)	85 g	
Fat (44%)	112 g	
Total THC intake	380 µg	
Effective daily energy intake	2,590 kcal	Results from high fat/protein ratio in hemp nut

The assumption of complete replacement of protein from animal and vegetable sources by hemp protein represents a highly conservative assumption and is expected to yield an upper-bound estimate of the actual THC intake from hemp foods. This scenario does not consider THC intake from beverages. Because of the low additional contribution from hemp beverages (see Table 3.7, page 70), daily THC intake under this scenario is not likely to exceed 400 µg, even for people who consume such beverages extensively.

In addition to this conservative screening scenario without consideration of the actual substitution potential by specific hemp foods, two more scenarios analyzed the impact of selectively replacing conventional foods with hemp foods.

Scenario 2: Typical American diet

The composition of a typical American diet, differentiated by food category, was based on a the most recent survey by the U.S. Department of Agriculture's (USDA) *Continuing Survey of Food Intakes by Individuals* (CSFII 1996) (USDA 1997), discussed below. Energy intake was reported as mean over all age groups and genders. The resulting mean caloric intake was 1986 kcal/day; the breakdown for macronutrient composition is summarized in Table 3.6.

For each food category listed in the survey, the potential for substitution by hemp foods was evaluated. Complete replacement of all food items, except for meat, by technically feasible, functionally similar or equivalent hemp foods was assumed. Based on the above listed typical and maximum content of hemp seed derivatives and their respective THC content (Table 3.3), the typical and maximum daily THC intakes were calculated for this scenario. Because food surveys are prone to underreporting (see below), this scenario was assumed to produce a lower bound estimate of the daily intake of hemp seed derivatives of an individual who replaces **all** conventional foods, with the exception of meat products, with hemp seed products.

Scenario 3: High-caloric vegetarian diet (reasonable worst-case)

To account for individuals with nutritional habits prone to cause higher THC intake, a reasonable worst-case scenario was analyzed. Such a scenario represents the upper end of the population exposure distribution regarding caloric intake and food composition. In accordance with U.S. EPA guidelines for conducting a health risk assessment (U.S. EPA 1992) this scenario was chosen over a "worst-case" scenario for a hypothetical individual with the maximum possible exposure, *i.e.* under an extreme set of nutritional conditions. Again, dietary composition was based on the food consumption in the U.S. according to the CSFII 1996 (USDA 1997)and food replacement study described above. Instead of the median energy intake, we selected, in accordance with the procedures recommended by U.S. EPA, the 95th percentile of caloric uptake from CSFII 1996 (see Scenario 2) to represent the upper end of the population distribution. The food energy intake of the 95th percentile (141% of the 1989 RDA caloric intake) amounts to 3182 kcal.

In addition to the higher caloric intake, this scenario assumed a strictly vegetarian diet, in which all meat products from Scenario 2 were replaced on a protein basis with hemp protein based products, such as hemp seed-based tofu. As hemp protein isolates are currently not available, hemp nuts were assumed as the basis of hemp protein. This scenario thus refers to individuals who routinely consume large quantities of "natural foods" and avoid the use of animal protein. Such persons generally lead a more active life, including physical exercise, which necessitates the higher caloric uptake.

3.3.2 Sources of dietary information

To develop characteristic food uptake information for the North American population, we referred to the two most comprehensive studies available: a) the most recent interview-based USDA Continuing Survey of Food Intakes by Individuals (CSFII 1996)—commonly called "What We Eat in America"—(methodology described in Enns *et al.* 1997) and b), the most recent economic "food disappearance" study on food consumption by the USDA's Economic Research Service(Putnam & Allshouse 1999). The latter bases its estimate of per capita food consumption in the U.S. on commodity availability and food disappearance in the market place. Both studies suffer from methodological limitations, likely resulting in an under- and overestimation of the true daily food intake, respectively. The following paragraphs provide short descriptions of the methodology of both studies, point out their strength and shortcomings for the purpose of an accurate dietary exposure assessment, and describe their use, if any, in this present study. Table 3.6, page 68, summarizes the main findings of two studies regarding daily intake of macronutrients and energy.

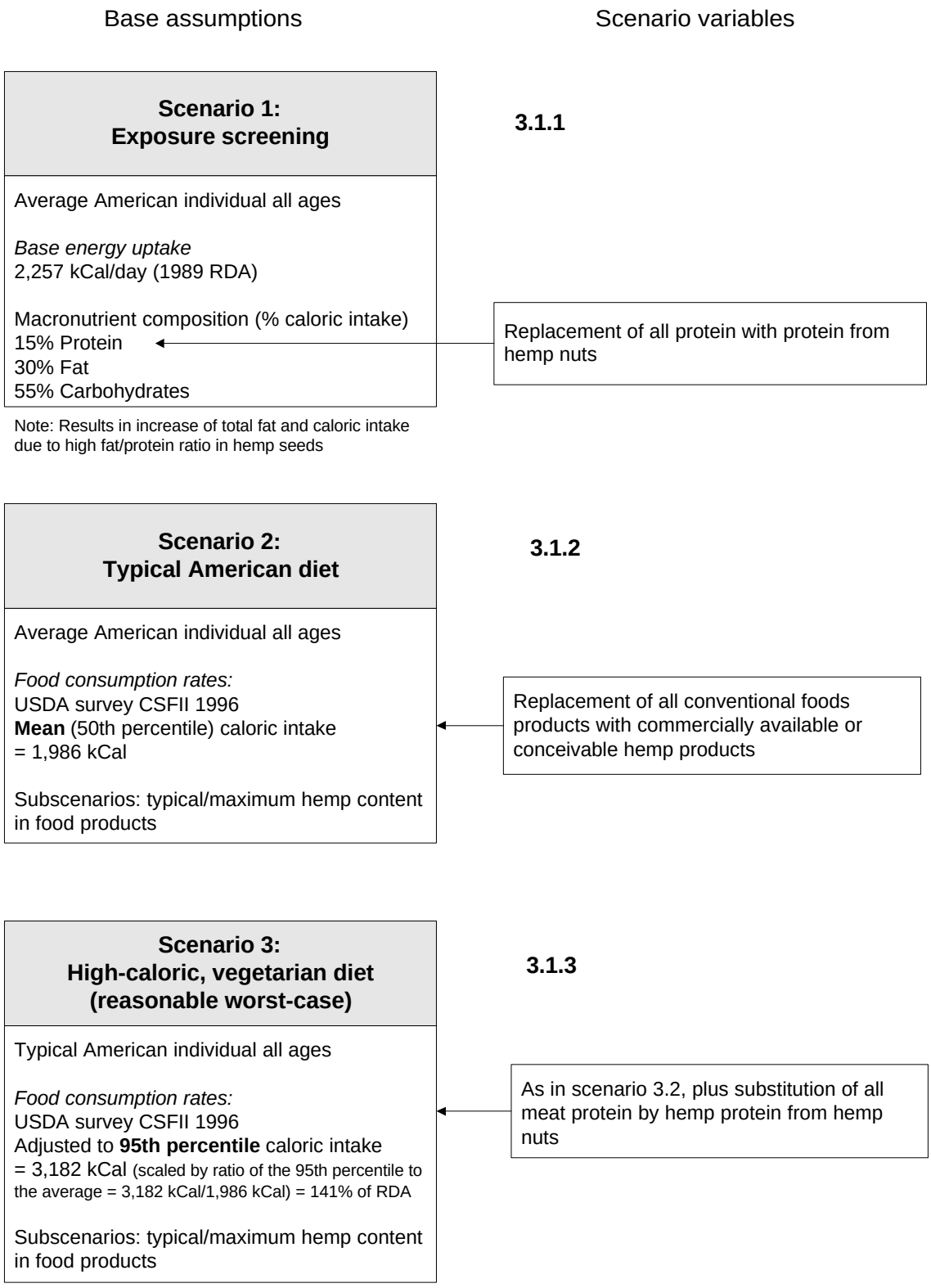


Figure 3.1 Chart of important parameters of exposure assessment scenarios

CSFII 1996

For this study (USDA 1997), a nationally representative sample (~16,000 individuals) of non-institutionalized individuals residing in all 50 states of the U.S. was interviewed. Subjects were interviewed in a multiple-pass approach and provided information on food intakes on two nonconsecutive days by means of a 1-day dietary recall (Enns *et al.* 1997).

Foods were reported in different categories with a relatively high resolution, *i.e.* breakdown to singular items. Food mixtures were reported and coded according to their main ingredient, *e.g.*, pizza was reported as grain mixture.

These survey-based results of the CSFII are widely used in exposure assessments. However, several problems are inherent in this approach to determining mean daily food intakes and their usefulness to the assessment of food substitution potential. The main issues relevant to the following exposure assessment are briefly mentioned in the following:

– Reporting mixtures under their main ingredient, *e.g.*, pizza under the grain category, tends to mask the actual intake of foods that are widely used as minor ingredients in mixtures, such as cheese. Because of the increasing popularity of mixtures, this will tend to underestimate these nutritionally important foods.

– Interview-type surveys are prone particularly to underreporting of certain food items. This is suggested by the fact that, while the mean food energy intakes were estimated to be 1805 kcal for women >20 years (80% of RDA) and 2031 kcal for men >20 years (90% of RDA), almost one third of all individuals surveyed in this age range were overweight. Underreporting and sedentary lifestyles are two possible explanations for the disparity between energy intake and the prevalence of overweight people.

Despite these shortcomings, the CSFII provides an excellent breakdown of diets. Both its caloric intake and the composition of the diet were used as the basis for Scenario 2. Since it is subject to underreporting, it can be assumed to represent a lower bound estimate of the daily intake of hemp seed derivatives of an individual who replaces all conventional foods, with the exception of meat products, with hemp seed products.

Table 3.5 summarizes the findings and intake by food categories for an American (mean of all ages) on an typical diet based on the CSFII 1996. Food categories were simplified to the extent possible in order to reflect the potential for substitution by hemp foods without losing depth of detail.

Table 3.5 Typical diet composition of American of all ages on a 1986 kcal diet (USDA 1997)

Category	**CSFII 1996 mean food uptake** g/day
Grain Products	**303**
Yeast bread, rolls	50
Cereals	76
Ready-to-eat	17
Rice	19

Category	CSFII 1996 mean food uptake g/day
Pasta	21
Other (grits, oatmeal, cooked cereals)	19
Quick breads, pancakes, French toast	20
Cakes, cookies, pastries, pies, snack/nutrition bars	38
Crackers, popcorn, pretzels, corn chips	12
Mixtures mainly grain	107
Vegetables	**194**
Fruits	**162**
Milk and Milk Products	**263**
Milk, milk drinks (flavored and unflavored), infant formulas, dry milk	210
Whole milk	62
Low fat	83
Skim milk	34
Milk drinks, flavored milk, meal replacements with milk, milk-based infant formulas, unreconstituted dry milk and powdered mixtures	31
Yogurt	8
Milk desserts (ice cream, imitation ice cream, ice milk, sherbet, frozen yogurt, pudding, custard, baby-food pudding, etc.)	24
Cheese (natural hard and soft cheeses, cottage cheese, cream cheese, processed cheese and spreads, imitation cheeses, dips, cheese sandwiches)	16
Fluid and whipped cream, half-and-half, sour cream, milk sauces, gravies	5
Meat, Poultry, and Fish	**192**
Beef	23
Pork	10
Lamb, veal, game	1
Organ meats	1
Frankfurters, sausages, luncheon meats	21
Poultry	23
Fish and Shellfish	11
Mixtures mainly meat, poultry, fish	99
Other	3
Other	**49**
Eggs	18
Legumes (includes tofu, pulse-based spreads, meal replacements)	28
Nuts and seeds (includes peanut butter, nut mixtures)	3
Fats and Oils	**14**
Table fats (butter, margarine)	4
Salad dressings	8
Other (cooking oils, mayonnaise)	2
Sugars and Sweets	**25**
Sugars	3
Candy (includes all types of candy, chocolate covered-nuts, fruit leather, chewing gum, dietetic sweets)	7
Other (marmalade, honey, sweet toppings, frostings)	15
Beverages	**923**
Alcoholic	
Wine	10
Beer and ale	81
Other	6
Nonalcoholic	
Coffee	254
Tea	128
Fruit drinks and ades	102
Carbonated soft drinks	342
Other (near beer, non-alcoholic beer)	<0.5

Consumption rates for most product categories were taken directly from the survey. In cases where minor product categories were not specifically listed, they were grouped as “other” and calculated by subtraction from the listed categories. For products without a substitution potential by hemp seed derivatives, notably vegetables and fruits, consumption rates were only provided for the major categories.

Food disappearance study

This study analyzed the availability, and implicitly the consumption, of food for human use, based on food disappearance into the market. It is estimated based on sampling and statistical analyses of the balance between commodity supply (total of production, beginning inventories, and imports) and utilization (export, consumption, and waste).

While this approach eliminates the potential for under- or over-reporting by individuals interviewed in surveys, it has several shortcomings for use in an exposure assessment:

– Food disappearance analyses tend to overstate actual consumption, because they include spoilage and waste accumulated through the value chain. As stated on page 25 of the study, “nutrient values [reported] exclude nutrients from the inedible parts of foods, such as bones, rinds, and seeds, but include nutrients from parts of food that are edible but not always eaten, such as the separable fat on meat. Nutrient estimates are based on food disappearance data; thus, they represent nutrients in foods available for consumption and not actual nutrient intakes by individuals.”

In other cases, the disappearance might be understated because of a lack of accurate supply data. A few obvious over- or underestimates of food intake based on food disappearance shall be pointed out.

– The amount of fat used per capita is overestimated due to the increasing numbers of meals eaten away from home. Particularly fast food restaurants use large amount of fats as frying fats, of which about 50% are discarded after use and thus are not available for human consumption. This factor likely constitutes the most relevant source of overestimation in these disappearance studies.

– Data on meat are given in retail-equivalents, which includes the excess fat that is typically removed before cooking.

– An increasing proportion of the total turkey supply is used for pet foods. Since no official estimates of this amount are available, the human consumption of turkey is overstated.

– The lack of reliable estimates of game fish supplies leads to an under-representation of this food category.

– Intake of fruit and vegetables is overestimated because a considerable portion is lost during cleaning, both at home and in the processing industry.

Table 3.6 compares the mean daily food intake for an American (all ages) based on the data obtained from the CSFII 1996 and the food disappearance studies. It shows that the mentioned methodological shortcomings of the food disappearance approach cause in fact a significant overestimation of daily caloric intake. Also, since the food disappearance study provided less differentiation within food categories and is prone to potentially significant over-representation of fat and oil, the main ingredient in hemp seeds, we opted not to use it as the basis for a reasonable worst-case scenario. Rather, this scenario was to be based on the food composition obtained from the CSFII 1996, adjusted for a high caloric intake and complete replacement of animal protein with hemp protein.

Table 3.6 Daily caloric intake and macronutrient composition of typical diet of an American of all ages according to CSFII (USDA 1997) and food disappearance study (Putnam & Allshouse 1999)

	CSFII 1996	**Food disappearance study**
Food energy	1,986 kcal/day	3,800 kcal/day
Protein	15.1%	11%
Total fat	32.7%	38%
Carbohydrates	52.1%	51%
Nutrients		
Protein	75.1 g/day	110 g/day
Total fat	74.1 g/day	159 g/day
Total carbohydrates	257.9 g/day	491 g/day

3.3.3 Replacement with hemp foods

As discussed in Section 3.2.3, this exposure assessment considered substitution of all conventional food items by hemp foods both commercially available and conceivable for use in homemade foods and future commercial products. Table 3.7 shows, for each category, the percentage of foods possibly replaceable with hemp foods in both scenarios. The categories were adjusted according to the breakdown of the CSFII study. In case more than one hemp food product existed as a possible substitute for a category, it was either broken down into reasonable subcategories, whenever feasible, or the product with the highest THC content was chosen.[1] Where necessary, rationales for the choice of replacement factors are provided

[1] For example: the CSFII category "Nuts and Seeds" contains nuts, peanuts, coconut, peanut butter and peanut butter sandwiches, nut mixtures, and seeds. Possible replacements for some of these items are hulled hemp seeds, nut butter (as replacement for peanut butter), and trail mix with hulled hemp seeds. No further breakdown for these items is available or could be reasonably constructed. Therefore, replacement of the entire category, and, thus, its THC content, was calculated based on nut butter because it had the highest THC content of those products mentioned above.

as notes. The reasonable worst-case scenario, the vegetarian on a high caloric diet (Scenario 3), further assumed substitution of **all** meat products with a de-fatted hemp tofu-product on a protein basis (20% protein in meat). Particularly, the latter assumption underlying these scenarios is, for technical, nutritional, taste, and cost reasons, not likely to be complied with, even by individuals who promote the use of hemp foods.

3.3.4 Exposure calculations

Daily uptake rates for hemp foods and THC were calculated for an individual with a body weight of 70 kg. They were based on the following quantities:

– The amount of hemp foods consumed daily for each product or product category, as estimated under Scenarios 1 and 2 and shown in Table 3.7, page 70;

– The content of individual hemp seed derivatives in each product, both for typical and maximum content, as shown in Table 3.3, page 59;

– The THC content of the various hemp seed derivatives, as shown in Table 3.2, page 57.

No adjustment was made for the lower bioavailability of oral THC, compared to inhalative or intravenous administration, since the hazard assessment in Section 2 had been based on oral THC ingestion.

Total daily THC uptake via food (Q^{THC}) was calculated as

Equation 3.1 $$Q^{THC} = \sum_i Q_i^{HF} \times C_i^{THC}$$

The daily THC intake per kilogram of bodyweight, Q_{BW}^{THC}, was calculated as

Equation 3.2 $$Q_{BW}^{THC} = Q^{THC} \div BW$$

The concentration of THC in each product, C_i^{THC}, was calculated as

Equation 3.3 $$C_i^{THC} = \sum_j f_j^i \times p_j^{THC}$$

where

Q^{THC} = daily THC ingestion rate (µg/day)

Q_{BW}^{THC} = daily specific THC ingestion rate (µg/(kg body weight * day))

Q_i^{HF} = daily ingestion rate for hemp food product/product category i (g/day)

C_i^{THC} = concentration of THC in hemp food item i (µg/g)

f_j^i = fraction of hemp seed derivative j in product i (g/100 g)

p_j^{THC} = THC concentration in hemp seed derivative j (µg/g)

BW = average body weight (70 kg)

3.4 Results

Table 3.7 summarizes the estimates of daily THC intake for Scenarios 2 and 3, assuming both typical and maximum content of hemp seed derivatives in food products.

Table 3.7 Typical and maximum (in parentheses) THC uptake for Scenarios 2 and 3 by food category based on percentage replacement by hemp foods

Category	CSFII 1996 mean food uptake g/day	Replacement of food category with hemp foods	Notes	Typical (maximum) THC uptake Scenario 2 µg/day		Scenario 3 µg/day	
Grain Products	**303**			**52.1**	**(95.3)**	**83.5**	**(152.7)**
Yeast bread, rolls	50	100%		12.5	(17.5)	20.0	(28.0)
Cereals	76						
Ready-to-eat	17	100%		1.2	(2.4)	1.9	(3.9)
Rice	19	0%					
Pasta	21	100%		3.2	(6.4)	5.1	(10.3)
Other (grits, oatmeal, cooked cereals)	19	100%		1.2	(2.4)	1.9	(3.9)
Quick breads, pancakes, French toast	20	100%		7.0	(12.9)	11.3	(20.6)
Cakes, cookies, pastries, pies, snack/nutrition bars	38	100%	*1*	11.7	(24.4)	18.7	(39.2)
Crackers, popcorn, pretzels, corn chips	12	100%		2.1	(4.6)	3.4	(7.3)
Mixtures mainly grain	107	100%		13.2	(24.8)	21.2	(39.7)
Vegetables	**194**	0%					
Fruits	**162**	0%					
Milk and Milk Products	**263**			**5.7**	**(35.5)**	**9.13**	**(56.8)**
Milk, milk drinks (flavored and unflavored), infant formulas, dry milk	210						
Whole milk	62	100%			(6.9)		(11.1)
Low fat	83	100%			(6.8)		(10.9)
Skim milk	34	100%			(2.1)		(3.4)
Milk drinks, flavored milk, meal replacements with milk, milk-based infant formulas, unreconstituted dry milk and powdered mixtures	31	100%			(3.5)		(5.6)
Yogurt	8	100%			(0.6)		(1.0)
Milk desserts (ice cream, imitation ice cream, ice milk, sherbet, frozen yogurt, pudding, custard, baby-food pudding, etc.)	24	50%	*2*	2.1	(4.2)	3.4	(6.7)
Cheese (natural hard and soft cheeses, cottage cheese, cream cheese, processed cheese and spreads, imitation cheeses, dips, cheese sandwiches)	16	100%		3.6	(7.2)	5.8	(11.5)
Fluid and whipped cream, half-and-half, sour cream, milk sauces, gravies	5	100%			(4.1)		(6.6)
Meat, Poultry, and Fish	**192**	*See note 3 for scenario 3*		**7.4**	**(22.3)**	**143.5**	**(167.4)**
Beef	23	0%					
Pork	10	0%					
Lamb, veal, game	1	0%					
Organ meats	1	0%					
Frankfurters, sausages, luncheon meats	21	0%					
Poultry	23	0%					
Fish and Shellfish	11	0%					
Mixtures mainly meat, poultry, fish	99	100%		7.4	(22.3)		

Category	CSFII 1996 mean food uptake g/day	Replacement of food category with hemp foods	Notes	Typical (maximum) THC uptake Scenario 2 µg/day		Scenario 3 µg/day	
Other	3	0%					
Other	**49**			**11.2**	**13.4**	**17.9**	**(21.6)**
Eggs	18	0%					
Legumes (includes tofu, pulse-based spreads, meal replacements)	28	50%	*4*	4.5	(6.8)	7.1	(10.8)
Nuts and seeds, nut butter, trail mix	3	100%	*5*		(6.7)		(10.7)
Fats and Oils	**14**			**11.5**	**(16.1)**	**18.5**	**(25.8)**
Table fats (butter, margarine)	4	100%	*6*		(4.0)		(6.4)
Salad dressings	8	100%		7.4	(11.9)	11.9	(19.1)
Other (cooking oils, mayonnaise)	2	30%	*7*	0.1	(0.2)	0.1	(0.3)
Sugars and Sweets	**25**			**0.2**	**(0.5)**	**0.3**	**(0.8)**
Sugars	3	0%					
Candy (includes all types of candy, chocolate covered-nuts, fruit leather, chewing gum, dietetic sweets)	7	10%	*8*	0.1	(0.2)	0.1	(0.3)
Other (marmalade, honey, sweet toppings, frostings)	15	10%	*9*	0.1	(0.3)	0.2	(0.5)
Beverages	**923**			**8.5**	**12.4**	**13.6**	**(20.0)**
Alcoholic							
Wine	10	0%					
Beer and ale	81	100%			(0.3)		(0.4)
Other	6	0%					
Nonalcoholic							
Coffee	254	100%		6.6	(10.5)	10.5	(16.9)
Tea	128	0%					
Fruit drinks and ades	102	100%					
Carbonated soft drinks	342	100%	*10*		(1.6)		(2.6)
Other (near beer, non-alcoholic beer)	<0.5	100%			(<0.1)		(<0.1)
		Total		**97**	**(196)**	**286**	**(445)**

* Totals of major categories may be different from sum of their subcategories due to rounding

Notes:

1 Assumes 30% of category are snack (energy or granola) bars

2 Assumes a conservative value of 50% of category replaceable with hemp products

3 Scenario 3 assumes entire meat category (100%) replaced with hemp tofu (de-fatted) on a protein basis (20% protein in meat)

4 Assumes 50% of category replaceable (excluding whole pulse seeds, which are listed under category "Other/Legumes"); thereof 50% hummus or other spreads and 50% tofu

5 Conservatively assumes replacement of entire category (100%) with hemp nut butter

6 Assumes replacement of entire category (100%) with hemp seed-based margarine

7 Conservatively assumes that 30% of category is mayonnaise; cooking oils, which make up most of this category, are only to a small percentage replaceable with hemp oil because of its low smoke point

8 Assumes most candy-type sweets not replaceable with hemp foods

9 Assumes most frostings, etc. not replaceable with hemp foods

10 Assumes energy drinks included

3.5 Discussion

Comparison of the results from the three nutritional scenarios evaluated in this exposure assessment and summarized in Tables 3.4 and 3.9 suggest the following:

Complete replacement in a "typical American diet" of conventional food products, including meat, by currently available hemp foods will, even under "reasonable worst-case" assumptions, not cause a daily THC uptake in excess of 500 µg. This worst-case scenario makes the following assumptions:

- Complete substitution of all meat and non-meat food items by hemp foods, wherever technically feasible;
- A high daily caloric intake at the 95th percentile of the U.S. population (3182 kcal/day),
- The use of the maximum technically conceivable hemp content in all food products, irrespective of the higher relative cost of hemp seed ingredients; and
- A THC content at the level now generally not exceeded in hemp seed derivatives.

Contribution of food categories to THC intake

For a non-vegetarian diet, major potential contributions to THC intake result from baked goods and other grain products, including snack/nutrition bars and manufactured foods. In these items, hemp seed derivatives may replace nuts, soy based protein or grains. In a vegetarian diet, complete replacement of animal protein with hemp protein based products would cause the single largest contribution to total THC intake.

No single food category or sub-category contributes sufficiently high THC uptake rates to the maximum conceivable THC intake, such that much higher than normal intake of these items would result in THC uptake in excess of 500 µg/day. For example, increasingly popular hemp nutrition bars typically contain no more than 10 g of hulled hemp seeds per bar, corresponding to 15 µg of THC. Excessive, yet conceivable, consumption of such bars at a rate of 10 bars/day, would contribute 150 µg/day of THC. Because of the high caloric value of these products (typically 200–250 kcal/bar) this uptake would supply the majority of daily caloric intake and come at the expense of other hemp food items and the associated THC uptake.

- **Typical THC intake from extensive consumption of hemp foods**

  The selected scenarios represent eating patterns unlikely to characterize even the most devoted consumers of natural foods or hemp foods. The authors' personal experience and extensive anecdotal evidence from other consumers of hemp foods suggest the presence of several limitations to the hypothetical exclusive consumption of hemp foods containing high proportions of hemp seed derivatives. Depending on the specific product, these limitations may be related to impaired taste, other negative impacts on food quality and durability, and the higher cost of natural foods in general and hemp foods in particular. Thus, the assumptions of the reasonable worst case are most unlikely, if not impossible, to be met concurrently, even by the most committed consumer of hemp foods. The more realistic typical daily THC uptake by individuals who consume hemp food items regularly and extensively will rarely exceed the lower level of Scenario 2, *i.e.* 100 µg/day. This assumes implicitly increased future commercial availability of these items and the maintenance of the current THC levels.

– **Consistency of Scenarios 1 and 3**

Similarity of the THC uptake in Scenarios 1 and 3 (maximum hemp content) supports the conclusion that these scenarios reasonably reflect complete substitution of daily protein demand by hemp protein and that THC uptake is not likely to be exceeded, except by individuals who deliberately ingest hemp protein quantities in excess of recommended daily protein intake rates. The somewhat higher THC intake resulting from Scenario 3 is due in part to the explicit use of hemp oil, assumed to contain 5 ppm of THC, and to the inclusion of cannabis-flavored beverages.

– **Sensitivity to variations in THC content**

Conceivable further reductions in maximum observed THC levels in hulled seeds and oil would cause a decrease in THC intake to less than 300 µg/day. Again, typical daily intake even of routine users of hemp foods will decrease to 70 µg/day, the lower boundary of Scenario 2. The unlikely consumption of products made from hemp nuts containing 2 µg/g would raise the typical intake of routine users to 110 µg/day, while intake at the upper limit of the reasonable worst case would increase to 540 µg/day (see Table 3.8).

Table 3.8 Sensitivity of total THC intake to THC level variations of hemp seed derivatives (estimated intake of cannabidiol (CBD) shown for THC levels used in exposure assessment)

THC content in hemp seed derivatives (µg/g)			**Estimated range of THC (CBD) uptake** (in µg/day) **under**	
Hulled seeds	**Flour**	**Oil**	**Scenario 2**	**Scenario 3**
1.5	2	5	100–200 (CBD: 1,000–2,000)	280–440 (CBD: 2,800–4,400)
1	2	2	70–140	200–300
2	2	5	110–230	350–540

– **Impact of hemp oil use as food supplement**

Neither scenario explicitly considered the use of hemp oil as a supplement. Hemp oil supplements are primarily taken to compensate for deficiencies in the omega-3 essential fatty acid (EFA), alpha linolenic acid (ALA), or the higher omega-6 fatty acid gamma linolenic acid (GLA). The diets assumed in Scenarios 2 and 3, in which fats are predominantly provided by hemp seeds, show omega 6/omega 3 ratios in their EFA intake of typically less than 3, *i.e.* more desirable than the generally recommended ratio of 4–6. Under these conditions, use of a hemp oil supplement does not add nutritional benefits, and rather just increases caloric intake. For individuals consuming only small amounts of hemp foods—and correspondingly less THC—and take hemp oil supplements to improve their EFA balance, the often recommended daily consumption of one tablespoon (15 ml) of hemp oil (at 5 µg/g THC) would add a THC intake of 75 µg/day.

– **Impact of future use of protein isolate**

At this time, the assumption of complete replacement of animal protein by hemp protein in the reasonable worst-case scenario is highly conservative. The high fat/protein ratio in hemp nuts, the only relevant form of hemp protein acceptable to consumers impairs the feasibility of "hemp tofu" and other hemp protein based products. The projected market introduction of hemp protein isolate may allow for implementation of such products and the increasing likelihood of the reasonable worst case scenario for "hemp food enthusiasts". Preliminary information on THC levels in these isolates indicates THC levels of 0.5–1.5 µg/g. This lower level would tend to reduce THC intake compared to the levels of 1.5 µg/g for hemp nut and protein isolate assumed in this study (Table 3.2).

– **Exposure to other cannabinoids**

To date, compliance monitoring and research have focused almost exclusively on the cannabinoid of highest concern, *i.e.* THC. Consequently, very limited information has been gathered and published on the relative content of other cannabinoids, primarily cannabidiol (CDB) and cannabinol (CBN) in hemp seed derivatives from industrial hemp varieties. As discussed in Section 2, industrial—or fiber—hemp varieties appear to contain CBD at levels approximately 2–17 times that of THC. For several relevant French cultivars, commonly grown in Canada, CBD/THC ratios appear to range from 5–10 (de Meijer 1995). Other varieties grown in Canada, such as the Ukrainian USO-13, have CBD/THC ratios of 10–20. As a result of their particularly low THC content they also appear to achieve generally lower THC levels in hemp seeds derivatives (hulled seeds and oil generally below 1 µg/g) (Moravcik 2001). Thus, estimating typical daily CBD intake from hemp foods at ten times the rate for THC appears to be reasonable. The corresponding daily intake for the range of conditions considered in this exposure assessment is shown in Table 3.8. The figures suggest a daily CBD uptake of between 1 and 4.4 mg under worst-case conditions. No comparative information on CBN levels in industrial hemp cultivars was available and no estimate of the daily intake was attempted.

4. CONCLUSIONS AND RECOMMENDATIONS

The *exposure assessment* for THC intake via hemp foods generated the following major conclusions:

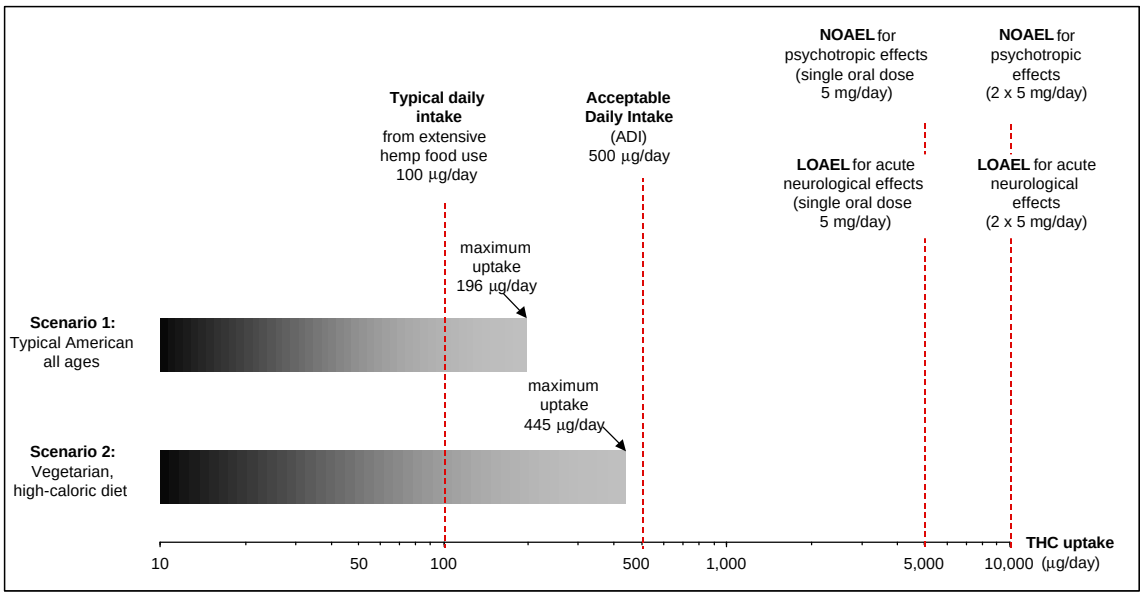
- Complete replacement of conventional food items in a "typical American diet", including meat products, by currently available hemp food items containing common levels of THC will not, even under **"reasonable worst-case"** assumptions, cause a daily THC uptake via hemp food in excess of 500 µg. This worst-case scenario makes the following assumptions:
  - Complete substitution of all meat and non-meat food items by hemp foods, wherever technically feasible;
  - A high daily caloric intake at the 95th percentile of the U.S. population (3182 kcal/day); and
  - The use of the maximum technically conceivable hemp content in all food products, irrespective of the higher relative cost of hemp seed ingredients.
- The more realistic typical daily THC uptake by individuals who consume hemp food items regularly and extensively will rarely exceed the lower level of **Scenario 2**, *i.e.* 100 µg/day. This assumes implicitly increased future commercial availability of these items and the maintenance of the current THC levels.
- The corresponding range of daily intake of cannabidiol (CBD) under the two scenarios is estimated at 1–5 mg.
- Consequently, the daily THC ingestion even by extensive users of hemp foods will remain consistently and, in general significantly, below the proposed ADI for oral THC, and thus will not cause any acute or chronic adverse health impacts. Specifically, the highest conceivable intake THC via hemp foods is far below the psychoactive threshold for THC.

Generally achieved THC levels in hemp seed derivatives thus represent a conservative choice for achievable and enforceable THC limits in these materials. The estimated 10–20% contribution by the two non-psychoactive THC acids A and B to total THC in hemp seed derivatives, predominantly measured by gas chromatography/ mass spectrometry (GC/MS), provides an additional small margin of safety from potentially adverse effects of THC. Figure 4.1 illustrates the maximum daily intake of THC under the Scenarios 2 and 3, the ADI, and LOAEL and NOAEL for different effects.

THC uptake from the use of hemp oil cosmetics is much lower than from hemp food ingestion. A recent study estimated that exclusive and extensive use of hemp oil cosmetics containing high amounts of hemp oil, or pure hemp oil, on compromised skin will not contribute more than 10 µg/day to total THC uptake. Typical THC uptake from the extensive

application of commercially available hemp oil cosmetics to healthy skin is typically less than 1 µg/day. Thus, compared to hemp foods, hemp cosmetics do not contribute significantly to total THC intake.

Figure 4.1 Daily THC intake from hemp food use, ADI, and LOAEL and NOAEL for various effects



Extensive hemp food consumption also no longer appears to have the potential for causing confirmed positive urine tests for marijuana. A recent study showed that daily THC ingestion with hemp oil, in single doses of up to 600 µg/day and over a 40-day period, failed to cause confirmed positive urine test according to the protocol used by most public and private employers in the U.S. Positive screening tests at a lower cutoff level are conceivable but unlikely.

Little representative information on the content in hemp seed derivatives of cannabinoids other than THC, notably cannabidiol (CBD) and cannabinol (CBN) is currently available. It is estimated that CBD intake is typically 10 times that for THC. CBD is considerably less pharmacologically active than THC. Studies suggest that typical CBD intake via food is far too low to cause measurable effects on humans. Findings of low-dose adverse effects of CBN on the hormone secretion of male rats are contradicted by human studies at higher doses. Thus, uptake via hemp foods of other relevant cannabinoids does not appear to pose the risk of adverse health effects. However, this subject requires further study.

The findings and conclusion from this present study support the following recommendations:

- Generally achieved THC levels in hemp seed derivatives—less than: 2 μg/g for whole seeds, meal and flour; 1.5 μg/g for hulled seeds and protein powder; and 5 μg/g for hemp oil—should be considered by regulatory agencies as a conservative and enforceable choice of THC limits in hemp seed derivatives.
- The apparently safe use of hemp foods relative to the presence of generally achieved THC residues and the lack of evidence of other adverse health effects supports the industry's position that hemp seed derivatives and foods should be recognized as safe and not be subjected to regulations for "novel foods".

Two controversial issues regarding the toxicity of THC and other cannabinoids require clarification by future studies. These issues are:

- The reported effects via intraperitoneal dosing (direct injection through the peritoneum into the abdominal cavity) of very low THC doses on the rodent fetus and the outcome of pregnancies observed in animal studies with intraperitoneal dosing (versus no observed effects in human mother/fetus studies with much higher orally ingested doses of THC by the mother), and an analysis of their relevance to humans; and
- The importance of other cannabinoids to the pharmacological activity of hemp food products.

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John Roulac, Nutiva, Sebastopol, CA

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UNITS AND GLOSSARY

Common units of measurement for small concentrations

Relative units	Symbol	Metric units
Parts per million	ppm	microgram per gram (μg/g)
		or milligram per kilogram (mg/kg)
Parts per billion	ppb	nanogram per gram (ng/g)
		or microgram per kilogram μg/kg

Absorption	The movement of a chemical into the bloodstream after its entrance.
Acute toxicity	Acute toxicity occurs after a single exposure to a chemical (or a limited number of exposures) and is seen immediately (within minutes or hours). One of the more common measures of acute toxicity is the LD_{50} measured in rats or mice.
Adverse effect	An adverse effect as defined by the U.S. EPA is "… any biochemical, physiological, anatomical, pathological, and/or behavioral change that results in functional impairment that may affect the performance of the whole organism or reduce the ability of the organism to respond to an additional challenge."
Anovulatory/anovulation	Absence of ovulation *i.e.* no mature eggs produced.
Cancer	A disease characterized by a malignant, uncontrolled growth of cells of body tissue.
Carcinogenicity	The ability of a substance to cause cancer in a living organism
Carcinogen	A substance capable of producing cancer in a living organism.
Chronic toxicity	Chronic toxicity occurs after repeated long-term exposures and effects are seen months or years after the initiation of exposure. Although a large variety of toxic effects can occur after repeated exposure over a long time, one is of particular concern: cancer. Because of the seriousness of this effect, it is typically attempted to determine if chemicals can cause very small increases in the incidence of this disease, *e.g.*, one additional cancer victim in one million people. Because the cost of using large numbers of experimental animals is prohibitive, chronic toxicity is typically tested with an extremely high dose that could produce a high incidence in a small number of animals. The studies typically last for 1-2 years and may be used for determining the long term NOEL, LOEL, or cancer formation (oncogenicity). These tests provide information only about the top (high-dose) part of the cancer dose-response curve. They do not indicate what the incidence of cancer is at lower doses – doses corresponding to commonly occurring levels in the environment. To estimate what might happen at low doses in humans, many assumptions are made and then calculations of the risks are made from

	these assumptions and the laboratory animal results. Often, epidemiological evidence is used in conjunction with results of studies conducted on laboratory animals to show that effects, which occur in animals, can also occur in humans. This type of evidence has proven useful in cases in which people were exposed to a single chemical or toxicant that produced unusual toxic effects, *e.g.*, nicotine while smoking, or occupational exposure to vinyl chloride or asbestos.
Dose	A specified amount; a measure of exposure usually expressed as an amount per unit of body weight.
Dose-response assessment	The dose-response relationship clarifies the relationship between dose of a toxicant and the magnitude and type of biological response in order to determine the potential risk faced by a human population when exposed to this toxicant.
Effect	The response produced due to a drug or chemical. A local effect occurs at the site of first contact; a systemic effect requires absorption and distribution of the substance and affects the body at a site distant from the entry point.
Epidemiological studies	Epidemiological studies focus on the frequency, distribution, and cause of disease within a human population. They are considered the best source of information because they are based on human exposures. The best epidemiological studies will give a clear and direct link between exposure and adverse effects.
Exposure	Exposure characterizes the reception of a dose of a substance, *i.e.* contact with a chemical substance. Acute exposure describers a single, large dose; chronic exposure describes repeated doses over a period of time.
Exposure assessment	Exposure assessment determines the actual levels of exposure and absorption of a toxicant among the population of exposed individuals. The levels of exposure are measured based on the *frequency* and *duration* of exposure as well as the *levels of contaminant* in the exposure media, *i.e.* in this case *food*. The actual absorption is determined by toxicokinetic studies.
Follicle-stimulating hormone (FSH)	FSH is a hormone secreted from the anterior pituitary gland. In the woman, FSH stimulates production of ovarian follicles (eggs) and estradiol (another reproductive hormone) during the first half of the menstrual cycle. In the man, FSH stimulates production of sperm in the testicular tubules.
Gonadotropin-releasing hormone (GnRH)	GnRH (also called luteinizing hormone-releasing hormone) is a peptide hormone secreted from the hypothalamus. GnRH stimulates the synthesis and release of LH (luteinizing hormone) and FSH (follicle-stimulating hormone). After puberty the secretion of GnRH, and also of LH and FSH, becomes pulsatile (rhythmic).
Hazard	A hazard is the inherent adverse effect potential that a chemical poses.
Hazard identification	Hazard identification is the step in a risk assessment that identifies the substance of concern and evaluates its inherent toxicity. The risk

	assessor determines then whether there is an actual threat to our health from a contaminant.
Intraperitoneal, i.p.	Administered through the peritoneum. The peritoneum is a thin, transparent membrane that lines the walls of the abdominal (peritoneal) cavity and contains/encloses the abdominal organs such as the stomach and intestines.
LD_{50}	The LD_{50} is a measure of the relative toxicity of different chemicals and is usually expressed in terms of grams/kilogram (g/kg). It is defined as the dose that is calculated to be lethal to 50 percent of experimental animals being tested. The lower the LD_{50} the more acutely toxic the chemicals; the higher, the less acutely toxic the chemical. LD_{50} values determined for experimental animals can be used to estimate LD_{50} values for humans. These estimates are rather inexact, because they assume that humans are identical to rats, mice, and other species, except for weight.
Luteal hormone (LH)	LH is a protein hormone secreted by the anterior pituitary gland. In women, an LH surge at mid-cycle causes ovulation. For the next week or so, LH maintains the corpus luteum which synthesizes progesterone. If a woman does not become pregnant the corpus luteum disintegrates after about 10 days. In men, LH stimulates production of testosterone by the Leydig cells of the testes.
LOAEL	The LOAEL (lowest observable adverse effect level) is the lowest dose or exposure level of a toxicant that still produces a noticeable effect in an experimental animal.
NOAEL	The NOAEL (no observable effect level) is the highest dose or exposure level of a toxicant that produces no noticeable adverse effect on experimental animals. If the dose response is determined by several different species of laboratory animals, the NOAEL will vary from species to species.
Response	Response describes reaction of the body to a chemical substance
Risk	The term risk describes the probability that a substance will cause harm
Risk assessment	Risk assessment consists of four steps: hazard identification, exposure assessment, dose-response assessment, and risk characterization.
Risk characterization	Risk characterization compiles the information from the hazard identification, exposure assessment, and dose-response assessment in order to characterize the magnitude and probability of an adverse health effect on the population being exposed.
Subacute toxicity	Subacute toxicity occurs after repeated exposures over about 10 percent of the lifetime of the subjects. The highest dose at which no toxic effect occurs is called the “no-observable adverse effect level” (NOAEL).
Toxicant	A harmful substance, *e.g.*, a poison or a pathogen.