THC in Hemp Foods and Cosmetics:
The Appropriate Risk Assessment

by

James Geiwitz, Ph.D.,
and the Ad Hoc Committee on Hemp Risks

January 15, 2001

EXECUTIVE SUMMARY

In 1998, industrial hemp became a legal crop in Canada, promising environmentally-sound farming and processing of fibre for paper, textiles, and building products. In addition, hemp seed is among the world's most nutritious foods, and its oil is an exceptional bodycare emollient.

In 1999, Health Canada issued a draft report entitled *Industrial Hemp Risk Assessment*. The report dealt only with hemp foods and cosmetics (bodycare products) and focused on tetrahydrocannabinol (THC), the psychoactive ingredient in cannabis hemp. By law, hemp foods and cosmetics must contain less than 10 parts per million THC. Health Canada concluded that, even with THC content limited to 10 ppm, "inadequate margins of safety exist between potential exposure and adverse effect levels for cannabinoids in cosmetics, food, and nutraceutical products made from industrial hemp." Health Canada, therefore, is considering a ban on hemp foods and cosmetics.

The purpose of the Ad Hoc Committee on Hemp Risks is to respond scientifically to the Health Canada risk assessment. We focused on four allegations by Health Canada: acute neurological effects and toxic effects on brain development, reproductive system, and immune system. In contrast to the Health Canada conclusions, we found absolutely no health risks from the extremely low doses of THC present in hemp foods and bodycare products. In fact, the best research indicated some health benefits of THC, most notably in the strengthening of the human immune system.

How can it be that scientists at Health Canada review the research literature on the effects of THC and conclude that hemp foods and cosmetics are unsafe, while another group, our Ad Hoc Committee, reviews the same research and concludes the exact opposite? In our analysis of the science of THC risk assessment, we identified the major problems with the research referenced by Health Canada, including extreme dosing, inappropriate extrapolation to humans from animal studies, and political pressures on scientific disinterest. Also, contrary to assumptions made by Health Canada, children are at less risk from THC than adults;

hemp THC must be heated to be biologically active (which means the THC in cold-pressed hemp oil is inactive); and only two or three cannabinoids are candidates for investigation in hemp foods, not 66.

We next calculated, from our data, the appropriate standards for THC in hemp foods and cosmetics. Although there are no health risks from THC, we set the standard at the threshold for psychoactive effects, with a safety factor of 10. Scientifically determined, the maximum THC in hemp oil (the most efficient carrier) should be set at 20 parts per million – a conservative estimate, with other studies recommending limits as high as 50 ppm. Current Canadian regulations,which set the standard at 10 ppm, represent a difficult but achievable practical limit for bulk hemp manufacturers.

Finally, to complete a cost / benefit analysis, the health benefits of hemp foods and cosmetics were explored. In foods, the essential fatty acids (EFAs) and the high level of protein make hemp nuts an exceptionally nutritious food; a healthy heart is perhaps the most well-documented benefit. The EFAs and the protein are basic building blocks of the body, involved in health at the cellular level. The same EFAs are the primary ingredient in hemp bodycare products, which heal and nurture the skin and prevent infections.

We conclude that a ban on hemp foods and cosmetics would be ill-advised policy based on a flawed review of the research literature. Rather than protecting the health of Canadians, such a ban would be damaging. We propose instead that current THC regulations be retained, and the health benefits of hemp foods and cosmetics be the topic of Health Canada reports on industrial hemp.

Contact: James Geiwitz, Ph.D., <geiwitz@home.com>, 250-598-4075

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TABLE OF CONTENTS

1.0 INTRODUCTION

Industrial hemp (*Cannabis sativa* L.) became legal in Canada on March 13, 1998, and the first crops were planted in the summer of 1998.

On March 3, 1999, Health Canada (HC) issued a draft report entitled *Industrial Hemp Risk Assessment*. The report was prepared by Joan Orr, M.Sc., and Mary Starodub, M.Sc., for Hugh Davis, Head of the Microbiology and Cosmetics Division of the Product Safety Bureau of Health Canada. On July 27, 1999, the Toronto Globe & Mail published a story on the draft risk assessment. The report was revised several times, the latest dated September 9, 1999.

The HC report dealt only with hemp foods and cosmetics, not the fibre products such as paper and textiles. The focus of the report was tetrahydrocannabinol (THC), the psychoactive ingredient in *Cannabis*, responsible for the "high" in marijuana, the high-THC cousin of industrial hemp. Other cannabinoid ingredients were occasionally considered, although research on the other cannabinoids is sparse.

By law, industrial hemp must contain less than 0.3% THC, 10-100 times less than the amount of THC in marijuana. The industrial hemp seed (botanically, a nut), from which hemp foods and cosmetics are made, contains only trace amounts of THC, but it cannot be cleaned and processed without some microscopic contamination from the bracts and leaves of the hemp plant, the primary sites of THC production by the plant. By law, industrial hemp foods and cosmetics must contain less than 10 parts per million (ppm) THC.

The question posed by the HC report was this: Do hemp foods and cosmetics containing 10 ppm THC or less present health risks for Canadian consumers?

Here is their answer: "Overall, the data considered for this assessment support the conclusion that inadequate margins of safety exist between potential exposure and adverse effect levels for cannabinoids in cosmetics, food, and nutraceutical products made from industrial hemp."

Dr. Hugh Davis, for whom the risk assessment was performed, believes that hemp foods and cosmetics should be prohibited unless the industry can develop techniques for the total elimination of THC (and 65 other cannabinoids) from the hemp seeds. As the hemp nutmeat itself may contain faint traces of THC (Ross et al., 2000), such absolute elimination may not be practical.

A further problem is that methods for detecting THC levels in hemp products are constantly evolving, detecting more and more minute quantities. Thus, the definition of "zero tolerance" is constantly shifting, and an industry "in compliance" today might be violating the standards tomorrow. The concept of "zero

tolerance" developed from the U.S. War on Drugs, not from health research practices. Not even deadly food contaminants (e.g., pesticides) are held to such impossible restrictions, and popular foods containing trace amounts of other natural drugs (e.g., morphine, cocaine) are not a matter of official concern.

Dr. Davis suggested that the industry explore genetic engineering of the hemp plant to eliminate the THC. We believe that genetic engineering might pose significantly more and greater risks than THC, both to the environment and to the health of Canadians, although longterm studies have yet to be done. Elimination of cannbioids may also affect crop susceptibility to pests (Pate, 1999a). In any case, genetic engineering would violate official definitions of "organic" food and thus significantly damage the marketability of hemp products.

1.1 The Ad Hoc Committee

To evaluate the claims in the risk assessment and to provide an industry response to the report, Dr. James Geiwitz and Dr. Chuck Schom formed the Ad Hoc Committee on Hemp Risks and invited hemp scientists from around the world to join. Here is a list of current members, briefly identified:

B. Marc Alfred, Ph.D., Professor of Biological Anthropology (emeritus), University of British Columbia, Vancouver, BC

Jace Callaway, Ph.D., Department of Pharmaceutical Chemistry, University of Kuopio (chemistry of hemp foods), Kuopio, Finland

Paul Consroe, Ph.D., Professor of Pharmacology and Toxicology, University of Arizona (research on cannabis and cannabinoids; founding member of the International Cannabinoid Research Society), Tucson, Arizona, USA

Jozsef A. Durgo, Ph.D., D.Sc., Hemp Scientific International, Richmond, BC

Jason Freeman, President of Biohemp Foods (hemp food research), Regina, Saskatchewan

James Geiwitz, Ph.D., Director of Research, Transglobal Hemp Products (experimental design and analysis), Victoria, BC

Franjo Grotenhermen, M.D., nova Institute; chair, International Association for Cannabis as Medicine (toxicology of THC in hemp foods), Hurth, Germany

David Hadorn, M.D., health research (pharmacology and toxicology of hemp), Victoria, BC

Arthur Hanks, Editor, *The Hemp Report* (formerly the *Commercial Hemp Farm Report*), Regina, Saskatchewan

Eric Hughes, President of Zima Foods (hemp food research), Victoria, BC

Peter Kendal, C.Eng., M.I.Mech.E., formerly Engineering and Administration Manager, Omega Biotech Corporation (a nutraceutical company), Vernon, BC

John P. Morgan, M.D., Professor of Pharmacology, CUNY Medical School, New York, NY, USA

David W. Pate, Ph.D., M.Sc., Senior Technical Officer, HortaPharm BV (botany and chemistry of cannabis), Amsterdam, The Netherlands
Chuck Schom, Ph.D., New Brunswick integrated hemp industry (hemp genetics and agriculture), St. Andrews, NB
Phil Warner, Managing Director and Chairman of the Board of Australian Hemp Resource and Manufacture (AHRM), Brisbane, Australia

In addition to the members of the committee, we have 14 associates who follow our research and exchange information. These include scientists from The Body Shop (England), which markets hemp cosmetics. The Body Shop has produced its own response to the HC risk assessment; we incorporate their findings into our response.

The Committee's work was accomplished entirely by e-mail, from July 27, 1999, to the present. The Committee relied entirely on volunteer labour, which accounts for the brevity of this response. A rebuttal of Health Canada's risk assessment, over 400 pages long, deserves a point-by-point, fully referenced response of comparable length, which, unfunded, we were unable to provide. For instance, we were unable to reference the original data sources for many of the statements in this document, although, for critical issues, the primary research is cited. In other cases and especially for research summaries, our secondary sources were book-length reviews of THC research by two committee members, Dr. Franjo Grotenhermen (Grotenhermen et al., 1998) and Dr. John P. Morgan (Zimmer & Morgan, 1997). In these documents, the reader will also find references to primary sources. (It is worthy of note that the Grotenhermen and the Zimmer/Morgan reviews agree in every significant conclusion.)

1.2 Outline of the Committee's Response

An outline of Health Canada's Risk Assessment report is provided in the Appendix. Our response comprises three major sections. The first (Section 2) focuses on research on the toxicology of THC, specifically four toxic effects alleged by HC:

- acute neurological effects
- brain development
- reproductive system
- immune system

Section 3 will examine some of the inappropriate methods and conclusions of the Health Canada risk assessment: what went wrong with this badly flawed report, and why.

Section 4 of this response will focus on the determination of safe exposure levels for THC in hemp foods and cosmetics, that is, the *appropriate* risk assessment. Topics covered include:

- determination of No Observed Effect Levels (NOELs)
- exposure versus NOELs in hemp foods and cosmetics
- acceptable margins of safety
- determination of appropriate limits to THC in hemp products
- comparison of Canadian, Swiss, and German exposure standards

Section 5 provides a brief description of the health benefits of hemp foods and cosmetics, benefits that would be lost to Canadians if hemp foods and bodycare products were banned.

2.0 THE TOXICOLOGY OF THC

It is our position that THC is one of the least toxic chemicals that humans ingest. At normal doses, there is no evidence of genetic damage due to THC exposure or effects on fertility, pregnancy, or offspring. Similarly, there is no evidence of damage to the hormonal or immune systems. These statements apply to humans who ingest large quantities of marijuana daily, and much more so to humans who ingest trace amounts of THC through hemp foods. Ingestion through hemp bodycare products is completely undocumented and highly unlikely.

Research that finds damaging effects of THC generally falls into one of two categories: 1) studies that are not replicated by later research using more appropriate experimental designs; and 2) studies that use massive quantities of THC, far beyond the doses employed by heavy marijuana users.

2.1 Genetic Effects

In doses typical for consumers of marijuana, THC is not genotoxic, mutagenic, or carcinogenic, and it has no effect on cell metabolism. THC does not result in chromosomal breaks.

At extremely high doses applied directly to cells, THC reduces the synthesis of DNA, RNA, and proteins. These effects are nonspecific, that is, unrelated to the typical receptor activation in the human body.

In regard to genotoxic effects, the trace amounts of THC in hemp foods and cosmetics are obviously safe for consumers.

2.2 Pregnancy and Offspring

Animal studies of the effects of THC on pregnancy are inconsistent, even with doses of 10-20 mg/kg, a hundred times higher than the LOEL for psychotropic effects. A few studies purported to show impairment of cerebral development in children of chronic cannabis consumers, but these studies were never replicated and are now discredited. The NOEL for pregnancy variables (parturition, duration of pregnancy, infantile abnormalities, birth weight) is above the range of human consumption by chronic marijuana consumers, which is much higher than THC levels from hemp foods and cosmetics.

There is no realistically demonstrated danger to pregnant women or their offspring from consumption of hemp foods, and clearly none at all from use of hemp bodycare products.

2.2.1 Pregnancy

Greenland et al., 1982, found more meconium staining and longer duration of labour in marijuana users, but this study has never been replicated, even by Greenland's lab. For centuries, cannabis has been used for pain relief during birth. The general conclusions permitted by the research are that no birth complications can be observed in mothers who ingest marijuana levels of THC over a long period of time and that the trace levels of THC in hemp foods and cosmetics are obviously safe.

Gibson et al., 1983, found more premature births in marijuana users, but this study has never been replicated. Most studies find no marijuana-induced change in the duration of gestation.

2.2.2 Birth defects and brain development

Birth defects associated with THC have been found only in animal studies in which the THC was injected, in very high doses, directly into the abdomen. In humans, there is no evidence whatsoever for a link between marijuana use and fetal malformations or Minor Physical Anomalies (MPAs).

Studies that show a decreased birth weight in rat pups after THC ingestion have been clearly discredited. The decrease, when it occurs (at high doses), is due to reduced food and water intake of exposed dams; there is no difference between these animals and pair-fed controls.

Evidence is accumulating that the cannabinoid-anandamide receptor system might play a role in cerebral development in fetuses and neonates. Daily administration of 5 mg/kg THC to pregnant rats doubles the activity of the enzyme tyrosine

hydroxilase (TH) in specific brain cells of their fetuses (Hernandez et al., 1997). TH is believed to be a key factor in the development of neurons. In contrast, one animal study has established a disturbance of mesolimbic dopaminergic neurons among perinatally THC-exposed males which persists in adult animals (Garcia-Gil et al., 1997). However, the significance of these data for humans using hemp foods and cosmetics is very probably nil.

Animal studies have generally found behavioural problems only at high doses. For example, no behavioural effects in offspring were observed after dosing the pregnant rats with 50 mg / kg / day. Hutchings et al., 1987, found nipple attachment problems in rat offspring exposed to 50 mg / kg / day, but the problems were clearly related to decreased food and water intake in the dams; the offspring of pair-fed controls were indistinguishable from the offspring of experimental animals.

In humans, the offspring of chronic users show no differences from normal in sleeping, eating, mental tests, and psychomotor tests. One researcher (Dreher, 1994, 1997) found the offspring of chronic users to be more lively and less irritable, with fewer tremors; these babies were more easily quieted, yet more responsive to novel stimuli. These results have not been replicated, but they show the extreme inconsistency of marijuana studies. The more common finding is, simply, no difference.

Studies that have attempted to find brain damage from THC have been unsuccessful. Marijuana levels of THC do not kill brain cells. In one study, monkeys were forced to inhale five marijuana cigarettes a day for a year; there was no evidence of brain damage (Zimmer & Morgan, 1997). In humans, with brain damage assessed by CAT scans, no damage was observed in spite of the high dose: nine marijuana cigarettes a day.

2.3 Hormonal Systems and Reproductive Capabilities

Some high-dosage animal studies suggest that THC may act on the hypothalamus-pituitary-adrenal axis and adversely affect the sex steroid hormones. However, there is no reliable finding of adverse effects in animals (male or female) within the range of human consumption of marijuana. The slight effects that sometimes appear, disappear with repeated doses (tolerance). In humans, no effects were discovered regarding the function or concentration of sexual hormones or other parameters relevant for reproduction such as sperm quantity and quality.

In one representative study, men were dosed with up to 20 marijuana cigarettes a day for a month (Hembree et al., 1979). The researchers found some decrease in sperm concentrations and motility. The decreased factors were not outside of "normal" range, and by the end of the month, the sperm factors had returned to normal, despite continued dosing.

In men, a few studies found effects of chronic marijuana use on luteinizing hormone (LH), which is related to testosterone production, although the effect disappears with time, even if THC doses remain constant. Other studies found no such LH effect. There is no effect of THC on testosterone, follicle stimulating hormone (FSH), or prolactin. There are no effects on puberty. A representative study (Mendelson et al., 1978) found no effect of marijuana smoking on testosterone level, in spite of the high doses: 120 marijuana cigarettes in 21 days.

In women, the conclusions are the same: There are no reliable effects of THC on the menstrual cycle, estrogen levels, progesterone, prolactin, LH, or FSH. The few studies of positive effects involved high-dosage inhalation, effects that quickly disappeared as tolerance developed.

In some animal studies, THC reduced the level of adrenocorticotropin (ACTH), which is secreted by the adenohypophysis and stimulates the production of glucocorticoids (cortisol) in the suprarenal cortex. This result could not be replicated in human chronic consumers of marijuana. THC has no effect in humans on the thyroid hormones or on glucose metabolism.

2.4 Immune System

> "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 analysed parameters required extremely high doses to exhibit any significant effect and the 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. For many immune parameters the NOEL is ... irrelevant to the human consumption situation. In studies of man or of cells of marijuana users the effects observed were often contradictory. If such effects were found at all, they were weak even in case of heavy cannabis use and of questionable relevance to health. The World Health Organisation summarised in its most recent cannabis report: '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 (WHO, 1997, p. 27)'" (Grotenhermen et al, 1998, p. 53).

2.4.1 Suppression versus enhancement

THC and the immune system is the most thoroughly researched topic in the area of subliminal biological effects. Much of the early research, which demonstrated

immune-system suppression, has been discredited. For example, Nahas et al. (1974) found that THC decreases the number of T-lymphocytes – which control cell-mediated, acquired immunity. Later studies found no such decrease. Dax et al. (1989), for example, found no change in T- or B-lymphocytes (humoural immunity) or in T-cell subtypes before, during, or subsequent to administration of THC to chronic users. Wallace et al. (1988) reported similar findings, with a twist: an increase in helper T-cells (CD4). These findings should be interpreted as **immunoenhancement**, because helper T-cells stimulate the proliferation and activation of other immune cells.

In a study cited in the Health Canada risk assessment, Nahas et al. (1977) found *in vitro* suppression of T-cell proliferation in response to mitogens, which stimulate cell division. Other researchers criticized Nahas's method – applying THC in massive doses to human cells in a petri dish – and called the results "meaningless." Better studies failed to replicate Nahas's work and, instead, found immune system **stimulation** at lower doses (Pross et al., 1993; Luo et al., 1992).

Let us be clear about these findings: What the research shows is immune system suppression at very high doses, but immune system stimulation (enhancement) at low doses. These effects have been demonstrated for both the T- and B-lymphocytes. This means that the trace amounts of THC in hemp foods probably strengthens the immune system of humans. High doses have nonspecific toxic effects, likely the cause of any damage, whereas low doses act through specific receptor-based effects. It's a basic principle of pharmacology: low doses may be curative whereas high doses are poisonous.

One last point: With an oral dose of THC of 0.1-0.2 mg / kg (the psychotropic threshold), the blood plasma reaches a maximum concentration of 3-5 ng / ml. In the cell studies, the concentration is 10 ug / ml, or 10,000 ng / ml – 2000 to 3000 times the dose that produces the marijuana "high."

2.4.2 Humans and disease

Marijuana smokers show an enhanced response to antigens (which trigger antibodies) compared to cigarette smokers and cancer patients (Hollister, 1992), which supports the conclusion of THC strengthening the immune system and casts additional doubt on the high dosage cell studies. On a more general level. absolutely no epidemiological evidence exists relating marijuana use and infectious diseases (Hall et al., 1994). In cancer and AIDS patients, THC is used to reduce pain and depression, stimulate appetite, and prevent nausea and vomiting. AIDS patients, who suffer from a damaged immune system, are not harmed by THC (Di Franco et al., 1996).

2.5 THC and Cancer

Immune-system stimulation by THC at low doses should be apparent in macro-level health benefits. The stunning (but rarely reported) success of THC treatments of cancer may be representative. One of the first studies had rats ingest a large dose (50 mg/kg) of THC daily for two years. At the completion of the experiment, 70 percent of the dosed animals were still alive, but only 45 percent of the control (undosed) animals survived. This sizeable difference was due almost entirely to a reduced incidence of cancer in the animals given THC (Chan et al., 1996).

A more direct test of THC's cancer-fighting properties was performed on rats with brain tumours (Galve-Roperh et al., 2000). The tumours, called gliomas, are fatal in humans. The researchers infused THC directly into the rats' brains. The control rats (no THC) died in two to three weeks. In a third of the THC-dosed rats, the tumour was eliminated. Another third lived eight to nine weeks, instead of the two to three weeks of the control (no THC) rats. A third of the THC-dosed rats gained no benefit. The researchers claim that the THC works by stimulating the cancer cells to "commit suicide" in a natural process called "apoptosis." Normal cells were unharmed. The THC in this experiment was very low dosage, and the cancers were at a late stage, when untreated rats were already starting to die. The researchers suggest that THC would work even better if given earlier.

3.0 THE SCIENCE OF THC RISK ASSESSMENT

Section 4 will focus on the determination of safe exposure levels for THC. Before we turn to the appropriate risk assessment for THC in hemp foods and cosmetics, we will examine some of the inappropriate methods and conclusions of the Health Canada risk assessment. We have come to precisely the opposite conclusions to those of Health Canada regarding the risks of hemp products. Both of us claim scientific data in support of our position. In this section, we will list some of the ways in which Health Canada was mistaken, by inadvertently citing inadequate science.

The science of THC is not unlike other areas of science: Science does not **prove** anything. It deals in probabilities, and its methods are designed to estimate the degree of error in an estimate or in a probabilistic relationship. Most scientists view their procedures as a search for error, whereas the general public perceives it as a search for truth. In reality, it is a search for truth by way of estimating error.

The nature of science is such that one can always argue the opposite to a suggested proposition, with some evidence in support. Global warming, for example, is supported by the bulk of the evidence, but there are enough data leaning toward the opposite conclusion that the National Post can claim that global warming is a hoax. Similarly, scientists paid by the tobacco industry can mount a claim, with data

support, that smoking does not cause lung cancer.

When a scientific question has political ramifications (such as global warming or smoking), the goals of science are often perverted, as different camps seek to generate evidence for their position. The US War on Drugs is such a camp. Beginning in the 1960s, the US government offered scientists millions of dollars to "prove that marijuana is harmful." The research cited by Health Canada includes much of this "advocacy science," which produced misleading conclusions about the effects of THC.

The following section is, in effect, a manual on how to do advocacy science.

3.1 Extreme Dosing

The major deficiency with most reports of harm from THC is the massive doses required to demonstrate such effects. In one study, monkeys were given the human equivalent of 15 kg of marijuana in a single dose. Similarly, the petri-dish studies of the effects of THC on body cells used concentrations 2000 to 3000 times the threshold level for psychotropic effects.

The Body Shop, which markets hemp cosmetics, noted that the Health Canada estimate of skin penetration of THC (33%) is wildly inaccurate because the oil used to calculate the estimate had extremely high levels of THC (26mg/g). The high concentration of THC outside the skin encourages penetration, which is a function of the difference between outside and inside (where the concentration is essentially zero). If hemp oil with 4 ug/g THC constituted 10 percent of a cosmetic, as is the case with Body Shop lotions, then about 0.4 ug/g THC would be available for skin absorption, that is, about 65,000 times less than the dose used by Health Canada (Adams, 1999). In addition, attempts to deliver therapeutic THC via skin patch have been unsuccessful (ElSohly, 1998), a further indication of the safety of hemp bodycare products.

In a review of the effects of THC on the human immune system (which found none), the reviewers note that some animals given large doses do show effects; doses are forty to one thousand times the psychoactive doses for humans (Zimmer & Morgan, 1997). Similarly, an attempt to find brain damage in monkeys failed to do so, in spite of the dose: five marijuana cigarettes a day for a year.

These are extreme examples, but far from rare. Almost all of the studies that show damage from THC use high to very high doses, even compared to marijuana levels. When compared to the low doses from hemp foods and cosmetics, the high-dose studies are irrelevant.

THC at reasonable levels such as those in marijuana and hemp foods acts on

compound-specific binding sites (cannabinoid receptors). Only at high concentrations (which are not encountered in hemp foods and cosmetics) do nonspecific, toxic effects occur. Most if not all chemicals will damage body cells and systems at high concentrations – for example, numerous deaths have been recorded in people who for psychiatric reasons drink excessive amounts of water. And pharmaceuticals that are toxic at high concentrations are beneficial at low doses, as seems to be the case with THC and the immune system.

3.2 Cannabinoid Receptors and Tolerance

The fact that THC at reasonable doses acts not nonspecifically but, rather, specifically at receptor sites on neurons provides a further margin of safety for hemp foods and cosmetics. For one reason, neurochemical receptors generally show tolerance – that is, decreasing effect with repeated or sustained exposure. For most harmful chemicals, the toxicity increases (and the NOEL decreases) with duration of exposure. But, with THC, the opposite occurs, because of tolerance. For example, high doses of THC in female monkeys resulted in hormonal changes and a disruption of their menstrual cycle. After six months of high doses, the hormone levels and the menstrual cycles returned to normal (Smith et al., 1983). Tolerance can be observed in the cases of most THC effects.

Chronic exposure to THC does not irreversibly alter the cannabinoid receptors (Westlake et al, 1991).

At the low doses of hemp foods and cosmetics, THC's effects are almost entirely receptor based, with little or no nonspecific toxicity. This means that even if a troubling effect of low-dose THC were to be established, the risk would be shortlived.

3.3 Cannabinoid Receptors in Children

According to the Health Canada risk assessment, infants experience greater exposure to THC from hemp foods and cosmetics for four reasons:

- they have less fat to sequester the lipophilic THC
- they have less lipoprotein for binding THC
- they have an immature hepatic microsomal enzyme system, therefore less capacity for metabolism and excretion
- the infant brain has a greater density of cannabinoid receptors than the adult brain

We have some concern with the first three points. First, compared to adults, infants have a higher percentage of body fat relative to lean mass, although the absolute volume of fat is of course less. Second, although infants do have less lipoprotein,

the level reaches adult proportions by two to three years. And third, hepatic metabolism may not be a desirable function, if THC metabolites are more psychoactive than THC itself. In any case, we consider these facts irrelevant, since low levels of THC present no risk.

Our research indicates that the fourth point is mistaken. Children have a significantly lower density of cannabinoid receptor sites. They are therefore less, not more, susceptible to the effects of THC (Grotenhermen et al., 1998). We recognize that this issue is a controversial one, with research supporting both positions. Because this is such an important point, we examine the research in some detail.

The preponderance of research data supports our position. One of the studies that does not, one that is the basis for Health Canada's claim, attempted to determine the density of cannabinoid receptors in the fetus and neonate (Glass et al., 1997). These researchers concluded that concentrations of receptors in these subjects were "extremely high." One fetal brain (33 weeks gestation) and two neonatal brains (3 and 6 months of age) were examined, a sample too small for valid conclusions. The fetus died in utero of bowel obstruction, one neonate died of congenital heart disease and the other of asphyxia; the first two subjects must be considered "abnormal." What this means we do not know. It's possible that the fetus was reacting to its bowel obstruction by producing high levels of endocannabinoids, which could stimulate the production of cannabinoid receptors (Callaway, 2000).

There was a post mortem delay of up to 21 hours, a delay that may affect receptor profiles. The autoradiograms of fetal and neonatal tissue were of poor to fair quality, in contrast to those of adult tissue, which were extremely high quality. The fetal and neonatal tissue was processed separately from that from adults, which even the authors agree, requires considerable care in comparing results from children and adults. And their conclusion of more receptors in young brains is qualified: "Due to the small number of cases available for the study, it is not possible to draw any definitive conclusions of the precise levels of cannabinoid receptors ... within the developing brain" (Glass et al., 1997).

This is hardly a "definitive study," certainly not one on which to base public policy.

Research that supports our position includes a study of rats that discovered an increase of cannabinoid binding from birth to day 30, which corresponds roughly to human adolescence (Rodriquez de Fonseca et al., 1993). These data indicate a lower density of receptors in younger subjects. Another rat study found a 470% increase from birth to day 60, in all brain areas investigated (Belue et al., 1995). A third found receptor binding increasing almost 50 percent with increasing age (McLaughlin et al., 1994).

It is true that children generally respond more severely to chemical toxins and

require a greater margin of safety than adults. But in the case of THC, which operates on specific receptors, children require a smaller margin of safety because they have many fewer receptors. Children with cancer, for example, tolerate considerably higher doses of THC than adults, with no symptoms of psychoactivity (Abrahamov et al., 1995). This research group later studied, in mice, the response to anandamide and THC; there was no response to anandamide for the first 23 days, whereas a small response to THC began between days 15 and 20. The researchers felt that their results were compatible with their human data showing that children respond to the antiemetic effects of THC without psychotropic side effects (Fride & Mechoulam, 1996). A similar study of children with cancer taking nabilone, a THC analog, found that high doses were well tolerated: "Particularly for some adolescent patients, it can turn a five day course of chemotherapy from a dreaded ordeal into something accepted with a shrug of the shoulders" (Dalzell et al., 1986).

To summarize, most researchers find cannabinoid receptors in newborns, but receptor populations in children are significantly smaller than in adults; also, receptor binding in children is significantly less. Clinical studies of children with cancer find that children tolerate much higher doses of THC than adults. While more research needs to be done, the pattern of data is quite clear: **Children can tolerate much higher levels of THC in hemp foods and bodycare products than adults.**

3.4 Effective Forms of THC

In unprocessed hemp, THC occurs in the form of a monocarbon acid (THCA) that is not absorbed well by the intestines. One cannot, for example, eat uncooked marijuana and expect much of an effect. THC must be converted (decarboxylated) to its phenolic form to be bio-effective, which is accomplished by the application of heat. Smoking and baking are typical conversion methods. This means unheated hemp foods, such as cold-pressed oils, contain mostly inactive forms of THC.

Absorption of THC by human intestines depends on properties of the carrier. Lipophilic carriers, such as hemp oil, promote absorption of decarbosylated THC. If the carrier is less fatty, as in hemp breads or beverages, the bioavailability of THC is reduced by 50 percent or more. Even Health Canada accepts that hemp beer and wine presents no risks.

3.4.1 Cannabinoids other than THC

The Health Canada risk assessment repeatedly makes the point that there are 66 cannabinoids in industrial hemp, that THC is only the best known and most frequently studied. This number is misleading. It represents the sum total of cannabinoids found in detectable quantity in at least one cannabis variety in at least one study in the history of cannabis research. Health Canada contends that, even if

the risks of hemp foods and cosmetics from ingestion of THC are shown to be minimal, the hemp industry must also show that the risks from the other 65 cannabinoids are also so. Such research would require years, if not decades. This open-ended contention is unprecedented for a natural food product or drug source (e.g., coffee, alcohol, tobacco), which may contain scores of untested chemical components.

The only cannabinoids proven to be manufactured by the hemp plant are THC, CBD, CBC, and (presumably) their common biogenetic precursor, CBG (Pate, 2000). CBD predominates, with an accompanying fraction of THC. CBC is found in significant quantities only in tropical marijuana. CBG is found only in very small amounts. To this short list can be added minor quantities of the THC degradation products, CBN and delta-8 THC. The remaining 60 cannabinoids exist in almost undetectable amounts – in fact, usually none at all – in any given hemp sample. Health Canada admits that CBD poses few risks. CBN, according to Health Canada, is as dangerous as THC, but the research that "proves" this is the same research that "proves" that THC is risky. We believe this research to be problematic, if not invalid.

Since we have been unable to discover any significant health risks from the far more potent marijuana, it is unlikely that any ingredient of hemp foods and bodycare products pose health risks to human consumers.

3.5 Extrapolation from Animal Studies

A major disagreement exists between the Health Canada report and our research group regarding the value of animal studies for the determination of risks to human consumers of hemp foods and cosmetics. Many of the risks reported by Health Canada come from studies in which high doses were given to rats or mice. That's OK, says Health Canada, because of "similarities" between humans and rodents in the pharmacokinetics and metabolism of THC and in the brain distribution of cannabinoid receptors.

However, the application of rat data to human risk assessments is an uncertain and often misleading extrapolation, with numerous pitfalls. For example, the extrapolation of doses is problematic. Typically, a dose given to rats is reported in milligrams of THC per kilogram of body weight. The dose for humans to produce the same effects is then calculated using the body weight of humans. The average human weighs about 70 kg. So an effect caused by a 2 mg dose to a rat weighing 0.2 kg translates to a 700 mg dose to humans (about 50 times the dose for a human "high").

This kind of extrapolation may be meaningless, because many biological processes (e.g., metabolic rate) are unrelated to body weight. For this reason, some researchers

use comparisons of body surface (mg/m^2) instead of body weight. It has been found that body-surface comparisons predict more accurately human tolerance for anti-cancer drugs from animal data than do body-weight comparisons. But body surface is also a poor basis for extrapolation for many drugs. Other bases include pharmacokinetics (absorption, metabolism, excretion, etc.) and toxicological estimates such as the "lethal dose" studies.

The lethal-dose studies are a lesson: In rats, the lethal dose is around 1300 mg/kg. Extrapolated on the basis of body surface, the lethal dose in dogs should be about 350 mg/kg and in monkeys, about 650 mg/kg. But dogs lived after a dose of 3000 mg/kg, and monkeys survived 9000 mg/kg. The lethal dose in these animals could not be established. The primates should have been 50 percent more sensitive to THC than rats, but were at least five to ten times less sensitive. The extrapolation from rats to higher mammals was wildly inaccurate.

There are significant differences between the reproductive and hormonal systems of rats and mice and those of humans (Mendelson and Mello, 1984). Mice, for example, are especially disposed to fetal malformations. In general, data on smaller animals leads to highly inaccurate estimates of THC toxicity in larger animals.

Reliable data on the toxicity of THC in humans must be based on studies with human subjects.

3.6 The Fallibility and Abuse of Science

Studies of the effects of THC on humans are inconsistent, for a number of reasons: Many studies use small samples (that is, few subjects), and small-sample studies are notoriously unreliable (that is, inconsistent). For scientific purposes, small-sample studies are practically worthless. A young man who smokes pot fails to go through puberty; the child of a pot smoker develops cancer: These are meaningless anecdotes, although such studies are widely touted as proof of THC's dangers.

Most of the marijuana studies on humans compare chronic users with "matched" control subjects. This experimental design produces data that are often misleading, because the researchers are comparing two groups that differ in many ways. True matching is impossible, since one can never know all the factors that influence the life of a test subject. For example, many chronic marijuana smokers use other drugs as well, including cigarettes and alcohol. In addition, human subjects often lie about their drug use, making assignment to groups difficult. Results from such studies are often unreliable or difficult to interpret.

As we've mentioned, the US War on Drugs has distorted the scientific infrastructure and produced a plethora of biased findings. A study that purports to have found deleterious THC effects is quickly published, whereas a study that finds

THC safe is not. In the latter case, researchers may suppress the data or peer review might disparage the experiments (Levy and Koren, 1990). Finally, if well-designed experiments demonstrating the safety of THC are published, government publications often ignore them, focusing instead on the studies that support the official view. This pseudo-science we have termed "advocacy science."

True science consists of a search for conclusions to explain previously established facts, theories to explain observed data. Advocacy science consists of a search for facts to support a previously established opinion.

4.0 DETERMINATION OF TRUE HEMP RISKS

In this section, we present our determination of a THC level in hemp foods and cosmetics that is clearly safe for human consumption. This determination was conducted for the German hemp industry by Dr. Franjo Grotenhermen, a member of our committee (Grotenhermen et al., 1998).

4.1 LOELs and NOELs

Our first step is to determine the No Observed Effect Levels (NOELs) and Lowest Observed Effect Levels (LOELs) for the psychoactive effects of THC. Our review of the research clearly shows that if THC levels are below the NOEL for psychoactive effects, there will be no other risks to health.

The LOEL for THC's psychoactive effects is 0.2 to 0.3 mg/kg, about 10 - 20 mg THC in a single dose to an average adult. The NOEL, the level of THC that cannot be distinguished from placebo (no THC) effects, is .07 mg/kg, about 5 mg for an average adult. At the effect duration of four hours, the NOEL is 5 mg twice a day, or 10 mg/day.

The application of a safety factor of 10 results in a tolerable daily dose of 14 ug/kg, about 1 mg THC for a 70 kg adult. This dose will have no psychoactive effects and no adverse health effects.

4.1.1 Appropriate safety margins

Health Canada applied a safety margin of 1000 to its flawed determination of THC LOELs. We believe that this safety margin is ridiculously large, a hundred times the industry standard of 10 (Kendal, 2000). Health Canada justified its safety margin as follows: 10-fold for interspecies differences, 10-fold for intraspecies differences, and 10-fold for lack of data from chronic studies. As we have seen in the review of research, the interspecies differences (especially comparing human risks to toxic effects from high-dose rodent studies) are in the opposite direction from that proposed by Health Canada, that is, humans are **less** at risk than would be assumed

from the rodent findings (even if extrapolation calculations were accurate, which they are not). Similarly, the intraspecies differences are such that estimation of NOELs with adults will protect children, with fewer receptors, even more.

Chronic consumption of THC will not increase risk, it will decrease it. THC receptors typically develop tolerance, so that a continuous supply of THC does not lead to an increase in possible health impairments (and a decrease in NOEL), as is common with most toxic chemicals. And, although we can always use more chronic studies of humans, there is no evidence that we will be misled by using the many chronic studies we now have.
We believe that a safety factor of 10 is conservative.

4.2 Exposure and NOEL

The research on absorption of THC clearly shows that the greatest risk is with adults ingesting hemp oil that contains THC in its active phenolic form. (We disregard the fact that cold-pressed hemp oil is likely to contain more inactive THC acids than active THC forms.) Lipophilic carriers such as oils promote absorption; THC absorption in hemp breads, in contrast, is reduced by 50 percent; in hemp beverages and cosmetics, absorption levels are even less, or nil.

The average daily consumption of hemp oil for Germans who consume this product is 33g / day. The German figure is probably high for the Canadian situation, since Germany has had a vital hemp industry for many years. But we will use it anyway, and add a further safety factor, 1.5, to account for increased consumption as the world recognizes the health benefits of hemp foods. So our exposure figure is 50g / day / consumer.

4.2.1 Maximum levels of THC, properly determined

The NOEL for THC, as determined in Section 4.1, is 1 mg for an average adult. With consumption of hemp oil (in which absorption is greatest) of 50 g / day / capita, the maximum THC content of the oil, if we don't want to exceed the NOEL, should be .020 mg per g of oil, or 20 mg / kg. **Scientifically determined, the maximum THC in hemp oil should be set at 20 parts per million (20 ppm).**

4.2.2 Comparisons of THC limits

Our recommendation for THC limits in hemp foods and cosmetics is 20 ppm. Current Canadian legislation sets Canadian limits at 10 ppm, and the Health Canada report erroneously determined that even this amount was dangerous. The hemp oil available in Canada before industrial hemp was legalized (from Don Wirtshafter's Ohio Hempery, for example) had 15 ppm and was rejected by Health Canada.

Switzerland is the only country other than Canada to set limits on the THC in hemp foods. After careful scientific evaluation, the Swiss set limits of **50 ppm** for hemp oil, with less restrictive limits for other foods and bodycare products. In Europe, the Swiss standard is thought to be liberal, the German standard (20 ppm) is considered conservative. The Canadian standard of 10 ppm is considered severe, and the "zero tolerance" recommended by the Health Canada risk assessment is considered draconian.

5.0 BENEFITS OF HEMP FOODS AND COSMETICS

Health authorities typically do cost/benefit analyses of new drugs, trying to determine whether the benefits outweigh the toxic costs associated with the drugs. Health Canada has chosen not to pursue the "benefits" portion of such analyses, asserting that their mandate is only to identify possible risks to the health of Canadians. Of course, all drugs and all foods have health risks. However, the notable risks of aspirin or red meat are deemed insufficient to warrant banning these substances.

The risks of THC in hemp foods and cosmetics are practically nil, as we have shown. However, even if minor risks could be demonstrated, we would argue that the depriving Canadians of the health benefits of hemp foods and bodycare products would constitute more of a threat to their health than unregulated consumption.

The purpose of this paper is to refute the flawed conclusions of the Health Canada risk assessment. For that reason, we will not dwell excessively on the virtues of hemp foods and bodycare products, which are well-described elsewhere (e.g., Conrad, 1997). Instead, we will briefly list some of their abundant health benefits.

5.1 Benefits of Hemp Foods

Hemp foods are made from the hemp seed, which is botanically a nut. There are two major components of the hemp nut, the oil and the nutmeat. Hemp oil is made by cold-pressing the seed; what's left is the hempseed "press cake," which is commonly converted to flour for hemp breads and similar foods. The hemp nut can be eaten whole, as it's very nutritious and quite tasty. Hemp foods have been a dietary staple for millions of people in Europe for centuries and for tens of millions in China and other parts of Asia for millennia.

5.1.1 Hemp oil

Hemp oil has many desirable ingredients (Pate, 1999b), the most important of which are the essential fatty acids (EFAs), linoleic acid (Omega 6) and linolenic acid (Omega 3). These fatty acids are present in hemp oil in the ratio of 3:1, which is the "optimal ratio" for health benefits (Erasmus, 1993).

> "The membrane (coating) of every cell in our body is composed of oil. It is this oil that acts as a superconductor allowing an unimpeded flow of the bio-electric currents that govern nerve, muscle, heart and membrane functions. The oil component of our diet normally comes from fresh, well stored seeds, nuts, vegetables, and a few fruits. If the oils in your diet are primarily of low quality, such as supermarket oils and fats that stay solid at room temperature, then the oil coating on your cells are going to have some of the insulating properties of tar and be a less than ideal conductor. Conversely, if the oils in your diet are in a pure, unadulterated form, the bio-electric current will flow much smoother, and all our bodily functions will be easier to perform: everything from the pancreas secreting insulin to keep our blood sugar levels balanced, to keeping our hormone system in check, to alleviating the buildup of the heavy LDL cholesterol that plugs our arteries leading to heart disease and arterial sclerosis. Pioneers in the fields of biochemistry and human nutrition now believe cardiovascular disease (CVD) and most cancers are really diseases of fatty degeneration caused by the continued over consumption of saturated fats and refined vegetable oils that turn essential fatty acids into carcinogenic killers. One out of two Americans will die from the effects of CVD. One out of four Americans will die from cancer. Researchers believe cancers erupt when immune system response is weakened" (Thorpe, 1999, p. 32).

If, however, cell membranes are constructed from "fats that heal" – the best of which is hemp oil (Erasmus, 1993) – the health benefits are considerable. Perhaps the primary benefit is the effect of the EFAs on the heart. Hemp oil reduces the level of bad cholesterol (LDL), reduces inflammation in blood vessels, thins the blood (by reducing platelet stickiness), and reduces blood pressure. Thus, hypertension is relieved and the risk of heart attacks and strokes is reduced. The chances of heart disease in general are significantly reduced. In October, 2000, the American Heart Association issued a recommendation that Americans consume foods with high levels of Omega 3 (Gorman, 2000); the most balanced common source of this EFA is hemp oil.

A second major benefit of hemp oil is a strengthening of the immune system. It inhibits tumour growth, kills bacteria (including staph), and heals wounds (Erasmus, 1993).

In summary, the EFAs in hemp oil are used to

- construct cell membranes, which create and carry electrical currents
- bring toxins within cells to the surface, where they can be removed, and deliver nutrients from the cell surface
- facilitate recovery of fatigued muscles by delivering oxygen, producing hemoglobin, and removing waste products
- strengthen the immune system, preventing infections and allergies
- develop nerve cells in the CNS
- promote healthy liver function
- increase stamina, vitality, and calmness
- reduce inflammation, pain, and swelling in muscles and joints
- promote production of prostaglandins, an important system of hormones related to health

The EFAs in hemp oil will beneficially affect (partial list)

- heart disease, hypertension
- cancer
- stroke
- arthritis
- allergies, asthma
- AIDS
- Alzheimer's disease
- multiple sclerosis
- cystic fibrosis
- chronic fatigue syndrome
- PMS
- fibrosystic breast disease
- endometriosis
- enlarged prostate
- hair loss in men
- dyslexia
- Attention Deficit and Hyperactivity Disorder (ADHD)
- mental disorders: bipolar depression disorder, schizophrenia
- tuberculosis
- violent personality disorders
- yeast infections
- obesity
- cellulite, aging spots, cataracts
- ulcers, constipation, diarrhea, digestive problems
- diabetes
- lupus

5.1.2 Hemp nuts, hemp flour, and hemp protein

When the oil is squeezed from hemp seed, the remaining press cake is made into flour for hemp breads, pastries, and other products. This press cake contains two high-quality proteins called edestin and albumin. These proteins contain all eight of the essential amino acids in highly favourable proportions, and they are easier to digest than the protein in soybeans and other foods. Like EFAs, proteins are the basic building blocks of the human body. There are few bodily functions that are not affected, in a positive way, by hemp protein.

The dehulled hemp seed (hempnut) is perhaps the best way to ingest hemp foods. The delicious hempnut contains not only the proteins mentioned above, but also the highly beneficial EFAs, better preserved in the nutmeat matrix.

An interesting report has turned up on the use of hemp protein to treat tuberculosis in Czechoslovakia during and after World War II (Sirek, 1954). At an institution for children with TB, doctors had no medicine and very little food. The doctors decided to treat the children with hemp seeds, because of the protein (edestin) in the nuts. Edestin contained not only the appropriate amino acids (including arginine, essential for formation and growth of new tissue) but also a wealth of healthy enzymes. A total of 26 children were treated with a diet of hemp seed, oats, and cottage cheese. All 26 were cured or significantly improved, and all grew to be healthy young adults.

5.2 Benefits of Hemp Bodycare Products

Hemp oils are used to make body lotions, soaps, and other products that heal the skin, restoring natural health and beauty. The essential fatty acids (EFAs) that are used by the body to build and maintain healthy body cells (especially the membranes) work directly on epidermal cells, entering the lipid layers of dry skin cells to replenish their oils (Ohio Hempery, undated).

The EFAs also repair skin damage, promoting healing in wounds and burns, and they are antibiotic. Research has shown that EFAs are effective treatments for atopic dermatitis, eczema, and psoriasis (Fitzpatrick, 2000).

6.0 CONCLUSIONS

Hemp foods and bodycare products are among the healthiest substances that humans consume. In their essential fatty acids and proteins, hemp products provide the basic building blocks that our bodies use to construct cells and tissue for healthy and efficient functioning.

Health Canada, in a draft risk assessment, has raised the question of possible health

risks associated with 10 ppm levels of THC, the psychoactive ingredient in hemp. We have reviewed the relevant research and concluded that there are no health risks from low level doses of THC. None. There may indeed be health benefits: several studies have shown strengthening of the immune system.

The Health Canada risk assessment is based on poorly-designed research. Most of the research showing possible health risks with THC ingestion uses massive doses of THC, far more than even those levels consumed by the heaviest marijuana smokers. Every study showing health risks has been discredited or refuted; cannot be replicated; or has been shown to be in error by a majority of studies on a given topic.

The appropriate risk assessment for hemp foods and cosmetics would show that there are no health risks, only benefits. We believe that the current Canadian standard, requiring less than 10 ppm THC in hemp products, is too low; we have calculated 20 ppm as sufficient to protect consumers from any possible psychoactive reactions (and even these reactions are not a health risk). But with considerable effort, the hemp industry has found it possible to prepare hemp products with less than 10 ppm, and is willing to accept that standard.

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APPENDIX

The Health Canada Industrial Hemp Risk Assessment (draft)

Outline of the Argument

(Changes from March 3 to September 9 are boldfaced in C4)

A. Toxicology

1. Hazards of THC exposure include acute neurological effects and long term effects on brain development, the reproductive system, and the immune system.
    a. Latter effects appear to be mediated through disruption of the hypothalamus-pituitary axis through a receptor-dependent mechanism.
2. Good concordance between animal and human assessments of adverse effects.
    a. Animal/human similarities in pharmacokinetics and metabolism of THC; and brain distribution of cannabinoid receptors.
    (Therefore, we can extrapolate from animal data to humans for this report.)
3. Human epidemiology studies suggest correlation between marijuana use during pregnancy and three types of cancer in offspring, plus neurocognitive effects.
    a. re: neurocognitive effects based on:
        1). temporal association between cause and effect
        2). plausible biological mechanism
        3). adverse effects are correlated with similar exposures in animals
        4). concordance among effects across species
        5). consistency in epidemiology findings
        6). cohort studied has consistently shown effects over the years
4. 17 rat studies and one monkey study provide **unequivocal proof** that exposure to THC and other cannabinoids during gestation and/or lactation can cause permanent neuroendocrine disruption in **adult** offspring.
    a. may occur after single dose to pregnant animal
    b. effects include:
        1). reduced sensitivity to morphine
        2). increased self-administration of morphine
        3). changes in density of brain opioid receptors
        4). changes in brain catecholamines
        5). increased corticosterone release in response to stimulus of the hypothalamus-pituitary-adrenal axis
        6). enhanced response to novelty in males
        7). reduced copulatory behaviour in males

8). inhibition of testosterone release in response to a receptive female

9). abnormal estrus and altered hypothalamic regulation of gonadotropin secretion in females

c. of concern because THC crosses the placenta and appears in fetal brain within minutes of maternal exposure

d. fetus and nursing infant could experience greater exposures than adults because of:

1). less fat to sequester the lipophilic THC

2). less lipoprotein for binding THC

3). immature hepatic microsomal enzyme systems, therefore less capacity for metabolism and excretion

4). human fetal and infant brain have greater density of cannabinoid receptors than adult brain, therefore greater sensitivity to cannabinoid exposure

e. adolescents also particularly sensitive because:

1). developing reproductive system sensitive to neuroendocrine disruption

2). consumption of snack/fad foods is higher at this age

B. Causes of Toxic Effects

1. What causes neuroendocrine disruption by cannabinoids? Receptor-dependent interference with neurotransmitters.

a. neurotransmitters affected include dopamine, serotonin, acetylcholine, GABA, norepinephrine, histamine, prostaglandins, and opioid peptides

b. cannabinoid receptors are part of endogenous cannabinoid system

1). suggested functions of cannabinoid system: neuroprotection; immunomodulation in the brain; immunomodulation; modulation of reproductive and endocrine function; control of motor activity; functioning of perception, cognition, memory, and learning; control of mood; emotion; food intake; regulation of body temperature and blood pressure

c. THC and other cannabinoids interfere with binding of the endogenous ligand to the cannabinoid receptor and thereby disrupt normal functions

C. Lowest Observed Effect Levels (LOELs) and No Observed Effect Levels (NOELs)

1. Neuroendocrine disruption in rats at doses as low as 1 ug/kg/d, no lower doses studied.

a. therefore, no NOEL

b. absence of NOEL and also chronic exposure studies precludes determination of Tolerable Daily Intake (TDI)

2. **Approach** of this risk assessment: compare estimated exposures through

hemp foods and cosmetics with LOEL for neuroendocrine effects in animals and LOEL for acute neurological effects in humans.

a. no NOEL for acute effects in humans either

b. acute effects in humans included because "of the focus that has been given to psychoactive effects and the importance of maintaining exposures below the threshold for neurological impairment"

3. LOEL for neuroendocrine effects in animals is 1 ug/kg/d (see C1)

a. observed effects are changes in hormone levles in pregnanat rats and in their fetuses; permanent adverse effects on reproductive parameters when given to peripubertal rats

4. LOEL for acute neurological effects in humans is 60 ug/kg **(change to 70 ug/kg)**

a. observed effect is significant decrement in performance scores in a battery of tests after single oral exposure in adult males **(change to adults)**

D. Exposures

1. Exposure to THC from hemp foods, cosmetics, and nutraceuticals was estimated for adult female, adult male, and child, age 5-11.

a. consumption based on dietary intake studies for food, industry use data for cosmetics, and recommended intakes for nutraceuticals

b. THC concentrations estimated as 4 ug/g (lowest concentration detectable, reported by industry), 10 ug/g (Health Canada maximum), or 15 ug/g (hemp oil in 1997)

c. concentrations in consumer products based on concentration in raw materials and information on product preparation or formulation

2. Exposure through food was based on the assumption that hemp products would replace 10% of the traditional products in each product category

E. Exposure vs. LOELs for Foods

1. **Exposure through foods exceeds LOEL for neuroendocrine effects by 5-10 times for adults and by 50-80 by children.**

2. Child's exposure is in range of LOEL for acute neurological effects.

a. worst-case exposures well above LOEL for neurological effects for children and adults

3. Exposure through beer was 1000 times below LOEL for neuroendocrine effects.

a. probably an overestimate because "concentration assumed to be the detection limit and 1/2 the detection, since none was detected at 5 ng/ml"

b. THC is extremely lipophilic, therefore would not be expected to remain in the aqueous fraction during beer production

c. therefore, hemp beer probably pose no health risks to adult males and nonpregnant females

d. probably the same for hemp wines, but no data available

F. Exposure vs. LOELs for Cosmetics

1. Exposure through cosmetics is much lower than for other products, 5-10 times below the LOEL for neuroendocrine effects.

a. **this exposure level does NOT provide an adequate margin of safety**

2. Exposure for children is 10-30 times below the single dose LOEL for acute neurological effects in adult males.

a. **this exposure level does NOT provide an adequate margin of safety**

G. Other Cannabinoids

1. Only two with any data.

2. Cannabinol (CBN) was determined to be as toxic to the neuroendocrine system as THC.

a. could be present in products at 10%-100% concentration of THC

b. **therefore, the risks of hemp foods and cosmetics could be twice as high as estimated from THC alone**

3. Cannabidiol (CBD) appears to be less toxic than THC.

a. could be present at concentrations 10-30 times that of THC

b. single dose LOEL of 4.4 mg/kg for disruption of the hypothalamus-pituitary-adrenal axis in humans

c. **at 10-30 times THC, exposures of CBD would exceed or approach the LOEL for adults and children, for all product categories**

4. There are, in addition to THC, CBN. and CBD, over 60 other cannabinoids in cannabis, for which there are no data.

a. there is no reason to believe that these other cannabinoids are harmless

H. Acceptable Margins of Safety

1. Based on Health Canada practices, **a margin of safety of at least 1000 is required** between the animal NOEL (not established) and the human exposure level.

a. 10-fold for interspecies differences, 10-fold for intraspecies differences, and 10-fold for lack of data from chronic studies

b. additional uncertainty factor required for fetus, infant, and adolescent

2. Since the lowest predicted exposures for THC are in the range of 0.2 ug/kg/d (use of cosmetics in adult males), **product reformulation would have to reduce exposure over 1000 times before reaching acceptable range.**

a. assuming NOEL for neuroendocrine effects is in the same range as LOEL

3. **The detection limit for THC in raw materials have to be 1000 times below current detection limits.**

a. in order to prove reduced exposure if such reduction is possible

4. **Proof of exposure to other cannabinoids (N=66) would be required for a change in conclusions.**

HC'S FINAL CONCLUSION:
"**Overall the data considered for this assessment support the conclusion that inadequate margins of safety exist between potential exposure and adverse effect levels for cannabinoids in cosmetic, food, and nutraceutical products made from industrial hemp, and that the margins of safety are so small that refinement of the assessment based on additional data or reduction of cannabinoid concentrations to below the detection limit would not be expected to result in a change to this conclusion.**"