ASSESSING THE IMPACT OF THC UPTAKE FROM HEMP OIL COSMETICS ON WORKPLACE DRUG TESTING

by

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EXECUTIVE SUMMARY

The presence of low concentrations of delta-9-tetrahydrocannabinol (THC) in cosmetics from hemp oil has raised concerns that the use of these products may cause positive urine tests for marijuana in workplace drug tests, commonly administered in the U.S. This study's objective was to estimate a theoretical range of THC uptake rates from the extensive use of hemp oil cosmetics. They were compared to uptake rates previously found to cause no positive urine tests when ingested via hemp food.

Review of the scientific literature found only two relevant experimental studies on the transdermal uptake of THC. These studies suggest that skin penetration by THC is slow compared to other, less lipophilic (fat-liking) compounds. However, the high THC concentrations applied in these studies and other limitations did not allow for extrapolation of the results to the use of hemp oil cosmetics. Rather, transdermal uptake factors for THC, *i.e.* the fraction of topically applied THC that enters the blood stream, were estimated based on physico-chemical characteristics of THC, known uptake rates of similar organic compounds, and the consideration of skin condition.

Daily THC uptake from the use of hemp oil cosmetics was then estimated for two scenarios. Both scenarios assumed high, yet conceivable product application rates, reflecting exclusive use of hemp oil cosmetics. Based on vendor information, conservatively high hemp oil contents in all products considered were also assumed. Under the "high-exposure" scenario, a 5% uptake factor for healthy skin was conservatively assumed. The "worst-case" scenarios assumed use by persons with considerably compromised skin. THC levels in hemp oil of 5 and 10 µg /g or parts per million (ppm) were assumed for the two scenarios, respectively.

The exposure assessment indicates that THC uptake, even from the extensive application of commercially available hemp oil cosmetics to healthy skin, is typically less than 1 µg/day. In case of the highly unlikely full-body application of pure hemp oil with a 10 ppm THC content on partially compromised skin THC uptake could conceivably be raised to 11 µg/day. Even this higher rate is only a fraction of the 450 µg/day of oral THC intake, found not to result in a positive screening test for marijuana. Thus, our findings suggest that even extensive use of hemp oil cosmetics will not cause positive urine tests for marijuana or even contribute significantly to the THC uptake rates required to produce a confirmed positive test. In addition, ongoing efforts to reduce THC levels in hemp oil will further reduce transdermal THC uptake from hemp oil cosmetics.

The results of this exposure assessment show that specific regulatory action, such as limiting THC content in product formulation or formulations is not necessary. Limiting THC levels in hemp oil to 5 ppm appears to provide a sufficient margin of protection from impacts on health or drug tests by hemp foods and cosmetics. Considering the high margin of safety, an experimental study is not warranted for the sole purpose of assessing interference of hemp oil cosmetics with drug testing. However, such a study would provide useful information on the kinetics of THC uptake as a function of product formulation and skin conditions.

1. INTRODUCTION

1.1 Background

Use of hemp seed products

Since the mid 1990s, oil pressed from the seeds[1] of the hemp plant (*Cannabis sativa* L.), commonly referred to as hemp oil, has increasingly been used by U.S. and Canadian manufacturers for natural foods and body care products.

Food uses of hemp oil include salad dressings, cooking oil for cold and warm dishes, and food supplements. The oil's fatty acid spectrum is claimed to provide several nutritional benefits. They include the presence of signifycant amounts of the omega-3 essential fatty acid (EFA) alpha-linolenic acid, a balanced ratio of omega-3 to omega-6 EFAs and smaller quantities of other physiologically relevant polyunsaturated fatty acids (PUFAs) such as gamma-linolenic acid (GLA) and stearidonic acid (Leson & Pless 1999).

Hemp oil is being used in a variety of cosmetics or body care products[2] such as bar and liquid soaps, shampoo and hair conditioner, body lotion, creams, massage oil, lip balm, and salves. Manufacturers and users of hemp oil cosmetics claim that hemp oil has preventive and therapeutic benefits for the skin. The PUFA content may alleviate dry-skin defects, such as cracking and scaling, improve the smoothness of dry and scaly skin, and slow down skin aging and the formation of wrinkles (Idson 1992, Anstey *et al.* 1990, Wright & Burton 1982).

THC residues and drug testing

The presence of—albeit minute—amounts of cannabinoids in hemp oil such as delta-9-tetrahydrocannabinol (THC)[3], the major psychoactive ingredient in marijuana, creates a major obstacle to the expansion of such cosmetics and foods into the natural products market.

Hemp seed meat itself contains virtually no THC or any other cannabinoids. Rather, these compounds are produced in glands of flowers, whose resinous excretions adhere to the seed hulls. As a result, traces of cannabinoids are found on processed hemp seeds and in oil pressed from them (Leson *et al*. 2001, Crew 2000). While THC uptake via hemp food or cosmetics is too low to cause any psychoactive effects, the scientific literature had previously demonstrated that in particular the consumption of hemp foods could cause produce positives in workplace drug tests (Alt & Reinhardt 1998, Grotenhermen *et al.* 1998, Costantino *et al.* 1997, Fortner *et al.* 1997, Lehmann *et al.* 1997, Struempler *et al.* 1997). Since then, improved cleaning methods[4] have drastically reduced THC levels in hulled hemp seeds and oil and the resulting risk of testing positive. Typical THC levels in hulled seeds and oil produced in Canada are now 2 and 5 µg/g or parts per million (ppm), respectively (Webster 2001, Crew 2000).

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[1] In Canada, the seeds of hemp used for consumption, not for planting, are referred to as "hemp grain".

[2] The terms "*cosmetics*" and "*body care products*" are used interchangeably in this report; the term "*hemp oil cosmetics*" is summarily used to include all body care items containing any amount of hemp oil.

[3] Hemp varieties legal for cultivation in Canada, so-called "industrial hemp", are bred to contain less than 0.3% THC by weight (Bócsa & Karus 1998, Health Canada 1998), while drug varieties typically contain 2–5% and as much as 20% (ElSohly 1998, Grotenhermen & Huppertz 1997).

[4] Mechanical seed cleaning processes involve drying in aerated bins with heated air, screening, and dust removal.

For a summary of workplace drug testing procedures for marijuana, refer to the insert below.

Not surprisingly, numerous individuals subject to workplace drug testing have since claimed that their positive urine tests for marijuana were caused by the use of hemp foods and cosmetics (Cole 2000). Due to the resulting uncertainty, several military organizations and law enforcement agencies in the U.S. have recommended or demanded that their employees refrain from the use of any food or cosmetics items containing hemp seed (*e.g.*, Law Enforcement News 1999). The same concern often keeps U.S. retailers from carrying hemp seed products (Roulac 2000). Finally, the U.S. federal government is considering the adoption of "zero THC" limits in food and cosmetics, because *"…topical solutions, as well as products specifically designed for ingestion…are confounding our Federal drug control testing program, if they contain THC, and are of significant concern."* (McCaffrey 2000, U.S. Federal Register 2000). If adopted, such "zero THC" limits would in effect render the importation and distribution in the U.S. of hemp oil containing products illegal.

Hemp food products and drug testing

Recently, Leson Environmental Consulting (LEC), in collaboration with several experts on the metabolism and toxicology of THC evaluated the potential impact of hemp food consumption on the outcome of workplace drug tests (Leson *et al.* 2001). The study had been funded by the Agricultural Research and Development Initiative (ARDI), a joint program of the Canadian federal and Manitoba provincial governments, the North American Industrial Hemp Council (NAIHC), and several processors and distributors of hemp seed products. The results showed that extended daily ingestion of 450 µg of THC in hemp oil is not likely to cause positive results of urine tests for marijuana, as long as drug-testing procedures follow federal guidelines. These mandate confirmation by GC/MS of any sample screening positive. Uptake of such THC quantities would require an excessive consumption of hemp foods corresponding to about half a pound of properly cleaned, hulled hemp seeds.

Typical workplace drug testing procedures for marijuana in the U.S.

A urine sample—announced or random—is collected and screened for cannabinoids and their metabolites using an immunoassay test. Such immunoassays can be performed rapidly and at low cost, yet they are not highly specific for THCCOOH, the main metabolite of THC. If a screening test detects THCCOOH above a specified "cutoff" concentration—federal workplace testing programs apply a 50 nanograms /milliliter (ng/mL) or parts per billion (ppb) cutoff—the sample is then "confirmed" by the more specific GC/MS (gas chromatography/mass spectrometry) method. If GC/MS detects THCCOOH at levels above a certain confirmation cutoff—typically 15 ppb—a urine sample is considered "confirmed positive" for marijuana. Some employers and law enforcement agencies in the U.S. use a lower screening cutoff of 20 ppb and confirmation cutoff of 10 ppb. Very few drug-testing programs rely solely on the positive outcome of a screening test without automatic subsequent confirmation-testing by GC/MS.

Hemp oil cosmetics and drug testing

To date, no evaluation of the influence of the extensive use of hemp oil cosmetics on the outcome of drug tests has been conducted. Yet, soap and other body care products containing Canadian hemp oil have recently been implicated in court proceedings brought about by a positive drug test (*e.g.*, Dorazio 2000). Unless it can be established that even extensive use of commercially available hemp oil cosmetics cannot cause positive drug tests for marijuana, their blacklisting or federal ban in the U.S. could eliminate this relevant market for Canadian hemp oil.

1.2 Objectives

LEC was commissioned by the Agricultural Research and Development Initiative (ARDI), Morris, Manitoba and by Dr. Bronner's Magic Soaps, Escondido, CA, to conduct a desktop study. Its goal was to assess whether the extensive use of hemp oil cosmetics may produce sufficiently high urine levels of THC metabolites to cause or contribute to a positive urine test for marijuana.

Specifically, the study's objectives were to:

- Compile available information in the literature on transdermal THC uptake, *i.e.* uptake via the skin;
- Critically review and possibly modify existing exposure scenarios for the application of hemp oil cosmetics;
- Estimate transdermal THC uptake for several conservative usage and exposure scenarios representative of current hemp oil cosmetics;
- Compare the estimated uptake rates to those ingested during the previous study on hemp food and drug testing; assess the potential influence of the use of hemp oil cosmetics on the urine level of THC-metabolites;
- Discuss the implications for acceptable THC levels in hemp oil and the potential of hemp oil cosmetics to cause, or contribute to a positive drug test;
- Discuss the need for a controlled study on the use of hemp oil cosmetics and urine testing for marijuana.

1.3 Approach and sources of information

Initial review of the issue indicated that the low amount of hemp oil applied with cosmetics, the oil's low THC content, and the inefficient transdermal uptake[5] of THC will result in uptake rates considerably less than those from hemp food ingestion. Furthermore, relative THC uptake was expected to vary considerably with skin conditions and mode of application of hemp oil cosmetics. Thus, LEC conducted a desktop study to initially assess THC uptakes under various conditions. Variables to consider were the THC level in hemp oil, hemp oil content in the product, product application rates, and transdermal uptake factors. The outcome of this desktop study would indicate whether projected THC uptake was sufficient to considerably raise metabolite levels in urine. In that case, a toxicological study would be required to measure actual THC metabolite levels in urine following hemp oil cosmetics use.

[5] In the scientific literature the terms "percutaneous absorption" and "transdermal uptake" are used synonymously.

To achieve the above objectives, this study involved the following activities:

- An extensive search of the scientific literature for information on transdermal THC uptake was conducted (Grotenhermen 2001). It confirmed previous findings (Health Canada 2001) that very limited research of the issue had been conducted. Thus, in addition to the available publications, our exposure assessment relied on an evaluation of the research by Health Canada (Health Canada 2001) and unpublished reviews of this study, which currently are not in the public domain (Adams, Wilson & Associates 1999, Hadgraft 1999).
- To establish representative levels of hemp oil in cosmetics, relevant manufacturers in North America and the U.K. were contacted. Results were compared to those from a survey by Health Canada. Application rates for cosmetics used by Health Canada were reviewed and modified based on vendor information, literature, and personal experience.
- Transdermal uptake factors for THC were estimated based on the compound's physicochemical characteristics and extrapolation from the properties of other more extensively studied compounds.
- Based on the obtained range of THC application rates and estimated uptake factors, transdermal THC uptake was estimated for two scenarios, including a "high-exposure" and a "worst-case" scenario.
- The obtained THC uptake rates were compared to the previous study on hemp food products. Anticipated urine levels of THC-metabolites from cosmetics use were compared to "cutoff" levels commonly used in the U.S. to assess recent use of marijuana.
- Recommendations for future research and regulatory action were developed.

1.4 How to use this report

The reader who is primarily interested in the results of this study's exposure models and the relevance of our findings to the use of hemp oil cosmetics may skip to Sections 4.7–5. The various assumptions underlying these exposure models are detailed in Sections 4.1–4.6. Sections 2 and 3 provide introductory background information on the transdermal uptake of xenobiotics in general (Section 2) and THC in particular (Section 3) to readers unfamiliar with the subject.

2. PRINCIPLES OF TRANSDERMAL UPTAKE, METABOLISM, AND EXCRETION OF XENOBIOTICS

This chapter provides an overview of the mechanisms of transdermal uptake for xenobiotics (*i.e.* substances and pathogens) such as THC.

2.1 Structure of skin and transdermal absorption pathways

The healthy human skin is designed to present a robust barrier to the absorption of xenobiotics. Even so, it is well established that the human skin can absorb xenobiotics from topically applied products such as cosmetics or dermal patches. The extent of their uptake varies widely with the physico-chemical properties of the xenobiotic, the formulation and application of a product, and with skin conditions.

The process of transdermal absorption, *i.e.* the intake of compounds by an organism through its skin includes several phases: first, the compound is released from its formulation at the skin surface. This is followed by *penetration* of the compound into the outer layer of the skin, by *permeation*, *i.e.* the diffusion from one layer to another, and finally, the *resorption* through the vascular system[6] into the blood stream (Schaefer & Redelmeier 1996). Systemic distribution of the compound throughout the body is followed by its metabolism and excretion.

Figure 2.1 shows a schematic of the human skin. The main barrier to penetration of the skin for chemicals and pathogens alike is the stratum corneum, *i.e.* the superficial, horny layer of dead and dying cells covering the viable epidermis. Penetration through the stratum corneum layer can occur by *intercellular* uptake, *i.e.* transport of chemicals through the lipid[7] matrix *between* the cells, or by *transcellular* uptake, *i.e.* uptake directly *through* the cells. The intercellular lipid matrix holds the cells of the stratum corneum together like mortar provides structural stability

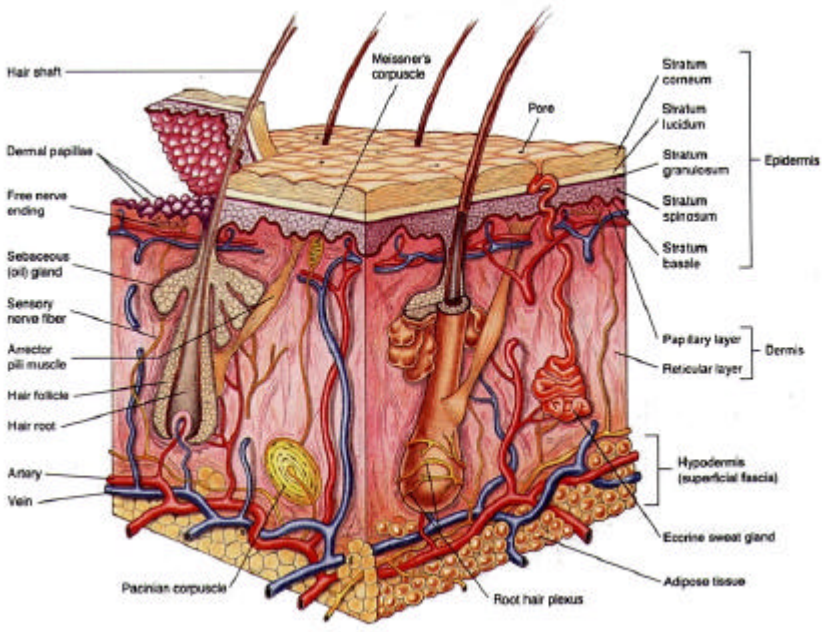


Figure 2.1 Schematic of human skin

[6] System of blood vessels.

[7] Lipids are "fat-like" compounds. A common characteristic of most groups of lipids is their high content of fatty acids. Fats and oils, which consist almost entirely of fatty acids, are the most relevant and well-known lipids.

to a brick wall. It forms the only continuous domain in the stratum corneum, and thus is of particularly importance as a penetration pathway. There is substantial evidence that the lipid matrix provides the major route for absorption through the stratum corneum into the underlying viable layers of the epidermis, particularly of lipophilic xenobiotics. In contrast, transcellular absorption of compounds follows a circuitous, complicated pathway alternating between absorption across the stratum corneum cells and crossing the lipid layers between them. It represents a less important pathway than the lipid matrix. Hair follicles or sebaceous[8] and perspiratory glands cover only a very small surface area of the entire skin. They are thought to present a relevant route of absorption only for small polar molecules. The resulting absolute rates of transfer appear to be small (Hadgraft 1996, Kalbitz *et al.* 1996, Berti & Lipski 1995, all in Grotenhermen *et al.* 1998; Schaefer & Redelmeier 1996). There is some evidence that hair follicles may also provide a viable route of transfer for larger compounds such as THC. For example, an *in vitro* study by Touitou *et al.* (1988) found by means of an autoradiograph that THC was concentrated around the shaft and epithelium of hair follicles in rat skin. The authors concluded that "*the main entry into the … skin is the pilosebaceous system*[9]". However, other sources suggest that these findings may have partially resulted from the inherent shortcomings of the applied autoradiograph technique (Schaefer & Redelmeier 1996) and that the transport via follicles will not significantly enhance THC transfer through the stratum corneum.

2.2 Dynamics of transdermal absorption

Transfer of any compound across the stratum corneum is driven by passive diffusion. It is proportional to the compound's concentration gradient between the formulation and the basal layer of the stratum corneum. The degree, to which uptake, storage in tissues, and systemic distribution occur, is largely determined by the physico-chemical characteristics of the compound, *e.g.*, its molecular size and diffusivity. Of particular importance is the compound's inclination to partition (or distribute) between adjacent aqueous and lipid compartments in tissues. Compounds, which are attracted to lipids, are called "lipophilic" (fat-liking). Large lipophilic compounds such as THC are also "hydrophobic" (adverse to water).

The degree to which xenobiotics partition between the aqueous and lipid compartments of the skin varies widely. It is quantified by a compound's equilibrium partitioning coefficient; most commonly used is the octanol /water partitioning coefficient K_{ow}. In general, the higher the K_{ow} and lipophilicity of a compound and the smaller the molecule, the faster the penetration of the stratum corneum[10]. The lipid matrix of the stratum corneum not only is the major pathway for lipophilic compounds, it also functions as a reservoir. To be released from the reservoir and

[8] Skin and hair glands, which secrete sebum, a semi-liquid, greasy substance.

[9] Includes hair shafts and associated sebaceous glands.

[10] The dimensionless partitioning coefficient (K_{ow}) is calculated from the equilibrium concentrations of a compound in a system with a solvent and an aqueous phase. As a rule, more lipophilic compounds have a higher K_{ow}. Because of the wide range of K_{ow} values (*e.g.*, 0.6 for acetone, 0.04 for water, 1–1,000 for many common organic compounds such as benzene, toluene, DDT, or atrazine, and more than >10,000 for highly lipophilic compounds, such as hexane) the logarithm (log K_{ow}) is often used. For THC, literature indicates K_{ow} values of 6,000–63,000,000 corresponding to a log K_{ow} of 3.8–7.8. This characterizes THC as a highly lipophilic compound.

to reach systemic circulation, the compound needs to permeate the layers of the viable epidermis underneath. Due to their aqueous nature, these layers effectively obstruct rapid resorption into the bloodstream, especially of highly lipophilic compounds. This explains why the permeability coefficient of a compound, a measure for the rate at which it moves through the entire skin, depends largely on its partitioning behavior, *i.e.* its K_{ow}, and to a lesser extent on its molecular weight (Potts *et al.* 1992 in Health Canada 1999; Guy & Potts 1992, Kastings *et al.* 1987, both in Schaefer & Redelmeier 1996).

2.3 Conditions affecting transdermal uptake of xenobiotics

Many topically applied cosmetics ingredients show low transdermal uptake factors[11] of only a few percent (Hadgraft 1999). Yet, the uptake of compounds via the skin can be influenced by the presence of other compounds in the formulation. Penetration *enhancers* may disrupt stratum corneum lipids, interact with intercellular proteins, or improve the partitioning of a compound. Enhancers include synthetic chemicals, surfactants, and certain unsaturated fatty acids, *e.g.*, oleic acid, a natural constituent of vegetable oils. Enhancement ratios vary from 1- to 2-fold for oleic acid to up to 200 for synthetic chemicals (Schaefer & Redelmeier 1996). The latter, *e.g.*, dimethylsulfoxide (DMSO) or Tween, temporarily destroy the functioning of the skin and are not used in cosmetics.

Some carrier materials, such as propylene glycol, one of the most widely used cosmetic ingredients, are known to act as solvents and have good permeation through the skin (Schaefer & Redelmeier 1996, Winter 1994). In cosmetics, if designed for penetration enhancement, the combined effect of the formulation containing any combination of such "enhancing" compounds influences absorption rates by no more than 10- to 20-fold (Schaefer & Redelmeier 1996).

For a given compound, actual transfer rates will also vary with anatomical location, skin conditions, and other parameters. *E.g.*, it is well established, that the skin on arms or legs has a 3–4 times higher barrier function than facial skin (Feldmann & Maibach 1974 in Schaefer & Redelmeier 1996). This implies that any extrapolation from results of absorption studies needs to consider the origin of the skin used. Moreover, if skin from different species, *e.g.*, mice, rats, or pigs, are used for studies, extrapolation is further complicated by interspecies variation.

There is also considerable variation in the rate of transdermal absorption of xenobiotics between (human) individuals, reportedly 35–48%, but also for the same individual from day to day and by site, reportedly up to 21% from day to day as measured by the transepidermal water loss (TEWL). TEWL is a convenient and oft-used parameter to characterize skin barrier function (Blichmann & Serup 1989 in Schaefer & Redelmeier 1996). Age, race, and gender appear to have only a minor influence on the relative skin barrier properties and thus on the transdermal absorption of xenobiotics in humans, with the exception of infants (Lotte *et al.* 1993, Guy & Maibach 1989, Roskos *et al.* 1989, Liron & Cohen 1984, all in Schaefer & Redelmeier 1996).

Studies have shown that the strongest skin-related enhancement of transdermal uptake may

[11] The transdermal uptake factor, or dermal absorption factor is defined as the ratio, measured under standardized conditions, of the amount of a xenobiotic entering the blood stream to the amount applied topically.

be caused by compromised skin, *e.g.*, chapped, irritated, injured, or sunburned skin, or skin with medical conditions such as ichthyosis, psoriasis, or atopic eczema. Such conditions may cause an up to 10-fold increased permeability (Schaefer & Redelmeier 1996, p. 201ff). Since hemp oil cosmetics are recommended for some of these skin conditions, the higher THC uptake through compromised skin must be considered in an exposure assessment.

It also is a well established fact that hydration of the skin, *i.e.* an increase in its moisture content, decreases the barrier function of the stratum corneum and increases the absorption of some compounds into the skin (about 3-fold at a 90% relative humidity (RH) compared to 60% RH) (Schaefer & Redelmeier 1996). Increased absorption is more effective for hydrophilic rather than lipophilic compounds such as THC (Hadgraft 2001). Thus, application of body oils or lotions on moist skin after showering is not expected to drastically increase the uptake of THC. The same is true for increased skin temperature, *e.g.*, after exercise, which has a similar effect as hydration, with increased absorption rates on the same order of magnitude (2- to 3-fold) (Schaefer & Redelmeier 1996).

In summary, Section 2 indicates that transfer of the lipophilic THC through the skin into the blood stream is slow and inefficient compared to other xenobiotics. Yet, compromised skin and the presence of transfer enhancers in a product formulation could cause higher uptake rates in some cases.

3. CHARACTERISTICS OF THC ABSORPTION AND METABOLISM

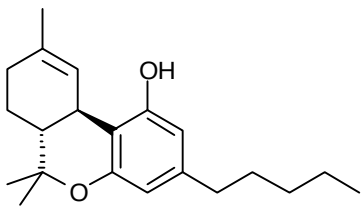
This chapter provides a summary of the physico-chemical characteristics of THC, its uptake via the skin, its metabolism and excretion, and a comparison to oral THC uptake.

3.1 Physico-chemical characteristics of THC

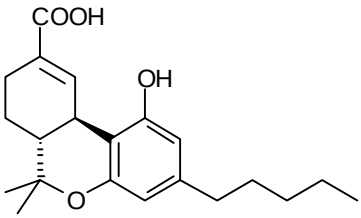
THC is a highly lipophilic compound with reported K_{ow} values ranging over four orders of magnitude from 6,000 to 63,000,000 (log K_{ow}=3.8–7.8) (Hadgraft 1999, Mechoulam 1981). THC's lipophilic nature is also reflected in its low water solubility; literature values range from 2.8 to 18 µg/mL (Hadgraft 1999, Touitou & Fabin 1988, Agurell *et al.* 1986, Garrett & Hunt 1974). Some literature values were measured, others were modeled using correlations (based on other experimentally determined parameters) or quantitative structure-activity relationships; all carry a rather wide margin of uncertainty. The wide range both for aqueous solubility and K_{ow} can be attributed to the difficulty of uniformly dissolving this essentially water-insoluble substance in a solvent and accurately measuring small amounts of it.

Figure 3.1 shows the chemical structure of THC and its major metabolite 11-nor-9-carboxy-delta-9-THC (THCCOOH).

As mentioned before, permeation of the stratum corneum is strongly influenced by a compound's hydrophobicity and, to a lesser extent, by molecular weight (Guy & Potts 1992, Flynn 1990, Kastings *et al.* 1987). Experimental studies involving chemicals of different lipophilicity in a variety of carrier substances showed that as the K_{ow} of lipophilic compounds, delivered in a lipophilic carrier increases beyond 2000, their permeability coefficients decrease rapidly (Bast 1987 in Grotenhermen *et al.* 1998, Schaefer & Redelmeier 1996). While the K_{ow} of THC has not been accurately determined, it can be assumed to be well above 2,000, thus categorizing THC as a compound with very poor permeation of the skin and uptake into the blood stream. The high molecular weight of THC further contributes to its slow transfer through the stratum corneum.



delta-9-Tetrahydrocannabinol (THC)



11-nor-9-carboxy-delta-9-Tetrahydrocannabinol (THCCOOH)

Figure 3.1 Chemical structure of THC and THCCOOH

3.2 Removal mechanisms for topically applied THC

THC is a photo-labile and easily oxidized substance (Touitou *et al.* 1988, Agurell *et al.* 1986); thus, some degradation of the applied THC will occur immediately after application of the body care product. Further, a large part of the skin is in contact with clothing and a portion of the applied body care products will adsorb to the fabric. Finally, washing, showering, or bathing, particularly when using soap, removes products and THC from the skin's surface or even the stratum corneum. These combined effects will cause a significant reduction of the applied THC dose available for absorption.

3.3 Impact of product formulation on THC uptake

As discussed on page 7, some natural constituents of plant oils *e.g.*, oleic acid (as a free fatty acid), are known to enhance transdermal uptake of lipophilic xenobiotics. In vegetable oils such as hemp oil, virtually all fatty acids are present as triglycerides and the *free* fatty acid (FFA) content even in unrefined hemp oil is generally less than 1%. However, significant hydrolysis of triglycerides is known to occur on the skin (Schaefer & Redelmeier 1996, p. 60) and the enhancing effect of free oleic acid cannot be discounted a priori. On the other hand, hemp oil also contains large amounts of the omega-6 PUFAs linoleic acid and GLA, which have been shown to improve the skin's barrier function (*e.g.*, Anstey *et al.* 1990). These PUFAs outweigh oleic acid by about 5:1 on a molecular basis (Leson & Pless 1999). Whether the transdermal uptake of THC will be enhanced or reduced by the FFAs present on the skin cannot be determined with certainty without experimental studies. Yet, information in the literature suggests that the net combined effect on the permeability of THC is likely not significant (Schaefer & Redelmeier 1996, p. 33).

Cosmetics formulations do generally not provide the conditions required for effective transdermal uptake of lipophilic compounds such as THC into the blood. These conditions include: high concentrations of the compound in the formulation to increase the concentration gradient across the skin, and the use of strong permeability enhancers. Such chemicals are only used for the express purpose of delivering chemicals transdermally into the bloodstream. For example, patches for transdermal uptake of THC as an anti-emeticum[12] have recently been patented (Brooke & Hermann 2000). The effective uptake from these patches relies critically on the use of strong skin permeation enhancers, *e.g.*, DMSO, Tween, or carbon tetrahloride. As previously mentioned, such compounds act by irreversible disruption of the stratum corneum; they are not used in body care products.

Transfer of moisturizing constituents in cosmetics into the stratum corneum is often enhanced by the use of "vehicles", such as propylene glycol. The literature suggests that, in conjunction with oleic acid these may also enhance permeability of the skin to other compounds (Schaefer & Redelmeier 1996). Propylene glycol or glycerine are used to enhance moisturization in some hemp oil creams and lotions. The use of alcohols in some formulations such as facial spritz or perfume may also slightly enhance THC absorption. However, for lipophilic compounds, such as THC the vehicle's impact on effective absorption and transfer into the blood stream appears to be limited. The authors assumed that their conservative choice of the

[12] Antiemetica are drugs used in the treatment of vertigo and dizziness, *e.g.*, for travel nausea, morning sickness, or in cancer chemotherapy.

transdermal uptake factor (see below) accounts for the potential effects of uptake enhancers.

3.4 Experimental studies on transdermal uptake of THC

In cosmetics, THC is contained in hemp oil and applied in either a lipophilic or a water based formulation to the skin. After release from the formulation and penetration of the stratum corneum, THC's lipophilic nature causes its efficient storage in the lipid matrix and poor permeation of the lower, more aqueous layers of the epidermis; both results in slow and inefficient absorption of THC into the vascular system. Uptake through hair follicles or sebaceous and perspiratory glands may also be a route of absorption for THC (Touitou *et al.* 1988).

The scientific literature provides little specific information relevant to the transdermal uptake of THC from topically applied hemp oil cosmetics. A literature database search (Grotenhermen 2001) and review of the Health Canada study (2001) produced only two relevant experimental studies of the transdermal uptake of THC (Touitou & Fabin 1988, Touitou *et al.* 1988).

Both studies were designed to develop an effective transdermal delivery system for THC to be used as an antiemeticum for treatment of the side effects of cancer chemotherapy. One study demonstrated the positive effect of several skin-permeation enhancing compounds (decylmethylsulfoxide, oleic acid and a water/ethanol solution) on transdermal uptake kinetics of THC on mouse skin *in vitro*. Water and oleic acid were both found to enhance skin permeability up to 10-fold, however their effects were not additive. The other study measured transdermal uptake of THC in both rat and human skin *in vitro*. Radiolabeled (H^3) delta-8-THC was formulated with and without 10% oleic acid. The formulations contained very high THC concentrations (26.5 mg THC/g formulation, compared to less than 1 µg THC/g typically found in hemp oil cosmetics). Permeability coefficients were determined from steady-state flux. The permeability coefficient K_p for human skin was determined at 1.3×10^{-4} cm/h, two orders of magnitude lower than the also lipophilic compound octanol (5.2×10^{-2} cm/h). Rat skin was found to be about 13 times more permeable than human skin, which corresponds well with the observed interspecies variation cited in the literature (Schaefer & Redelmeier 1996). The authors also estimated a lag time of 8.5 hours for human skin, i.e. the delay between topical application of the THC-containing formulation and a significant appearance of THC in the serum.

The study derived an estimated steady-state THC concentration C_{ss} in blood from a pre-viously published equation (Guy & Hadgraft 1985):

Equation 1 $$C_{ss} = A \cdot C \cdot K_p/(V_d \cdot K_e)$$[13],

where A is the area of skin application, C is the initial concentration of THC in the formulation, V_d is the volume of distribution, and K_e is the elimination constant. Assuming the topical application of a 26.5 mg THC/g formulation onto a 50 cm^2 patch and using the above derived K_p, a V_d of 734 L and a K_e of 2.0×10^{-2} h^{-1} from a previously published study (intravenous administration) in humans (Wall *et al.* 1984), the authors estimated a steady-state THC blood level of 12 ng/mL in humans. As the authors were cautious to point out, this "*is only a coarse estimation*" for several reasons that are discussed below. The authors did not attempt a mass balance to estimate the transdermal uptake factor for THC.

[13] Parentheses were missing in both Touitou et al. 1998 and Health Canada 2001 study; here corrected by authors.

3.5 Health Canada exposure assessment

Based on the study by Touitou *et al.* and the estimated steady-state concentration of THC in blood, Health Canada derived a theoretical conservative transdermal uptake factor for THC (in their report termed "bioavailability factor") of 33% over a 24-hour period (Health Canada 2001). This factor had previously been questioned by several reviewers of the study who noted that it appeared unrealistically high when compared to other lipophilic compounds and likely overestimated actual transfer rates (Adams, Wilson & Associates 1999, Hadgraft 1999). Hadgraft, an established expert in the field of transdermal uptake of xenobiotics, questioned the approach used to derive the 33% "bioavailability" factor and commented that he could not obtain the factor from the original study. Our analysis of the Health Canada approach found that the 33% factor was obtained through an improper mass balance and had no basis. In fact, the information and model provided by Touitou *et al.* do not allow for such a mass balance.[14] The same limitation applies to the lower bound estimate of 1% estimated in the Health Canada study.

Deriving a percent uptake factor from Touitou *et al.*'s data is further complicated by the following factors:

- Comparison of the results from an *in vitro* transdermal absorption study using animal skin to *in vivo* conditions is problematic for THC. While there are surprisingly few comparisons of *in vitro* and *in vivo* studies for humans, the ones that have been conducted indicate that results for hydrophobic compounds such as THC correlate less than those for hydrophilic compounds, especially, if different application conditions or formulations had been used (Scott 1987, Bronaugh & Stewart 1984, both in Schaefer & Redelmeier 1996).
- Touitou *et al.* used delta-8-THC, rather than the less stable, oxidation-prone delta-9-THC form that is found in hemp oil.
- The study used radiolabeled tracers rather than direct chemical analyses of THC. The radiolabel tritium (H^3) is easily quenched from and may diffuse through the skin more rapidly than its parent compound, thus causing overestimation of actual transfer rates (Schaefer & Redelmeier 1996).
- Finally, it is unlikely that the transfer of THC across skin follows first order kinetics with the same permeability coefficient K_p over a concentration range spanning 5 orders of magnitude (from 26.5 mg THC/g formulation in the Touitou *et al.* study to a typical concentration of less than 1 µg THC/g in cosmetics).

In summary, both studies by Touitou *et al.* were well designed and provide valuable information about the kinetic behavior of THC when applied topically in high concentrations with various penetration enhancers. However, they do not provide a basis for estimating transdermal uptake of THC from cosmetics with low THC concentrations. Specifically, the transdermal factors presented by Health Canada are without a basis. Thus, the authors opted to estimate uptake factors based on the characteristics of THC, product formulation, and skin conditions.

[14] Specifically, the Health Canada calculation had mistakenly assumed the THC concentration of 26.5 mg/g used by Touitou *et al.* to represent the *total amount* of THC applied (26.5 mg). They had then multiplied the steady state THC concentration in blood (12 ng/L) by the apparent volume of distribution (734 L). Dividing the obtained total amount of THC absorbed of 8.8 mg by the 26.5 mg applied, yielded their "bioavailability" factor of 33%.

3.6 Selection of a transdermal uptake factor

Hadgraft commented that several other compounds of similar or even lower lipophilicity—which generally enhances skin permeation—have a transdermal uptake factor of 3.3–4% of the amount applied (Hadgraft 1999, Hadgraft 1996). In the literature, recommended *conservative* transfer factors for transdermal exposure risk assessments range from 1 to 10% for easily penetrating compounds and a correspondingly lower percentage for poor penetrants through "normal" skin (Schaefer & Redelmeier 1996).

Based on the physico-chemical characteristics of THC[15] and the above referenced estimates by other researchers, the authors assumed a conservative transdermal uptake factor of 5% over a 24-hour period for THC applied in a lipophilic base to a healthy skin. This factor does not explicitly account for the removal of excess leave-on products or the degradation of THC once applied to the skin (see Section 3.2), which tend to reduce effective THC uptake. On the other hand, it also does not specifically incorporate the potential effect of skin hydration and mild penetration enhancers such as propylene glycol. Based on the discussions in Sections 2.3 and 3.3 these factors were deemed by the authors not to significantly increase transdermal THC uptake from hemp oil cosmetics. Thus, the uptake factor of 5% was considered sufficiently conservative to cover their potential impacts.

As noted in Section 2.3, damaged areas of skin show a higher permeability to xenobiotics, yet typically cover only small areas. Since hemp oil cosmetics are often advertised for their beneficial use on skin conditions such as atopic eczema or psoriasis, their use on compromised skin must be considered. For the "worst-case" scenario, a 50% absorption factor (10-fold increase over healthy skin) was chosen as a conservatively high estimate for compromised skin. The latter was assumed to cover a quarter of the total body surface area, with healthy skin accounting for the remainder. If more of the skin area on body or face is compromised, *e.g.*, in medical conditions such as atopic eczema, burns, or abrasions, patients will likely use dermatological preparations rather than commercial skin care products. The effective whole-body transdermal uptake factor for the above scenario is 16.25%.

3.7 Resorption and metabolism of THC

The occurrence and level of THC metabolites in urine for drug testing purposes also depends critically on the systemic distribution of THC and the kinetics of its metabolism. Because of its lipophilic nature, transdermally absorbed THC non-specifically binds to almost any non-aqueous matrix, *e.g.*, tissue fat or serum proteins. Once in the bloodstream, it is transported bound to serum proteins and rapidly catabolized in the liver to acidic metabolites.[16] About 95% of the THC dose is metabolized, mostly to 11-nor-9-carboxy-delta-9-THC (THCCOOH), only about 5% is eliminated unmetabolized (Grotenhermen *et al.* 1998).[17] Independent of the route of administration, about two thirds of the metabolites are excreted with the feces, one third with the urine (Huestis 1999, Agurell *et al.* 1986). Thus, the authors assumed that equal oral and transdermal uptake rates will

[15] For a summary see Table 3.1.

[16] Metabolism of xenobiotics in the skin during transfer is generally not of quantitative importance (Schaefer & Redelmeier 1996).

[17] Most drug testing programs rely on the presence of the major non-psychoactive THC metabolite THCCOOH in urine as the indicator of prior marijuana consumption.

result in the same total excretion of THC metabolites via urine. However, because of the considerably slower transdermal uptake and storage in fatty compartments, occurrence of peak metabolite concentrations in urine will be delayed and peak levels will be lower compared to oral uptake (see Section 4.8).

Typical for a highly lipophilic compound, THC has a very high apparent volume of distribution (V_d)[18] of 4–14 L/kg body weight (Baselt 2000), which indicates that it is mostly localized in lipophilic storage sites. After slow release from these reservoirs, it is initially found in the peripheral circulation. Due to its slow absorption through the skin and its affinity to tissue fat, transdermal uptake results in a much longer lag time for the presence of any THC in the plasma (~8–9 hours) than oral uptake (~1 hour). Additionally, unlike oral uptake, transdermal uptake is not subject to the "first-pass effect". This effect refers to the immediate and extensive metabolism of compounds in the liver after absorption from the gastrointestinal tract, which accelerates the appearance of metabolites in the urine.

3.8 Summary of physico-chemical properties and metabolic characteristics of THC

Table 3.1 summarizes the above-described physico-chemical properties and metabolic characteristics of THC compiled from the literature.

The above semi-quantitative discussion suggests that the transdermal uptake of THC is, compared to its ingestion with food, both slow and inefficient. Only a fraction of topically applied THC will be available for absorption, enter the blood stream, be metabolized to THCCOOH, and ultimately be excreted via urine and feces. A transdermal uptake factor for THC of 5% by healthy skin appears to represent a conservative estimate. Compared to THC ingestion, the slower uptake of topically applied THC and the absence of the first-pass will also delay appearance of THC metabolites in urine and cause a broader excretion profile with a lower peak concentration of THCCOOH.

Table 3.1 Physico-chemical properties and metabolic characteristics of THC

Solubility in water	S	2.8–18 µg/L
Octanol-water partition coefficient	K_{OW} (log)	6,000–63,000,000 (3.8–7.8) highly lipophilic
Permeability coefficient	K_p	1.3×10^{-4} cm/h
Elimination coefficient (intravenous)	K_e	2×10^{-2}/h
Volume of distribution	V_D	4–14 L/kg body weight
Excretion of metabolite THCCOOH		1/3 urine, 2/3 feces

[18] The V_D is the volume of body fluids into which a compound is apparently distributed. It quantifies the distribution between the plasma water, the interstitial water, and the intracellular water and is calculated as the dose of a compound in mg divided by its concentration in plasma water in mg/L. The V_D does not necessarily correspond to the actual body water compartments and exceeds the actual volume of body fluids by far.

4. EXPOSURE ASSESSMENT FOR UPTAKE OF THC FROM HEMP OIL COSMETICS

4.1 Methodology

The following exposure assessment for THC uptake from hemp oil cosmetics was conducted in analogy to the approach taken by Health Canada (Health Canada 2001). This methodology is also consistent with that adopted by the U.S. Food and Drug Administration (FDA) for estimating chemical exposure from topical administration of cosmetics and drugs. The maximum daily THC uptake by an individual using a body care product containing hemp oil was estimated according to following equation:

Equation 2

Maximum daily THC uptake =

$$C_{hemp\ oil} \cdot C_{THC} \cdot Q_{product} \cdot N_{app} \cdot F_{transdermal} \cdot T_{contact}$$

where:

$C_{hemp\ oil}$	Concentration of hemp oil in product (g/g)
C_{THC}	Concentration of THC in hemp oil (ppm by weight or µg/g)
$Q_{product}$	Quantity of product applied = application rate (g)[19]
N_{app}	Number of applications per day = frequency (/day)
$F_{transdermal}$	Transdermal uptake factor (%/day)
$T_{contact}$	Contact time (duration of exposure) (days)

Equation (2) assumes that the amount of THC *available* for transdermal uptake is proportional to the amount of hemp oil present in a product, the oil's THC content, the quantity and frequency of application, the product's contact time with the skin, the transdermal uptake factor of THC, and the specific skin condition. The uptake is assumed to be cumulative, *i.e.* each uptake from each product was assumed to be additive to that from all other products. Both product application and THC uptake by the bloodstream were also assumed to be constant over time, *i.e.* in a steady state condition.[20]

To obtain a range of conservative potential daily THC uptake rates from the use of hemp oil cosmetics we evaluated a "high-exposure" and a "worst-case" scenario. These respective scenarios represent conservative and high-end, yet still conceivable choices for he transdermal uptake factor and THC content in hemp oil, respectively.

We made conservative assumptions even for the "high-exposure" scenario because, when assessing interference of hemp oil products with drug testing, one is not concerned with the response of occasional low-quantity users. Rather, one must evaluate whether individuals with uncommonly extensive, yet conceivable usage rates, or persons which may show a higher than normal response to THC uptake, could produce a positive test result.

The following sections discuss the selection criteria for each parameter entering equation (2).

[19] In case an application rate for a product had been reported in units of volume, a conversion factor of 1 g = 1 mL was used for all products.

[20] Because of the slow transdermal uptake and comparatively rapid metabolism of THC, this assumption, which allows the use of time-averaged product application rates for estimating THC uptake appears to be acceptable.

4.2 Hemp oil content in body care products

Hemp oil cosmetics available in North America include body lotions, hand creams, facial moisturizers, massage oils, bar and liquid soaps, hair shampoos and conditioners, lip balms, sunscreen lotions, and salves. Only few direct measurements of the THC content in final products have been conducted. The results were most often below the detection limit. One survey found between 1–5 ppm THC (Health Canada 2001). These low levels reflect the typically low hemp oil content in cosmetics (<10%) and the low THC levels in the oil (<10 ppm). In this present study, estimates of the THC levels in products were based on available information on the hemp oil content of each product and a representative range for the THC content in hemp oil.

To establish representative levels of hemp oil in cosmetics, we contacted several suppliers in North America and Europe (Rothenberg 2001, Bronner 2000, Wilkes 2000). Results were compared to those from a survey by Health Canada (Health Canada 2001). Levels of hemp oil varied significantly for products from different manufacturers (see Table 4.1). *Rinse-off products*, such as bar soaps, shampoos, conditioners, and liquid soaps contain between 1–10% by weight (w/w) of hemp oil, which is added to the soap base as a super-fatting agent. A hemp oil content in bar soap of 60% is technically possible if the oil is saponified, but will yield a very soft soap. While excessive softness is an undesirable characteristic for a commercial product, some manufacturers may choose to produce soap this way. Moisturizing (*leave-on*) products, including body lotion, facial creams, hand creams, and sunscreen typically have hemp oil contents of less than 10%, with a range of 2–10%. Formulations for massage oils, salves, and lip balms tend to use higher amounts of hemp oil with contents in a few cases of up to 75%. Some individuals reportedly use pure, food-grade hemp oil for massage. This practice will not be used widely. Hemp oil rapidly oxidizes on the skin and causes a distinct body odor. Excess hemp oil on the skin also permanently stains towels, bed sheets, or clothes if brought in contact shortly after application. Even if pure hemp oil is used, it will most likely not be left on for 24 hours but washed off after a while to prevent these problems, thus reducing effective contact time. The hemp oil content of various other specialty products (foot protector, dry oil spray, face spritz) is typically less than 10%.

Table 4.1 summarizes the range of hemp oil content found in those products, which we deemed likely to be used on a regular basis. Specialty products such as facial spritz or dry oil spray were not considered since they are used on an infrequent basis and in small quantities only.

Table 4.1: Ranges of hemp oil content found in body care products

Product	Hemp oil content (% w/w)
Rinse-off	
Bar soap	1–60%
Liquid soap	1–3%
Bath oil	10%
Shampoo	0.5–1%
Hair conditioner	1–5%
Leave-on	
Body lotion	4–10%
Facial moisturizer	4–10%
Hand cream	4–10%
Sun screen	2–10%
Massage oil	6–10% (100%)*
Lip balm	10–75%
Salve	10–75%

* Use of 100% food-grade hemp oil

For this exposure assessment, we consistently used the upper limit of the above ranges. This may cause a potentially significant overestimation of the actual THC application rates and

represents a conservative choice. Since our initial exposure calculation found the use of full-body massage oil to be the most significant contributor to total THC uptake (see Section 4.7), two subcases for massage oil use were examined for each exposure scenario. The first case assumes a realistic, yet conservative full-body use of massage oil with a 10% hemp oil content every other day. The second case assumes use of pure hemp oil for massages instead, according to the above conceivable, yet highly unlikely scenario.

4.3 THC content in hemp oil

In Canada, currently the major source of hemp oil for cosmetics to be sold in North America, the maximum permissible content of THC in hemp oil as defined in the Canadian *Industrial Hemp Regulations 1089* is set at 10 ppm (Health Canada 1998). The actual THC content in commercially available oil is typically lower than this limit and ranges from <3–5 ppm (Webster 2001, Crew 2000). Our exposure estimates assumed a THC content in hemp oil of 5 ppm for the "high-exposure scenario" and of 10 ppm for the "worst-case scenario".

4.4 Product application rates, frequency, and contact time

The *application rate*, *i.e.* the amount of product per use, is critical to the amount of THC available for transdermal uptake. Rates vary considerably among users of hemp oil cosmetics. The Health Canada study (Health Canada 2001) based its application rates on a summary of use data prepared for the Cosmetic, Toiletry, and Fragrance Association by Environ Corp. (1985) and an unpublished Health Canada survey from 1998 (both cited in Health Canada 2001). The cited values compared well to another literature source (Schaefer & Redelmeier 1996). To be conservative, this present study assumed the higher application rates also used by Health Canada, except for body lotion and liquid soap, which, based on personal experience, vendor information, and literature sources may be used in larger quantities (see below).

We also adopted Health Canada's assumptions on usage *frequency*, *i.e.* number of product applications per day or week. Again, in some cases we assumed higher frequency of use to account for more extensive use of hemp oil cosmetics in unlikely, yet conceivable cases. In particular, the use of full-body massage oil, which results in high exposure, was assumed every other day instead of once per week. We also assumed somewhat higher daily numbers of applications of liquid soap and lip balm.

The use of sunscreen was not considered separately because it can be assumed that an individual will use either facial moisturizer and body lotion *or* sunscreen. Since the amount of hemp oil in sunscreen is similar to that in facial moisturizer or body lotion these products were assumed to be interchangeable. The use of bath oil was also not considered since only a small amount of the total quantity of THC present in bathwater (15 µg) will be in contact with the skin; instead, a twice-daily exposure to liquid soap as body wash was included.

This selected exposure model also requires consideration of the *contact time* of each product, *i.e.* the duration of its presence on the skin. Typically, *leave-on* products are left on the skin for 16 hours during the day or 6–8 hours at night (Schaefer & Redelmeier 1996). The exposure time, $T_{contact}$, for all leave-on products was conservatively considered as 24 hours; the exposure was calculated as a cumulative dose for products

with multiple applications per day (even though a shower twice-daily will rinse off any residual moisturizer). *Rinse-off* products typically have a much shorter skin contact, typically less than 10 minutes (Schaefer & Redelmeier 1996); for these products we used contact times typically twice those assumed by Health Canada.

Table 4.2 summarizes the application rates, frequencies of use, and exposure time for hemp oil cosmetics considered in the exposure assessment.

4.5 Transdermal uptake factor of THC

As discussed previously, no experimentally determined transdermal uptake factor for THC was available (see pages 9 ff.). Thus, we based our estimate on the compound's known physico-chemical properties, comparison to the known uptake of other lipophilic compounds, and advice from experts.

For the "high-exposure" scenario, we assumed a conservative, but reasonable absorption factor of 5% for THC by a healthy skin. For partially damaged skin, the "worst-case" scenario, a 16.25% whole-body uptake factor was assumed (for the derivation see page 13).

4.6 Summary of assumptions

Both scenarios assumed the same conservatively high hemp oil contents and application rates for products. The latter imply the extensive and exclusive use of hemp oil cosmetics, not likely to be practiced even by enthusiasts of hemp oil cosmetics.

The scenarios differ only in two key assumptions. The "high-exposure" scenario reflects the more representative, yet still conservatively high choice of a 5% uptake factor and a THC content in hemp oil of 5 ppm, a level typical for most commercial hemp oils. The "worst-case" scenario assumes a higher uptake factor (16.25%), reflecting the decreased barrier function of compromised skin. It also assumes a higher THC content of 10 ppm, the maximum legally permissible content in hemp oil in Canada.

Table 4.2: Application rates of body care products and daily frequency of use

Product	Application rate $Q_{product}$ (quantity of product applied)	Frequency N_{app} (number of applications per day)	Contact time $T_{contact}$ (minutes) or (hours)	
Rinse-off				
Bar soap (hand)	2.6 g	3	3	0.05
Liquid soap (body)	5 ml	2*	6	0.10
Shampoo	16.4 g	1	6	0.10
Hair conditioner	12.4 g	1	6	0.10
Leave-on				
Body lotion	10 ml	1		24
Facial moisturizer	2 ml	2		24
Hand cream	2 ml	2		24
Massage oil	10 ml	every other day		24
Lip balm	0.015 g	5*		24
Salve	0.02 g	3		24

* Health Canada frequency assumptions: liquid soap (body) once/day; lip balm 3 times/day

Table 4.3: Key assumptions for two exposure scenarios

		High Exposure	Worst Case
Hemp oil content in product	$C_{hemp\ oil}$	Upper limit of values in Table 4.1	
THC content in hemp oil	C_{THC}	**5 ppm (µg/g)**	**10 ppm (µg/g)**
Application rates and frequency	$Q_{product}$ N_{app}	As listed in Table 4.2; assumes exclusive and extensive use of hemp oil cosmetics	
Transdermal uptake factor	$F_{transdermal}$	**5%**	**16.25%** 5% on normal skin (3/4), 50% on compromised skin (1/4)
Contact time	$T_{contact}$	24 hours for leave-on products; 3 minutes for bar soap and 6 minutes for all other rinse-off products	
Sub-cases for massage oil		a) Massage oil containing 10% hemp oil b) Pure hemp oil	

The assumptions for the two exposure scenarios, *i.e.* the "high-exposure" scenario and the "worst-case" scenario, are summarized in Table 4.3. In addition, each scenario evaluated two sub-cases reflecting the use of massage oil with 10% hemp oil and of pure hemp oil, respectively.

4.7 Results

Table 4.4 summarizes the estimated cumulative daily THC uptake of an individual who uses hemp oil cosmetics in the amounts according to the scenarios summarized in Table 4.3. The results of using 100% hemp oil for massage are included in parentheses for both scenarios.

The table shows the following major results:

- Typical daily THC uptake, even from the extensive application of commercially available hemp oil cosmetics to healthy skin is less than 1 µg. The highly unlikely worst-case conditions—full-body use of pure hemp oil with a 10 ppm THC content on a partially compromised skin—could conceivably raise THC uptake to 11 µg/day. Typical uptake by more casual users of hemp oil cosmetics will be considerably below 1 µg/day.
- The largest contributions to THC uptake result from full-body products, *i.e.* body lotion and massage oil. If pure hemp oil is used for massages, it contributes by far the majority to THC uptake (>70%). When a 10% hemp oil content in massage or body oil is assumed, body lotion, hand and facial creams, and massage oil have similar contributions to total THC uptake.
- Because of the short contact time, rinse-off products contribute only insignificantly to total THC uptake.
- Inadvertent (and complete) ingestion of applied lip balm (5 times at 0.015 g/ application = 0.075 g) results in less than 1 µg THC/day even under worst-case assumptions, lower than the contribution from the use of massage oil or body lotion.

Table 4.4 Maximum THC uptake from hemp oil cosmetics for two scenarios

	$C_{hemp\ oil}$	$Q_{product}$	N_{app}	$T_{contact}$	Daily THC Uptake	
	(%)	(g)	(/24 h)	(h)	**High Exposure** (µg/day) $F_{transdermal}$ = 5% C_{THC} = 5 ppm	**Worst Case** (µg/day) $F_{transdermal}$ = 16.25% C_{THC} = 10 ppm
Rinse-off						
Bar soap (hand)	60%	2.6	3	0.05	<0.01	0.02
Liquid soap (body)	3%	5	2	0.10	<0.01	<0.01
Hair conditioner	5%	12.4	1	0.10	<0.01	<0.01
Shampoo	1%	16.4	1	0.10	<0.01	<0.01
Leave-on						
Body lotion	10%	10	1	24	0.25	1.63
Facial moisturizer	10%	2	2	24	0.10	0.65
Hand protector	10%	2	2	24	0.10	0.65
Lip balm	75%	0.015	5	24	0.01*	0.09*
Salve	75%	0.02	3	24	0.01	0.07
Massage oil	10% (100%)	10	0.5	24	0.13 (1.25)	0.81 (8.13)
Cumulative daily transdermal THC uptake (µg/day)					**0.60 (1.73)**	**3.92 (11.24)**

* In case of inadvertent ingestion of lip balm, a maximum uptake of 0.28 µg THC/day and 0.56 µg THC/day result for the two scenarios, respectively.

4.8 Discussion

THC uptake from cosmetics vs. foods

The above referenced hemp foods/drug testing study by Leson *et al.* (2001) demonstrated that daily ingestion of THC doses of up to 450 µg are unlikely to cause positive screening tests for marijuana at the currently employed cutoff of 50 ppb THC metabolites in urine. Confirmation testing by GC/MS according to U.S. federal guidelines is even less likely to produce "confirmed positives" at the 15 ppb level.

Oral availability of administered THC is almost 100% (Health Canada 1999, Wall *et al.* 1983). In comparison, uptake of 450 µg THC from topical use of hemp oil cosmetics would require an entirely unrealistic topical application rate. Even under the "worst-case" scenario, an application of more than 2,700 µg THC/day would be required[21]. This corresponds to more than *fifty* full-body applications of pure hemp oil each day. Instead, the above exposure models show that even under the "worst-case" scenario conditions—which consider individuals with compromised skin, high product application rates, and the maximum permissible THC content in hemp oil of 10 ppm—the resulting daily THC uptake is significantly below 20 µg. For the more realistic "high-exposure" scenario with a conservative uptake factor of 5% and the use massage oil containing 10% hemp oil, transdermal uptake will be less than 1 µg THC/day if an individual uses all of the products in the fashion described above.

[21] Assuming a THC content in hemp oil of 10 ppm.

These low daily intake rates suggest that use of hemp oil cosmetics alone cannot, with a wide margin of safety, cause sufficient THC uptake to cause a positive screening or a confirmed positive test for marijuana.

Excretion profiles from oral and transdermal uptake

Furthermore, because of the much slower transdermal uptake of THC, urine excretion patterns of THC metabolites are distinctly different from those for THC ingested via hemp foods. Touitou *et al.* estimated a lag time for transdermal THC uptake of 8.5 hours, compared to less than one hour for ingestion (Wall *et al.* 1983). Thus, while hemp food ingestion results in drastic increases in THCCOOH levels in urine, typically 4–8 hours after ingestion, the concentration profile caused by transdermal uptake will be much broader with less pronounced peaks. This further reduces the likelihood of a positive test results from transdermal THC uptake.

Can hemp oil cosmetics tip the balance?

It may be argued that THC uptake from hemp oil cosmetics could "tip the balance", *i.e.* critically affect the outcome of a urine test when a person consumes both hemp foods and hemp oil cosmetics. While this is possible in theory, it would require that a person testing positive routinely consumes large quantities of hemp food products. The additional contribution to THC uptake from hemp oil cosmetics of typically less than 2% can be considered insignificant. Our involvement in recent court cases where hemp oil products were implicated as the cause of a positive drug test also suggests that defendants claiming hemp seed products as the cause of a positive test, increasingly have to document their purchases of such quantities. In such cases, the legitimacy of their claim would be judged entirely on their demonstrable intake of hemp foods since interpersonal variations in urine metabolite levels, caused by the same THC intake, by far exceed the incremental contribution from hemp oil cosmetics.

Alternative explanations of positive drug tests

At least one person has suggested that his positive urine test was caused by external contamination of the urine sampling jar with residues from previous use of hemp oil soap (Bronner 2000, Dorazio 2000). This explanation is implausible for two reasons:

- Hemp oil cosmetics contain the unmetabolized form of THC and other cannabinoids, while urine tests, particularly confirmation by GC/MS, detect their metabolites. In some immunoassays, the inadvertent transfer of unmetabolized THC into a urine sample causes a low specific response. However, THC does not contribute to the levels of the main metabolite THCCOOH measured by GC/MS, and used to assess prior marijuana use.
- A simple mass balance indicates that even the total amount of THC present in a single application of most products is insufficient to account for the quantity of THCCOOH present in a confirmed positive sample. This applies even when assuming complete non-metabolic conversion of THC and its subsequent wash-off into a urine sample. Obviously, this represents an impossible scenario. For example, a single full-body wash with liquid soap contains 0.75 µg of THC (5 ml, 3% hemp oil, 5 ppm THC, see Table 4.4). In comparison, a confirmed positive urine sample (100 ml, 15 ng/ml THCCOOH) contains 1.5 µg of THCCOOH.

The THC content in other cosmetics applications, *e.g.*, the full-body use of massage oil, may

be higher. Yet, the lack of a plausible conversion mechanism to THCCOOH and the small fraction of product and consequently THC that could conceivably enter a sample jar refute this explanation.

Transdermal uptake and psychoactivity

Transdermal THC uptake is also not likely to cause or contribute to psychoactivity or other undesirable health effects. Uptake rates estimated under the "worst-case" scenario (~11 µg/day) are far below the maximum daily intakes for THC via hemp food of about 120 µg/day, recently recommended by the German Federal Government (BgVV 2000). These limits were derived to provide a wide margin of safety from psychoactive effects.

5. CONCLUSIONS AND RECOMMENDATIONS

The results of our exposure and uptake assessment for THC from hemp oil cosmetics strongly suggest that even unrealistically extensive use of such products cannot result in positive screening or confirmed urine tests for marijuana. Under highly conservative assumptions, daily THC uptake rates from cosmetics use would be no more than 1–2% of the minimum amount required to produce a positive screening test.

Thus, the authors do not deem any specific action necessary, such as limiting hemp oil content in product formulation to further reduce the exposure to or uptake of THC from hemp oil cosmetics. Rather, the acceptable THC limits for hemp oil will have to be determined by considerations relative to the protection of consumers from undesirable health impacts of THC ingestion via hemp foods and its potential impact on the outcome of workplace drug tests. As discussed previously (Leson *et al.* 2001), limiting THC levels in hemp oil to 5 µg/g (ppm) appears to provide a sufficient margin of safety in both areas. It will also systematically keep THC uptake from hemp oil cosmetics at the lower end of the range estimated in this study.

In our opinion, the low estimated THC uptake from hemp oil cosmetics also does not necessitate an experimental study of the correlation between topical application of THC and THC metabolite levels in urine for the sole purpose of confirming the lack of any significant impact on drug testing. However, if properly designed, such a study would provide useful information on the kinetics of THC uptake under conditions reflective of cosmetics use. Particularly, it would help identify whether the formulation of products, *e.g.,* presence of vehicles, such propylene glycol, may effect a significant increase in uptake. If such a study was to be conducted, conservatively high application rates of hemp oil with a THC content higher than now commonly found, applied to a large portion of the skin, would be required to produce measurable THC metabolite levels in urine.

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REFERENCES

Adams, Wilson & Associates Ltd. Comments on the Document 'Tetrahydrocannabinol and Other Cannabinoids in Foods, Cosmetics and Nutraceuticals – A Risk Assessment' Draft of 9 September 1999, prepared for Dr. Hugh Davis, Product Safety Bureau, Health Canada. Derngate, Northampton, UK, October 5, 1999.

Agurell S, Halldin M, Lindgren J-E, Ohlsson A, Widman M, Gillespie H, Hollister L. Pharmacokinetics and metabolism of delta[1]-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev* **38** (1): 21–43, 1986.

Alt A, Reinhardt G. Positive cannabis results in urine and blood samples after ingestion of hemp food products. Letter to the editor. *J Anal Toxicol* **22:** 80–81, 1998.

Anstey A, Quigley M, Wilkinson JD. Topical evening primrose oil as treatment for atopic eczema. *J Dermatol Treat* **1**: 199–201, 1990.

Baselt RC. *Disposition of Toxic Drugs and Chemicals in Man.* 5th Ed. Chemical Toxicology Institute, Foster City, CA, p. 812, 2000.

Bast GE. Influence of solubility and permanent size on absorption and metabolism of xenobiotics in rabbit skin. *Hum Exp Toxicol* **16**: 435–440, 1997.

Berti JJ, Lipsky JJ. Transcutaneous drug delivery: A practical review. *Mayo Clin Proc* **70**: 581–586, 1995.

BgVV (German Federal Institute for Consumer Health Protection and Veterinary Medicine). Press Release BgVV, March 16, 2000. www.bgvv.de/presse/2000/pr_00_07.htm.

Blichmann CW, Serup J. Reproducibility and variability of transdermal water loss measurements. *Acta Dermato-Venereol* **67**: 206–210, 1989.

Bócsa I, Karus M. The Cultivation of Hemp – Botany, Varieties, Cultivation and Harvesting. Hemptech, Sebastopol, CA, 1998.

Bronaugh RL, Stewart RF. Methods for in vitro percutaneous absorption studies. III. Hydrophobic compounds. *J Pharm Sci* **73**: 1255–1258, 1984.

Bronner D. Personal communication, David Bronner, President, Dr. Bronner's Magic Soaps, Escondido, CA, 2000.

Brooke LL, Hermann, CL. Cannabinoid patch and method for cannabis transdermal delivery. *U.S. Patent 6,113,940*, September 5, 2000.

Cole K. Personal communication, Ken Cole, Division of Forensic Toxicology, Armed Forces Institute of Pathology, Rockville, MD, 2000.

Costantino A, Schwartz RH, Kaplan P. Hemp oil ingestion causes positive urine tests for delta[9]-tetrahydrocannabinol carboxylic acid. *J Anal Toxicol* **21:** 482–485, 1997.

Crew S. Laboratory analysis of THC content in industrial hemp seed. Report prepared for Manitoba Rural Adaptation Council Inc, Winnipeg, MB, Canada, March, 2000.

Dorazio D. Personal communication, Lieutenant Derek Dorazio, U.S. Coast Guard, Houston, TX, 2000.

ElSohly MA, Ross S, Mehmedic Z, Arafat R, Bao Y, Bananhan B. Delta-9-THC and other cannabinoids content of confiscated marijuana: potency trends, 1980–1997. In: *1998 Symposium on the Cannabinoids.* International Canabinoid Research Society, Burlington, VT, p. 67, 1998.

Feldmann RJ, Maibach HI. Systemic absorption of pesticides through the skin of man. In: Occupational Exposure to Pesticides: Report to the Federal Working Group on Pest Management from the Task Group on Occupational Exposure of Pesticides. Appendix B, pp. 120–127, 1974.

Flynn GL. Physiochemical determinants of skin absorption. In: Gerrity TR, Henry CJ (eds.). *Principles of Route-to-Route Extrapolation for Risk Assessment.* New York, Elsevier, pp. 93–127, 1990.

Fortner N, Fogerson R, Lindman D, Iversen T, Armbruster D. Marijuana-positive urine test results from consumption of hemp seeds in food products. *J Anal Toxicol* **21:** 476–481, 1997.

Garrett ER, Hunt CA. Physicochemical properties, solubility, and protein binding of delta^{9}-THC. *J Pharm Sci* 1974, **63**: 1056–1064.

Grotenhermen F. Personal communication about results of literature search. Dr. Franjo Grotenhermen, Cologne, Germany, January 2001, Grotenhermen@cs.com.

Grotenhermen F, Karus M, Lohmeyer D. *THC-Limits for Foods—A Scientific Study.* nova Institute, Hürth, Germany, July 1998.

Grotenhermen F, Huppertz R. *Hanf als Medizin: die Wiederentdeckung einer Heilpflanze*. Karl F. Haug Verlag, Heidelberg, Germany, pp. 54–55, 1997.

Guy R, Hadgraft J. Pharmacokinetic interpretation of the plasma levels of clonidine following transdermal delivery. *J Pharm Sci* **74**: 1016–1018, 1985.

Guy RH, Maibach HI. Calculation of body exposure from percutaneous absorption data. In: Bronaugh, R.L., Maibach, H.I. (eds): *Percutaneous Absorption: Mechanism—Methodology—Drug Delivery*. Marcel Dekker, Basel, Switzerland, pp. 391–396, 1989.

Guy RH, Potts RO. Structure-permeability relationships in percutaneous absorption. *J Pharm Sci* **81:** 603–604, 1992.

Hadgraft J. Personal communication. Professor Dr. Jonathan Hadgraft, NRI University of Greenwich, Chatham Maritime, UK, 2001.

Hadgraft J. Comments on a Health Canada Report on the Dermal Absorption of Delta-9-tetrahydronnabinol. Unpublished, 1999.

Hadgraft J. Recent developments in topical and transdermal delivery. *Eur J Drug Metab Pharmacokinet* **21:** 165–173, 1996.

Health Canada. Basic method for the determination of THC in hempseed oil. Bureau of Drug Surveillance, Therapeutic Products Directorate, Health Canada. *Industrial Hemp Technical Manual/Standard Operating Procedures for Sampling and Testing*. TPP-BDS-004/Revision No. 002, pp. 16–20, 1998.

Health Canada. *Cannabinoids in Cosmetics, Foods and Nutraceuticals: An Assessment of the Health Risks.* Unpublished report and personal communication, 2001. Inquiries: H.G. Davis, Head, Health Canada Cosmetics Program, (613) 946–6470, cosmetics@hc-sc.gc.ca.

Huestis M. Pharmacokinetics of THC inhaled and oral preparations. In: Nahas GG (ed.). *Marihuana and Medicine*. Humana Press Inc., Totowa, NJ, pp. 105–116, 1999.

Idson B. Dry skin: moisturizing and emolliency. *Cosmetics and Toiletries* **107** (7): 69–78, 1992.

Kalbitz J, Neubert R, Wohlrab W. Modulation der Wirkstoffpenetration in die Haut. *Pharmazie* **51**: 619–637, 1996.

Kastings GB, Smith RL, Cooper ER. Effect of lipid solubility and molecular size on percutaeous absorption. In: Shroot B, Schaefer H (eds.): *Skin Pharmacokinetics.* Vol. 1. Karger, Basel, Switzerland, pp. 138–153, 1987.

Law Enforcement News. Watch what you eat: NYPD tries to clear up drug-test loopholes. *Law Enforcement News*, John Jay College of Criminal Justice, New York, NY, **25** (517), September 15, 1999, http://www.lib.jjay.cuny.edu/len/1999/09.15

Lehmann T, Sager F, Brenneisen R. Excretion of cannabinoids in urine after ingestion of cannabis seed oil. *J Anal Toxicol* **21:** 373–375, 1997.

Leson G, Pless P, Grotenhermen F, Kalant H, ElSohly M. Food products from hemp seeds: could their consumption interfere with workplace drug testing*? J Anal Toxicol*, accepted for publication in November 2000, to be published in 2001.

Leson G, Pless P. *Hemp Foods and Oils for Health.* 2nd Ed., Hemptech, Sebastopol, CA, p. 17, 1999.

Liron Z, Cohen S. Percutaneous absorption of alkanoic acids. I. A study of operational conditions. *J Pharm Sci* **75**: 534, 1984.

Lotte C, Wester RC, Rougier A, Maibach HI. Racial differences in the in vivo percutaneous penetration of some organic compounds in man: A comparison between black, Caucasian and Asian subjects. *Arch Dermatol Res* **284:** 459– 465, 1993.

McCaffrey B. Letter by Barry McCaffrey, Director of Office of National Drug Control Policy, to Representative Patsy Mink, July 10, 2000.

Mechoulam R. Chemistry of cannabis. *Handbook Exp Pharmacol* **55**: 119–134, 1981.

Potts R, Bommannan D, Guy RH. Percutaneous absorption. In: Mukhtar H (ed.). *Pharmacology of the Skin*. CRC Press, Boca Raton, FL, p. 13–27, 1992.

Rothenberg, E. Personal communication, Erik Rothenberg, President, Atlas Corporation, Culver City, CA, 2001.

Roskos KV, Maibach HI, Guy RH. The effect of aging on percutaneous absorption in man. *J Dermatol* **16**: 475–479, 1989.

Roulac J. Personal communication, John Roulac, President, Nutiva, Sebastopol, CA, 2000.

Schaefer H, Redelmeier T. *Skin Barrier – Principles of Percutaneous Absorption.* Karger, Basel, Switzerland, 1996.

Scott RC. Percutaneous absorption in vivo: in vitro comparisons. In: Shroot B, Schaefer H (eds.): *Skin Pharmacokinetics.* Vol. 1. Karger, Basel, Switzerland, pp. 103–110, 1987.

Struempler RE, Nelson G, Urry FM. A positive cannabinoids workplace drug test following the ingestion of commercially available hemp seed oil. *J Anal Toxicol* **21:** 283–285, 1997.

Touitou E, Fabin B, Dany S, Almog S. Transdermal delivery of tetrahydrocannabinol. *Int J Pharm* **43**: 9–15, 1988.

Touitou E, Fabin B. Altered skin permeation of a highly lipophilic molecule: tetrahydrocannabinol. *Int J Pharm*, **43**: 17–22, 1988.

U.S. Federal Register. Use of marijuana for industrial purposes. *U.S. Federal Register* **65** (231), November 30, 2000.

Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin Pharmacol Ther* **34** (3): 352–363, 1983.

Webster B. Personal communication, Dr. Barrie Webster, President, Websar Laboratories Inc., Ste. Anne, Manitoba, Canada, 2001

Wilkes P. Personal communication, Dr. Paul Wilkes, Head of Regulatory Affairs, The Body Shop, Littlehampton, U.K, 2000.

Winter R. *Consumer's Dictionary of Cosmetic Ingredients.* Three Rivers Press, New York, NY, 1994.

Wright S, Burton JL. Oral evening-primrose-seed oil improves atopic eczema. *Lancet* **2** (8308): 1120–1122, 1982.