

## **NHPD AND MHPD ISSUE ANALYSIS SUMMARY**

### ***Salvia divinorum* Regulatory Authority and Health Risks**

**Prepared by:** Jacinta Roberts and Robin Marles, NHPD, and Shahid Perwaiz, MHPD

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#### **ISSUES**

1. Which regulatory authority is most appropriate for *Salvia divinorum* under various conditions of use?
2. What are the risks to consumers of this substance?

#### **BACKGROUND AND ISSUE ANALYSIS**

##### ***Salvia divinorum* as a Health Product**

*Salvia divinorum* Epling & Játiva is an herb in the mint family (Lamiaceae), native to Mexico, that is smoked as a hallucinogen. As a substance it falls under Item 1 of Schedule 1 (inclusion list) to the *Natural Health Products Regulations*, which includes: "a plant or plant material, an alga, a bacterium, a fungus or a non-human animal material."

The main active ingredient of *Salvia divinorum* is a neoclerodane diterpene compound called salvinorin A, which currently falls under Schedule 1, item 2: "an extract or isolate of a substance described in item 1, the primary molecular structure of which is identical to that which it had prior to its extraction or isolation."

In Canada neither the herb, *Salvia divinorum*, nor its active ingredients, such as salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* (CDSA), nor any Schedule of the *Food and Drugs Act* or its Regulations that would remove it from the purview of the *Natural Health Products Regulations*.

*Salvia divinorum* and its active constituents therefore meet the substance aspect of the regulatory definition of a natural health product.

Whether or not *Salvia divinorum* products meet the function aspect of the regulatory definition of a natural health product depends on the purpose for which the product is being manufactured, sold, or represented for use. According to Section 1(1) of the *Natural Health Products Regulations*, a natural health product means a substance that is manufactured, sold, or represented for use in:

- (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- (b) restoring or correcting organic functions in humans; or
- (c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

*Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/ constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1982).

With respect to potential modern uses, there is one human case study from Australia suggesting a possible antidepressant effect (Hanes 2001).

Since *Salvia divinorum* and salvinorin A under some conditions of use meet both the functional and substance portions of the definition of a natural health product and are not currently subject to any regulatory exclusions, if associated with a health claim finished products containing these substances could be considered to be natural health products (NHPs).

Until such time as the herb and its active constituent are scheduled under the CDSA or Schedule F to the *Food and Drug Regulations*, the NHPD has jurisdiction to receive a Product Licence Application for a therapeutic use. However, the safety assessment will be sufficiently rigorous to protect consumers' health, particularly with respect to the following safety factors:

- “Does the medicinal ingredient or product have a demonstrated potential for addiction, abuse or severe dependency that is likely to lead to harmful non-medicinal use?”
- “Does the medicinal ingredient or product have known adverse effects at the recommended or therapeutic dosage level?”
- “Does the medicinal ingredient or product have a therapeutic effect based on recently established pharmacological concepts, the consequences of which have not yet been fully established?”
- “Does the medicinal ingredient or product possess a high level of risk relative to expected benefits?”

The answers to these questions are as follows:

- Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in way that is quite different from other hallucinogens such as heroin or LSD.
- Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions.
- It is subject to abuse as a street drug.
- It acts on the brain in a way that is quite novel and for which the consequences have not yet been fully established.

For all those reasons, the risks of *Salvia divinorum* use compared to any expected benefits suggest that if it were to be regulated as a health product, it should require a prescription under the *Food and Drug Regulations*, rather than being regulated as an over-the-counter natural health product.

### ***Salvia divinorum as a Hallucinogen***

As with many other NHP substances, there are other uses for the herb that may in future be more appropriately regulated under a different framework.

*Salvia divinorum* is used as a hallucinogen in traditional divination rituals (Valdés et al. 1982) and is being widely touted on internet sites aimed at young adults and adolescents as a "legal" alternative street drug.

The current use and advertising of *Salvia divinorum* as a recreational hallucinogen does not meet the intent of the function component of the *Natural Health Products Regulations*' definition of a natural health product. Nevertheless, even if it is being sold without labelled claims as leaf material in a plastic baggy, it is being represented for use in "modifying organic functions in humans" so from a compliance perspective *Salvia divinorum* falls under the jurisdiction of the *Food and Drugs Act*.

As a hallucinogen and drug of abuse, Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances will collect relevant information specific to this herb and its active constituents.

### ***Salvia divinorum in Other Regulatory Jurisdictions***

In the U.S. Congress, *Salvia divinorum* was the subject of a bill (H.R.5607) entitled "To amend the Controlled Substances Act to place Salvinorin A in Schedule I" introduced on October 10, 2002, seeking to place the herb and its active constituent salvinorin A onto U.S. Controlled Substances Act Schedule 1 (drugs or other substances with a high potential for abuse, with no currently accepted medical use in treatment in the United States, and with respect to which there is a lack of accepted safety for use under medical supervision). Since November 11, 2002, the bill has been referred to the Subcommittee on Crime, Terrorism, and Homeland Security (<http://thomas.loc.gov/cgi-bin/bdquery/z?d107:HR05607:@@L&summ2=m&>, accessed June 24, 2004). Currently, the FDA considers street drug alternatives such as *Salvia divinorum* to be unapproved new drugs and misbranded drugs under sections 505 and 502 of the Act (<http://www.fda.gov/cder/guidance/3602fnl.pdf>, accessed May 26, 2004) and has issued warning letters to a number of firms. Thus it appears that the U.S. has sufficient regulatory authority already to achieve the necessary level of control.

Both the herb and the active ingredient are listed on Schedule 9 of Australia's Standard for the Uniform Scheduling of Drugs and Poisons on the basis of "high potential for abuse and risk to public health and safety," but no substantiation of this risk was provided (<http://www.tga.health.gov.au/ndpsc/record/rr200111upd8.pdf>, accessed May 26, 2004). They are both also in Category B of the Danish list of controlled substances (<http://www.retsinfo.dk/delfin/html/b2003/0071405.htm>, accessed May 26, 2004).

### ***Scientific Details of the Potential of Salvia divinorum for Abuse***

*Salvia divinorum* is smoked to induce visual hallucinations, the diversity of which are described by its users to be similar to those induced by other hallucinogens such as

mescaline or psilocybin. Since neither *Salvia divinorum* nor any of its active ingredients are specifically listed in the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act* or its Regulations in Canada, some on-line botanical companies and drug promotional sites have advertised the herb as a legal alternative to other plant hallucinogens like mescaline. The objective of this section is to provide background on whether or not *Salvia divinorum* has the potential to induce dependence effects.

Salvinorin A (there are B and C forms) is a hallucinogen when vaporized and inhaled. Salvinorin A is a highly efficacious *kappa*-opioid receptor agonist of clinical interest for treatment and etiological studies of depression, dementia, bipolar disorder, and schizophrenia (Chavkin et al. 2004, Roth et al. 2002). Chemically, salvinorin A is a psychotropic diterpenoid.

Other plants with similar properties include *Cannabis sativa*, which contains the phenolic active principle, tetrahydrocannabinol (THC), and *Artemisia absinthium*, also known as wormwood and used to make the liqueur asbinthe, which contains the monoterpenoid active principle, thujone.

A dose of 200 to 500 micrograms of salvinorin A produces profound hallucinations when smoked. Its effects in the open field test in mice and locomotor activity tests in rats are similar to those of mescaline. A large body of evidence links the action of hallucinogenic agents (LSD, mescaline) to effects at serotonin (5-HT) receptor sites in the central nervous system (Aghajanian and Marek 1999). Salvinorin A's actions in the brain are not well elucidated. However, recent tissue testing (in vitro assays) have suggested that salvinorin A acts at the kappa opiate receptor site (Chavkin et al. 2004; Valdes 1994; Roth et al. 2002). Effects associated with kappa opioid receptor activation include analgesia, sedation, and dysphoria (Barker et al. 2002). Using in vitro methods, Margolis et al. (2003) have found evidence that the mechanism of action of kappa opiate receptor agonists may involve direct inhibition of midbrain (ventral tegmental area) dopaminergic neurons that play a critical role in motivation and reinforcement of goal-directed behaviours, and have also been implicated in the addictive process initiated by drugs such as morphine.

Drug dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal; it can be of two types, physical and/or psychological dependence. The existence of three major groups of opioid receptors (mu, delta and kappa) in the central nervous system is well documented (Suzuki and Misawa 1997). There are complicated interactions among opioid receptor types. The activation of the kappa opioid receptor suppresses physical and psychological dependence on mu and delta opioid receptor agonists, but the activation of the delta opioid receptor potentiates the dependence on mu opioid receptor agonists. Various studies provide arguments to support substantial roles for mu-opioid receptors and the possible involvement of delta-opioid receptors in the development of physical and psychological dependence on morphine (Narita et al. 2001; Suzuki and Misawa 1997).

Most of the drugs used clinically that are mu-opioid analgesics are habit-forming. While both receptor types (delta and mu) provide analgesia, only the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dexamethorpan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor (Gaveriaux-Ruff and Kieffer 2002; Narita et al. 2001; Pasternak 2003; Suzuki and Misawa 1997). From behavioural, biochemical and molecular biological studies, it is suggested so far that development of physical dependence on morphine results predominantly from an activation of mu 1 and mu 2 opioid receptors which cause functional changes in Gi/o, adenylate cyclase, protein kinases A and C, beta-adrenoceptor and NMDA receptor in the locus coeruleus. However, activation of the mesolimbic dopamine system may lead to psychological dependence on opioids (Narita et al. 2001; Suzuki and Misawa 1997).

It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect, i.e. dysphoria rather than euphoria (Kumor et al. 1986; Rothman et al. 2000). Recently, there have been significant advances in studies on the role of kappa opioid receptor agonists in producing an aversive effect of other stimulants such as morphine, cocaine, THC, alcohol, and in other non-opioid addictions (Cui et al. 2000; Hahn et al. 2000; Collins et al. 2001; Mori et al. 2002; Raffa et al. 2003; Rosin et al. 1999; Rothman et al. 2000; Schenk et al. 1999; Tao et al. 1994). The activation of kappa-receptors also leads to the suppression of unpleasant mu/delta-mediated side effects such as dependence and respiratory depression. Considering the functional interaction between opioid receptor types, the co-administration of morphine-like compounds with kappa-receptor agonists may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

Salvinorin A is unique in that it is a potent, non-nitrogenous, selective kappa opioid agonist distinct in its actions from other known opioid agonists. Therefore, it appears to be devoid of the mainly mu receptor-mediated side effects such as dependence and respiratory depression associated with morphine and its other analogues. It may thus be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, depression, and even excessive marijuana use. Being defined by its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

In conclusion, on the basis of available scientific literature, the potential addiction or dependence effects of *Salvia divinorum* are expected to remain very low because of the following:

- Most of the drugs which cause dependence and addiction are mu-opioid agonists, while salvinorin A acts as a full agonist at kappa opioid receptors and appears to possess no mu opioid receptor activity.

- Kappa opioid receptor agonists are characterized as being able to modulate dependence-related behavioural effects of drugs like morphine and cocaine rather than causing dependence.
- There have been no cases of dependence on *Salvia divinorum* or salvinorin A reported in the scientific literature.
- The precise mechanism of interaction between salvinorin A and the brain to produce its hallucinogenic effects remains unclear.
- The toxicity of salvinorin A is relatively low, even at doses many times greater than what humans are exposed to (Mowry et al., 2003).
- Many individuals have reported experiencing negative effects (bitter taste, unpredictable and occasionally disturbing short-term mental effects) during their first experience with *Salvia divinorum* and indicate that they would not use it a second time.

#### ***Canadian Reports of Adverse Reactions to Salvia divinorum Products***

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with products said to contain *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum* products. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of tablets said to contain *Salvia divinorum* and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

#### **PRESENT HEALTH CANADA ACTIONS:**

1. Adverse reactions to *Salvia divinorum* or salvinorin A reported through the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) and those reported in the United States and other jurisdictions are being monitored continuously, recognizing that it is unlikely that adverse reaction reports for these substances will be adequately documented due to *Salvia divinorum*'s use primarily as an hallucinogen. Some information might also be available from Poison Control Centres but there is apparently no uniform means for communication between Poison Control Centres at this time.
2. Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances is collecting relevant information specific to this herb and its active constituents.
3. A Customs Lookout is already in place and should be continued to restrict importation.

4. *Salvia divinorum* and its active principles are being represented for use in modifying organic functions in humans and are therefore classified as health products that fall under the jurisdiction of the *Food and Drugs Act*. To protect the health of Canadians, they are subject to compliance actions by the Health Products and Food Branch Inspectorate in accordance with their Policy 0001.

**NEXT STEPS:**

1. If the information collected warrants further action, the Office of Controlled Substances will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedule of the *Controlled Drugs and Substances Act*. These criteria include:
  - international requirements and trends in control/scheduling;
  - chemical and pharmacological similarity to other drugs listed in the CDSA;
  - dependence potential;
  - likelihood of abuse/misuse;
  - extent of abuse/misuse in Canada;
  - danger to public health and safety, and
  - legitimate use in Canada.
2. If *Salvia divinorum* is added to one of the Schedules to the *Controlled Drugs and Substances Act* it will become subject to compliance actions by the federal, provincial, and municipal police forces instead of the HPFB Inspectorate.

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## NHPD Internal Information Request Form

### Request Information

**Requestor Name:** Marie Morrisey                      **Directorate:** HPFBI / DGPSA

**Request Type:** Product Classification / Classification de produit

**Urgent?:** No / Non

**NHPD Submission #:** 100977                      **MECS #:** N/A

**Product Name:** N/A

**Ingredient Name:** Salvia divinorum

**Product Licence #:** N/A

**Company Name:** N/A

**Site Licence #:** N/A

**Subject:** Salvia divinorum

**Brief Description of Request or Concern:** Is Salvia divinorum an NHP?

**Attachment(s) or Supporting Documents:**

**Date Requested:** 2005-02-01 09:24 AM

**Designated Assignee:** Raymond W Tsang

### NHPD Acknowledgement and Response

**NHPSAS File #:**

**Comments/Resolution(s):** Salvia divinorum and salvinin A are NHPs presenting a risk for abuse and thus are subject to immediate compliance action by the HPFB Inspectorate.

**Supporting Document(s):**



**Status:** Salvia divinorum PC - 100977.w  
Completed / Complète

**Completed By :** Raymond W Tsang, 2005-02-04 12:41:22 PM

**Reviewed By :** Raymond W Tsang, 2005-02-04 12:41:23 PM

**Concurrence (if applicable)**

BGTD	Reviewed and Concurred by:	<u>Concur</u>
FD	Reviewed and Concurred by:	<u>Concur</u>
HPFBI	Reviewed and Concurred by:	<u>Concur</u>
Legal	Reviewed and Concurred by:	<u>Concur</u>
MHDP	Reviewed and Concurred by:	<u>Concur</u>
PMRA	Reviewed and Concurred by:	<u>Concur</u>
TPD	Reviewed and Concurred by:	<u>Concur</u>
VDD	Reviewed and Concurred by:	<u>Concur</u>

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Draft #6

October 17, 2006 (16:30 pm)

### **Media Response – CBC Sudbury’s questions on salvia divinorum**

#### **Q1. How is Health Canada monitoring the trend?**

A1. Health Canada is currently monitoring the trend of *Salvia divinorum* (Diviner’s Sage) use at the national and international level through ongoing scanning of media publications, published scientific articles, and public alerts issued by other regulatory authorities. Additionally, Health Canada staff continuously monitor adverse reaction reports submitted to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) for any reports that may involve *Salvia divinorum*.

#### **Q2. In what way is Health Canada assessing the potential for regulatory control of *Salvia divinorum*?**

A2. In December of 2005 Health Canada completed a review of the information currently available on the potential risks and benefits of *Salvia divinorum* use in humans. *Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico where it grows naturally, so a product with such health claims could meet the definition of a natural health product and therefore be subject to the *Food and Drugs Act* and the *Natural Health Products Regulations*. One of the advantages of these Regulations is the mandatory assessment of every product for its safety, effectiveness with regard to the claims on the label, and quality issues such as ensuring that it is the correct herb and that it is free of contamination by pesticides, toxic metals such as lead, bacteria and molds.

However, it is highly unlikely that a *Salvia divinorum* product would be licensed as a natural health product due to its safety issues. Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in way that is quite different from other hallucinogens such as heroin or LSD. Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions, it is subject to abuse as a street drug, and it acts on the brain in a way that is quite novel and for which the consequences have not yet been fully established. For all those reasons, the risks of *Salvia divinorum* use compared to any expected benefits suggest that if it were to be regulated as a health product, it should require a prescription under the *Food and Drug Regulations*, rather than being regulated as an over-the-counter natural health product.

While *Salvia divinorum* could be regulated as a health product, that is not how it is being used on Canadian streets. As a hallucinogen and drug of abuse, Health Canada’s Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances will collect relevant information specific to this herb and its active constituents. If the information collected warrants further action, the Office of Controlled Substances will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- international requirements and trends in control/scheduling;

- chemical and pharmacological similarity to other drugs listed in the CDSA;
- dependence potential;
- likelihood of abuse/misuse;
- extent of abuse/misuse in Canada;
- danger to public health and safety, and
- legitimate use in Canada.

**Q3. What would have to happen in order for Health Canada to decide to take action and include public risk communications or impose restrictions over its availability and use?**

A3. Health Canada is not aware at this time of any cases of dependency to *Salvia divinorum* having been reported, and has to date received few other sources of information suggesting there is a significant abuse problem or risk to public health or safety.

However, Health Canada will continue monitoring the trend of *Salvia divinorum* use at the national and international level. Should we receive sufficient information to suggest a significant abuse problem or risk to public health or safety, Health Canada will take appropriate action.

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Chris Turner, DG, MHPD (pending)

Julia Hill, DG, NHPD (pending)

Diana Dowthwaite, DG, Inspectorate (pending)

Carole Bouchard, Director, OCS, and A/DG, Drug Strategy and Controlled Substances Program (pending)

Kathleen Malone, A/Comm Exec, HECS-Comms (pending)

Ken Polk, Comm Exec, HPFB-Comms (pending)

Peter Yendall, A/Director, Public Affairs, PACRB (pending)

Legal Services (pending)

Neil Yeates, ADMO (pending)

## MHPD Risk Management (MHPD-RM)

### Issues Summary Report

[*Salvia divinorum* - a potential drug for abuse]

Date: December 16, 2005

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#### DIVISION:

- |  |   |
|--|---|
| <input type="checkbox"/> Marketed Biologicals & Biotechnology Products               | <input type="checkbox"/> Director General's Office              |
| <input type="checkbox"/> Marketed Health Products Safety & Effectiveness Information | <input type="checkbox"/> Marketed Pharmaceuticals               |
| <input type="checkbox"/> Marketed Medical Devices                                    | <input type="checkbox"/> Policy and Partnerships                |
| <input checked="" type="checkbox"/> Marketed Natural Health Products                 | <input type="checkbox"/> Therapeutic Effectiveness Surveillance |
- 

- Date of presentation at BEC-RM:
- Proposed date to present at BEC-RM:

#### Subject matter:

- Product's trade/generic names- *Salvia divinorum*
- Product class: Natural Health Products
- Main indication(s): used as a hallucinating agent
- Therapeutic class: Natural Health Products
- Status -  marketed  
X not marketed-authorized

#### Early Warning statement:

- *Salvia divinorum* is a plant from the mint family that has been used in traditional and spiritual practices by the Mazatec Indians of Oaxaca, Mexico to produce "mystical" or hallucinogenic experiences. Health Canada has received four reports of adverse reactions associated with the use of *Salvia divinorum*. In addition, there have been several reports (scientific articles, media enquiry/reports) which indicate that *Salvia divinorum* has a potential for abuse, and is being used by adolescents and young adults for its hallucinogenic properties. MHPD of Health Canada will share the issue summary report (ISR), summarizing all the information concerning the health risk associated with *Salvia divinorum* in Canada as well as recommendations for mitigating the risk with other directorates (NHPD, OCS, HPFBI) and will develop appropriate risk mitigation strategies, if deemed necessary.

#### Background provided by which Officer/Directorate:

- Shahid Perwaiz, MNHPD, MHPD

#### What is the issue?

- The Canadian Adverse Reaction Information System (CADRIS) has received four reports of adverse reactions (ARs) associated with the use of *Salvia divinorum* or its active constituents. All of these ARs involved psychotropic effects.

- A recently published article (Dennehy et al., 2005) has reported *Salvia divinorum* to be one of the most prevalent marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults.
- Recently, the media has shown interest in the issue of *Salvia divinorum*, specifically its presence on the market as a legal alternative to illicit drugs (<http://www.radio-canada.ca/radio/sansfrontieres/66659.shtml>).
- This information (case reports, media interest and publications) triggered MNHPD to review the safety of *Salvia divinorum*, and to provide recommendations to mitigate the potential risk of abuse associated with *Salvia divinorum* use.

### Why is this an issue?

- Salvinorin A is a constituent of *Salvia divinorum*, and is a powerful naturally-occurring non-nitrogenous hallucinogen that stimulates kappa-opioid receptors (KOR) (Chavkin et al., 2004). A minimum dose of 200-500 µg of purified salvinorin A, or 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled (Bucheler et al., 2005).
- *Salvia divinorum*, or its active constituents, are neither listed in any schedule to the *Controlled Drugs and Substances Act*, nor any schedule of the *Food and Drugs Act and Regulations*. Therefore, some on-line botanical companies and drug promotional sites ([www.salviasupply.com](http://www.salviasupply.com) , [www.wellcoolstuff.com](http://www.wellcoolstuff.com) , [www.salvia-divinorum.com](http://www.salvia-divinorum.com) , [www.sagewisdom.com](http://www.sagewisdom.com) , etc.) have advertised *Salvia divinorum* as a legal alternative to illicit drugs.
- In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long-term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the uniform Schedule of Drugs & Poisons. (TGA, 2002). In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of a psychoactive drug (Bucheler et al., 2005). The American Drug Enforcement Agency (DEA) has also placed *Salvia divinorum* on a list of drugs and chemicals "of concern," without legal implications (US DEA, 2002).
- Out of the 4 ARs reported to Health Canada, 3 cases involving inhalation were associated with hallucinogenic effects, and were considered to be non-serious reactions. The fourth case, however, was considered serious, and was associated with the oral use of the chemical constituent salvinorin A. As well, it should be noted that in this case-report, salvinorin A was consumed in a drug form (tablets containing 57 or 72 mg of salvinorin A) which now potentially becomes an unapproved health product offered for sale on the Canadian market.

Total number of cases	4
Route of exposure	Oral (1) & Inhalation (3)
Age range	16 yrs - 56 yrs
Gender	2 male, 2 female



Causality	oral - 1 possible; inhalation - 2 possible, 1 probable
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*Please see Appendix B for the detailed causality assessment report.*

- Recently, an international case report of *Salvia divinorum* poisoning was published in a scientific journal, in which a young man (19 years of age) described his perceptions after inhaling *Salvia divinorum*. The peak of psychotropic effects, including prickling of the skin, fever-like hot flashes, muscular tremor, and depersonalization, were reached in less than five minutes after inhalation of dried leaves of *Salvia divinorum* (Bucheler et al., 2005).
- Various studies have claimed that the psychotropic effects of *Salvia divinorum* closely resemble the symptoms of schizophrenia induced by other drugs such as LSD, phencyclidine or ketamine. Open field testing has also indicated that salvinorin A has a potency equivalent to that of mescaline (Hansen et al., 1988; Javitt and Zukin, 1991; Valdes, 1994).
- There has been a growing trend of cultivation of *Salvia divinorum* observed in South and North America as well as in Europe. Recently, several authors warned that *Salvia divinorum* might become a new recreational drug (Bucheler et al., 2005; Giroud et al., 2000; Halpern, 2004).

#### **Who is involved?**

- MNHPD, NHPD, HPFBI and the Office of Controlled Substances (OCS, HECS Branch)

#### **What action has been taken?**

- Neither *Salvia divinorum* nor its active constituent (Salvinorin A) have been authorised for sale in Canada, as confirmed by the Natural Health Products Directorate (NHPD) and TPD's Submission & Information Policy Division (SIPD).
- CADRIS has confirmed four case reports of poisoning associated with *Salvia divinorum* in Canada.
- HC has drafted an issue analysis summary (IAS) on the issue of health risks associated with the use of *Salvia divinorum* and its regulation in Canada (see Appendix A).
- Health Products and Food Branch Inspectorate (HPFBI) has been discussing the issue of *Salvia divinorum* with Office of Controlled Substances (OCS), HECS Branch for a number of years, because they often encounter products containing *Salvia divinorum* or pure *Salvia divinorum* on the Canadian market. OCS has advised to HPFBI that *Salvia divinorum* is on their "watch list".
- Additionally, HC has conducted causality assessments on the four Canadian ADRs associated with *Salvia divinorum* use. There are 4 domestic Canadian case reports of psychological adverse effect associated with the use of *Salvia divinorum* (3 inhaled and 1 oral). In the one 'serious' case, oral usage was associated with psychosis but alcohol was as significant confounder and the causality was assessed as 'possible'. The 3 inhaled case were judged to be 'non serious'. One of the inhaled cases was assessed as 'probable' (see Appendix B).

### **What are the key activities and time line?**

- Health Canada will develop appropriate risk mitigation strategies, if deemed necessary, following consultation with other Directorates (OCS, NHPD, TPD, HPFBI) within approximately two weeks.
- Health Canada will continue to monitor the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the internet, as well as through contacts with other Regulatory organizations and will share this information with OCS for their further regulatory actions.
- An anticipatory QP note on this issue has been drafted.

### **MNHPD's recommendation:**

Health Canada has received four domestic case reports of adverse reactions (ARs) associated with the use of *Salvia divinorum* (3 inhaled and 1 oral). Out of 4 ARs, one oral case was assessed as serious reaction, and other 3 inhaled cases were judged to be non serious. Since the 4 Canadian reports of adverse reaction associated with the *Salvia divinorum* use are all recent, this may further confirm a new trend in the use of this hallucinogenic plant in Canada. Although it is important to note that accumulated case reports cannot be used to determine the incidence of a reaction nor the risk of a product, since the total number of reactions, occurring and the number of people taking the product, is unknown

The Health Products and Food Branch of Health Canada will continue to collect relevant information concerning these, and other potential signals to determine whether or not risk mitigation strategies are required. This issue will be brought to the attention of the OCS, HECS Branch, for potential action. The OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada.

Although *Salvia divinorum* is on the watch list of the OCS, it may be appropriate to restrict *Salvia divinorum* and its active constituents by adding these to appropriate schedules under the *Controlled Drugs and Substances Act*.

### **Additional information/attachment (specify):**

Appendix A: IAS prepared by NHPD and MHPD.

Appendix B: Causality Assessments of Adverse Reactions associated with use of *Salvia divinorum*, conducted by MHPD.

**Peer-reviewed By:** Dr. Scott Jordan, MHPD

Date: Nov. 28, 2005.

Date: Dec. 7, 2005.

Date: Dec. 14, 2005.

**Peer-reviewed By:** Dr. Jenna Griffiths, MHPD

Date: Nov. 29, 2005.

**Approved By:** Dr. Mano Murty

**Date:** December 16, 2005

**References:**

Bucheler R, Gleiter CH, Schwoerer P, Gaertner I. Use of nonprohibited hallucinogenic plants: increasing relevance for public health? A case report and literature review on the consumption of *Salvia divinorum* (Diviner's Sage). *Pharmacopsychiatry*. 2005 Jan;38(1):1-5.

Chavkin C, Sud S, Jin W, Stewart J, Zjawiony JK, Siebert DJ, Toth BA, Hufeisen SJ, Roth BL. 2004. Salvinorin A, an active component of the hallucinogenic sage *Salvia divinorum* is a highly efficacious  $\kappa$ -opioid receptor agonist: structural and functional considerations. *J. Pharmacology and Experimental Therapeutics* 308(3): 1197-1203.

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother*. Oct;39(10):1634-9. Epub 2005 Sep 13

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TGA (Therapeutic Goods Administration) 2002. National Drugs and Poisons Schedule Committee Record of the Reasons, 33<sup>rd</sup> Meeting, 20-22 November 2001. URL: <http://www.tga.health.gov.au/ndpsc/record/rr200111upd8.pdf>, accessed May 26, 2004.

U.S. D.E.A (U.S. Department of Justice Drug Enforcement Administration). 2002. Drugs and Chemicals of Concern: *Salvia divinorum*, ska Maria Pastora, Salvia (Salvinorin A, Divinorin A). URL: [http://www.dea.gov/diversion.usdoj.gov/drugs\\_concern/salvia\\_d/summary.htm](http://www.dea.gov/diversion.usdoj.gov/drugs_concern/salvia_d/summary.htm), accessed May 26, 2004.

Valdes LJ. 1994. *Salvia divinorum* and the unique diterpene hallucinogen, Salvinorin (Divinorin) A. *J Psychoactive Drugs* 26 (3): 277-283.

## **APPENDIX B**

*Salvia divinorum* and Adverse Drug Reactions: Causality Assessments:

### **CAUSALITY ASSESSMENTS OF ADVERSE REACTIONS**

Updated December 1, 2005

Draft Subject to revision

**Natural Health Product:** *Salvia divinorum*

**Purpose of the assessment:**

To review the adverse reactions associated with the use of *Salvia divinorum*. (Domestic case reports are reviewed with respect to causality<sup>1</sup> and seriousness<sup>2</sup>.)

**Date of review commenced:**

May 2005

**Search Strategy:**

Adverse reactions suspected to be associated with *Salvia divinorum* were sought, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to May 31, 2005)

**Executive summary:**

There are 4 domestic Canadian case reports of psychological adverse effect associated with the use of *Salvia divinorum* (3 inhaled and 1 oral).

In the one 'serious' case, oral usage was associated with psychosis but alcohol was as significant confounder and the causality was assessed as 'possible'.

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<sup>1</sup> Based on the WHO causality algorithm unless otherwise specified.

<sup>2</sup> Internal Health Canada document. *Guidelines for reviewing Adverse Drug Reaction Reports*. Date of Revision August 2000.

*A serious adverse drug reaction is defined as: A noxious and unintended response to a drug, which occurs at any dose and requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above may also be considered serious.*

The 3 inhaled case were judged to be 'non serious'<sup>3</sup>. One of the inhaled cases was assessed as 'probable'.

**Conclusion:** In the serious case, Salvia was sold in a drug form, a tablet containing 57 or 72 mg of Salvinorin-A. In this case concomitant use of Salvia and alcohol most likely suggests a combined effect.

In the 3 non serious<sup>3</sup> cases, there was disorientation and hallucination after taking one "puff" of *Salvia divinorum*.

**Reviewer's comment:**

As a clinician, I find it worrisome that *Salvia divinorum* is so readily available for use and misuse by the Canadian public.

Salvia is also use in tablet form making it a drug, and is not authorized for sale by Health Canada.

Further evaluation/categorization is needed to regulate *Salvia divinorum*.

**Medical evaluator(s):**

Dr. T. Desjarlais-Renaud

Dr. M. Murty

Peer reviewed

Dr. T. Hall

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<sup>3</sup>\*These 3 reactions could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems is used: "d. concern for misuse or dependence".  
World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Source of ADR cases report	route	psychosis	hallucination disorientation	Causality certain	Causality probable	Causality possible	Not serious	Serious	Fatal outcome
CADRMP	oral	1				1		1	0
	inhalation		3		1	2	3 3	0	0

**Summary of Causality Assessment of reaction associated with the use of *Salvia divinorum***

Case ID/ date of gender r e c e i v e d r e p o r t e r		Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177867/F  c o n s u m e r  Jan 12,		-Unknown - Disorientation, hallucination, not recognizing people around her.	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No	Recovered (Effect lasted 5 minu tes)	Probable	No*



Case summary no 0177866

A 27 year old woman took *Salvia divinorum* for the purpose of experiencing hallucinations. She experienced disorientation, not recognizing people in the room, hallucinations for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial*, obtained from a boutique called "L'Ecologique", was inhaled through a pipe. The patient reported prior use of mescaline and LSD and that the effect of those were not as bad. ("moins pires"). The patient was on no other medications nor natural health products. This is not an unexpected reaction to *Salvia divinorum*. In this case there is a concern for misuse.

There is no evidence from the case report that she had recently taken other hallucinogenic substances.

The causality was assigned as 'probable'.

The adverse reaction was judged as 'not serious'.\*

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems<sup>4</sup> is used: "d. concern for misuse or dependence".

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<sup>4</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Case ID/ gender reporter  date  r e c e i v e d		Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
17785 35yr/M  c o n s u m e r  Jan 12, 2 0 0 5		-Unknown -Disorientation, hallucination, - foaming at the mouth	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No -no other medica tions -past med history - unkno wn	Recovered (Effect lasted 5 minu tes)	Possible	No*

Case summary no 0177865

A 28 year old man took *Salvia divinorum* for the purpose of experiencing hallucinations. He experienced disorientation, foaming at the mouth, and hallucinations for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial*, obtained from a boutique called "L'Ecologique" was inhaled through a pipe. There was no concomitant medication. Past medical history is unknown. This is not an unexpected reaction to *Salvia divinorum*. In this case there is a concern for misuse.

The causality was assigned as 'possible'.

The adverse reaction judged as 'not serious'.\*

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems<sup>5</sup> is used: "d. concern for misuse or dependence".

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<sup>5</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Case No/ Age/ gender reporter  d a t e r e c e i v e d	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
179989 39 yr/F  c o n s u m e r  Feb. 17, 2 0 0 5	-Unknown -Disorientation, hallucination, does not recognize husband	<i>Salvia divinorum</i> Al sasia encens special	Inhalation	1 puff taken	Unknown	Recovered (total effect 30 minu tes)	Possible	No*

Case summary no 0179969

A 56 year old woman experienced 30 minutes of disorientation and vivid hallucinations after taking 1 puff of *Salvia divinorum*. The reaction was very intense for 10 minutes and then decreased in intensity. The past medical history, concomitant medication and NHP usage are unknown. This is not an unexpected reaction to *Salvia divinorum*.

In this case there is a concern for misuse

The causality was assigned as 'possible'.

The adverse reaction was judged as not serious'.

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems<sup>6</sup> is used: "d. concern for misuse or dependence".

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<sup>6</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Case#/ Age/ gender/ reporter  date  r e c e i v e d	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
16/M 1 8 5 150lbs 2 8  C o n s u m e	March 29, 2005/ -drug induce psychosis -incoherent -suicidal - restrained -threatened to kill police officers -amnesia (does not remember any of these events) -jailed	Salvia/ aka Maria Pastora	oral/ 1 tablet "the 30\$ pil l"  57mg*	single dose	Yes  <u>Concomitant</u> <u>intake</u> <u>of:</u> Alcohol ("few drinks" )  <u>Concomitant</u> <u>conditi</u> <u>on:</u> ADD	Recovered	Possible	Y e s

Case summary no 0185128:

On March 23, 2005, a 16 year old male experienced drug induced psychosis: was incoherent, was suicidal, needed to be restrained, threatened to kill police officers, was jailed and had amnesia of these events after taking a single tablet of Salvia ( aka Maria Pastra). He had also consume a few drinks of alcohol. He has a underlying ADD but not receiving medication for this. He had previously taken Salvia "on its own" (route of administration unknown) with no adverse reaction.

Additional information obtained through the ADR specialist:

\* Follow up request for more information obtained July 28 2005, confirmed that the tablet was oral "30 \$ pill" purchased "behind the counter" at [REDACTED]  
This place sells a Salvia 10x containing 57 mg of Salvinorin-A for 29.98\$ and a Salvia 20x containing 72 mg of Salvinorin-A for 39.98\$.

Further information received August 18 2005: When Salvia taken before, it was the same dose (30\$ pill orally). The only thing different was that on previous occasions he did not have alcohol wit it.

This is a case where there was no adverse reaction with previous use of Salvia (same dosage, same distributer, same route of administration) but when associated with alcohol had a severe reaction.

The causality was assigned as 'possible' with alcohol as a confounder.

The adverse reaction was judged as 'serious' because it required intervention.

**s.19(1)**

C:\WINNT\Temp\ISR - Salvia divinorum.Approved-16 December 2005.wpd

[REDACTED]

125 237



Santé Canada

Health Canada

REÇU/RECEIVED

KPH

12-01-2005

Programme canadien de surveillance des effets indésirables des médicaments

Document Released under the Access to Information Act / Document divulgué en vertu de la Loi sur l'accès à l'information

s.19(1)

0177865

Direction générale des produits de santé et des aliments  
Health Products and Food Branch

- Voir au verso pour l'adresse de retour.
- The english version of this document is available upon request.
- See reverse for list of centres.

Notification concernant un effet indésirable présumé dû à un produit pharmaceutique commercialisé au Canada (Vaccins exclus)

PROTÉGÉ

A. Données relatives au patient

1. Identification [Redacted]	2. Âge au moment de la réaction [Redacted] ou [Redacted]	3. Sexe <input checked="" type="checkbox"/> Homme <input type="checkbox"/> Femme	4. Taille [Redacted] pi [Redacted] ou [Redacted] cm	5. Poids [Redacted] lb [Redacted] ou [Redacted] kg
Numéro de dossier [Redacted]	Date de naissance JJ MM AAAA [Redacted] 1976			

B. Effet indésirable

1. Suites de l'effet indésirable (cocher toutes les cases pertinentes)

<input type="checkbox"/> Décès (jj / mm / aaaa)	<input type="checkbox"/> Incapacité
<input type="checkbox"/> Met la vie en danger	<input type="checkbox"/> Malformation congénitale
<input type="checkbox"/> Hospitalisation	<input type="checkbox"/> Besoin d'intervention pour prévenir lésions / invalidités permanentes
<input type="checkbox"/> Hospitalisation prolongée	<input type="checkbox"/> Autre : _____

2. Date et heure de l'effet  
JJ MM AAAA

3. Date de la présente notification  
JJ MM AAAA  
11 01 2005

4. Description de l'effet ou du problème

Ce produit serait un dérivé de la sauge. Il est distribué par [Redacted] sous le nom de Puff encens spécial. Se prend à l'aide d'une pipe.

De la mousse apparaît au bord des lèvres

- désorientation
- Hallucination

Durée de l'effet : court, environ 5 minutes

5. Données (tests, analyses de laboratoire) pertinentes (avec les dates (jj / mm / aaaa))

Nil

6. Histoire médicale pertinente, y compris les facteurs préexistants (p. ex. allergies, grossesse, consommation de tabac et d'alcool, dysfonctionnement hépatique / rénal)

Inconnu

C. Produit(s) pharmaceutique(s) suspect(s). (Voir section «Comment déclarer un EIM» au verso)

1. Nom (préciser la teneur indiquée sur l'étiquette et le nom du fabricant, si connus)

N° 1 Salvia ? douce

N° 2 DIVINORUM

2. Dose, fréquence et voie d'administration

N° 1 1 puff

N° 2

3. Dates du traitement (si inconnues, donner la durée)

N° 1 Du (jj / mm / aaaa) - Au (jj / mm / aaaa)

N° 2 une seule fois

4. Indications relatives au produit pharmaceutique suspect

N° 1 pour provoquer des hallucinations

N° 2

5. Effet disparu après arrêt de l'administration ou réduction de la dose

N° 1  Oui  Non  ne s'applique pas

N° 2  Oui  Non  ne s'applique pas

6. N° de lot (si connu)

N° 1

N° 2

7. Date d'exp. (si connue)

N° 1 (jj / mm / aaaa)

N° 2

8. Effet réapparu après réadministration

N° 1  Oui  Non  ne s'applique pas

N° 2  Oui  Non  ne s'applique pas

9. Médication concomitante (nom, dose, fréquence et voie d'administration) et dates du traitement (jj / mm / aaaa) (exclure le traitement de l'effet)

Nil

Santé Canada  
JAN 18 2005  
M.F.D./D.P.S.C.

10. Traitement de l'effet indésirable (médicaments et / ou traitement), avec les dates (jj / mm / aaaa)

Ne plus en reprendre

D. Déclarant (voir section «Confidentialité» au verso)

1. Nom, adresse et numéro de téléphone

[Redacted]

2. Professionnel de la santé?

Oui  Non

3. Profession

[Redacted]

4. Également déclaré au fabricant?

Oui  Non

Une déclaration n'équivaut pas à reconnaître que le personnel médical ou le produit a causé ou



RIM Demandeur [redacted] Profession RIM - Patients Departement RIM  
Bureau 1-(418) 523-4702 Poste Fax -( ) - Autre -( ) - Lotus Notes/Email

Reçu GL 2005-01-11 13:18:47 Modifié GL 2005-01-12 16:28:31 Fermé GL 2005-01-12 16:28:31 Réouverture? - -

QUESTION

Elle veut qu'on la rappelle (répondeur)

Statut de l'appel

Closed

Priorité - Délai de réponse

Mots clé

n/a

Nature de la question RIM

Indexation dans FLS

Si non, raison:

R \* 11-1-05 13h30 GL

Elle veut faire une notification concernant une plante qui est vendu dans des boutiques telles que [redacted] (ce produit est donc sans contrôle). C'Est une produit qui se nomme Salvia ...?... qui provient de la sauge. Ce produit est vendu pour ses propriétés hallucinogènes. Sur le sac, elle peut aussi lire le nom "Puff encens spécial". C'Est un produit qui se prend à l'aide d'une pipe. TQS aurait fait un reportage sur ce produit.

RÉPONSE

Ses rapport (un pour elle et un pour son conjoint) portent les numéros: [redacted] et ([redacted])

[redacted] aussi appelé à une autre section de Santé Canada pour faire une plainte sur ce produit (c'est eux qui leur aurait donné nos coordonnées pour qu'ils rapportent cet effet).

Type de réf:

No Classe:

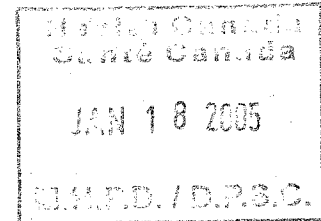
FP

Titre de réf:

GL

FP

Facture





Health Canada Santé Canada

Programme canadien de surveillance des effets indésirables (EI) des médicaments

s.19(1)

Le 12 janvier 2005.

**Objet : Numéro de référence de l'effet indésirable :** [REDACTED]

Madame,

Nous vous remercions pour la notification que vous avez récemment soumise au Programme canadien de surveillance des effets indésirables des médicaments. Les renseignements sur les effets indésirables sont maintenus dans une base de données informatisée et servent à l'évaluation continue des produits de santé commercialisés.

Votre notification pour le produit de santé suivant : Salvia avec l'identifiant RF a reçu le numéro de référence [REDACTED]. Si des informations supplémentaires sur ce cas deviennent disponibles, veuillez s'il vous plaît les faire parvenir à notre centre en mentionnant ce numéro de référence.

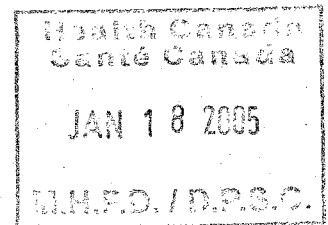
Nous profitons aussi de l'occasion pour vous inviter à vous abonner à la liste d'envoi "Info\_Prod\_Santé" afin de recevoir, par courriel, les mises à jour de la Direction des produits de santé commercialisés (DPSC), de la Direction des produits thérapeutiques (DPT) et de la Direction des produits biologiques et des thérapies génétiques (DPBTG) et la plus récente publication du Bulletin canadien des effets indésirables des médicaments, ainsi que les avis destinés aux professionnels de la santé ou les mises en garde aux consommateurs concernant les produits de santé. Le Bulletin canadien des effets indésirables des médicaments est une source fiable de renseignements sur les effets indésirables. Il s'agit d'une publication trimestrielle. Pour s'y abonner, il suffit d'aller à l'adresse suivante :

[http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe\\_f.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_f.html)

Votre contribution et votre engagement à l'égard de la surveillance de l'innocuité des produits de santé sont grandement appréciés.

Veillez agréer nos sincères salutations.

/lp



Les centres régionaux des EI oeuvrent en partenariat avec la Direction des produits de santé commercialisés

JP  
01/19/05

FOIR - DRUA  
ABUSE

YMS

R

LISORLEADRE (A)

HOWLUC (A) 15

s.19(1)

0177866

1 d 2 a 3 3 8

RECU/RECEIVED



Santé Canada

Health Canada

12-01-2005

Programme canadien de surveillance des effets indésirables des médicaments

Direction générale des produits de santé et des aliments  
Health Products and Food Branch

• Voir au verso pour l'adresse de retour.  
• The english version of this document is available upon request.  
See reverse for list of centres.

Notification concernant un effet indésirable présumé dû à un produit pharmaceutique commercialisé au Canada (Vaccins exclus)

PROTÉGÉ

**A. Données relatives au patient**

1. Identification [Redacted]	2. Âge au moment de la réaction ou Date de naissance JJ MM AAAA 19 11 1978	3. Sexe <input type="checkbox"/> Homme <input checked="" type="checkbox"/> Femme	4. Taille pi ou cm	5. Poids lb ou kg
---------------------------------	--	--	-----------------------------	----------------------------

**B. Effet indésirable**

1. Suites de l'effet indésirable (cocher toutes les cases pertinentes)

<input type="checkbox"/> Décès (jj / mm / aaaa)	<input type="checkbox"/> Incapacité
<input type="checkbox"/> Met la vie en danger	<input type="checkbox"/> Malformation congénitale
<input type="checkbox"/> Hospitalisation	<input type="checkbox"/> Besoin d'intervention pour prévenir lésions / invalidités permanentes
<input type="checkbox"/> Hospitalisation prolongée	<input type="checkbox"/> Autre :

2. Date et heure de l'effet JJ MM AAAA	3. Date de la présente notification JJ MM AAAA 11 01 2005
---	---

4. Description de l'effet ou du problème

Ce produit serait un dérivé de la sauge. Il est distribué par [Redacted] sous le nom de: Puff encens spécial. Se prend à l'aide d'une pipe

- désorientation
- Ne reconnaît plus les gens autour d'elle
- Sensation que la pièce grandit (Hallucination)

Durée de l'effet: court, environ 5 minutes

5. Données (tests, analyses de laboratoire) pertinentes (avec les dates (jj / mm / aaaa))

Nil

**6. Histoire médicale pertinente, y compris les facteurs préexistants**  
(p. ex. allergies, grossesse, consommation de tabac et d'alcool, dysfonctionnement hépatique / rénal)

Elle a déjà pris de la Mescaline et du LSD et les effets étaient moins purs.

**C. Produit(s) pharmaceutique(s) suspect(s).**  
(Voir section «Comment déclarer un EIM» au verso)

1. Nom (préciser la teneur indiquée sur l'étiquette et le nom du fabricant, si connus)

N° 1 Salvia ? douce

N° 2 DIDENORUM

2. Dose, fréquence et voie d'administration N° 1 <u>1 puff</u>	3. Dates du traitement (si inconnues, donner la durée) N° 1 Du (jj / mm / aaaa) - Au (jj / mm / aaaa) <u>Une seule fois</u>
N° 2	N° 2

4. Indications relatives au produit pharmaceutique suspect N° 1 <u>Pour provoquer des hallucinations</u>	5. Effet disparu après arrêt de l'administration ou réduction de la dose N° 1 <input checked="" type="checkbox"/> Oui <input type="checkbox"/> Non <input type="checkbox"/> ne s'applique pas
N° 2	N° 2 <input type="checkbox"/> Oui <input type="checkbox"/> Non <input type="checkbox"/> ne s'applique pas

6. N° de lot (si connu) N° 1	7. Date d'exp. (si connue) N° 1 (jj / mm / aaaa)	8. Effet réapparu après réadministration N° 1 <input type="checkbox"/> Oui <input type="checkbox"/> Non <input checked="" type="checkbox"/> ne s'applique pas
N° 2	N° 2	N° 2 <input type="checkbox"/> Oui <input type="checkbox"/> Non <input type="checkbox"/> ne s'applique pas

9. Médication concomitante (nom, dose, fréquence et voie d'administration) et dates du traitement (jj / mm / aaaa) (exclure le traitement de l'effet)

Aucun

10. Traitement de l'effet indésirable (médicaments et / ou traitement), avec les dates (jj / mm / aaaa)

Ne plus en reprendre

Santé Canada  
Health Canada  
JAN 18 2005  
1180:10330

**D. Déclarant (voir section «Confidentialité» au verso)**

1. Nom, adresse et numéro de téléphone

[Redacted]

2. Professionnel de la santé? <input type="checkbox"/> Oui <input checked="" type="checkbox"/> Non	3. Profession [Redacted]	4. Également déclaré au fabricant? <input type="checkbox"/> Oui <input type="checkbox"/> Non
---	-----------------------------	---

Une déclaration n'équivaut pas à reconnaître que le personnel médical ou le produit a causé ou contribué à causer l'effet indésirable

RIM Demandeur [redacted] Profession RIM - Patients Departement RIM

Bureau 1-(418) 523-4702 Poste Fax - ( ) - Autre - ( ) - Lotus Notes/Email

Reçu GL 2005-01-11 13:18:47 Modifié GL 2005-01-12 16:28:31 Fermé GL 2005-01-12 16:28:31 Réouverture? - -

QUESTION

Elle veut qu'on la rappelle (répondeur)

Statut de l'appel

Closed

Priorité - Délai de réponse

Mots clé

n/a

Nature de la question RIM

Indexation dans FLS

Si non, raison:

R \* 11-1-05 13h30 GL

Elle veut faire une notification concernant une plante qui est vendu dans des boutiques telles que la boutique l'Ecologique (ce produit est donc sans contrôle). C'Est une produit qui se nomme Salvia ...?... qui provient de la sauge. Ce produit est vendu pour ses propriétés hallucinogènes. Sur le sac, elle peut aussi lire le nom "Puff encens spécial". C'Est un produit qui se prend à l'aide d'une pipe. TQS aurait fait un reportage sur ce produit.

RÉPONSE

Ses rapport (un pour elle et un pour son conjoint) portent les numéros: [redacted] et [redacted]

... à une autre section de Santé Canada pour faire une plainte sur ce produit (c'est eux qui leur aurait donné nos [redacted] et).

*Spoke n/ Geneviève  
(see pencil filings)*

*[redacted] RC is  
trying to obtain  
more info*

*X*

*867*

F9 Titre de réf:

GL

F9

COMMUNICATIONS  
SANTÉ CANADA  
JAN 18 2005  
COMM.D./D.230



Health  
Canada

Santé  
Canada

Programme canadien de surveillance des effets indésirables (EI) des médicaments

Le 12 janvier 2005.

[REDACTED]

**Objet : Numéro de référence de l'effet indésirable :** [REDACTED]

Madame,

Nous vous remercions pour la notification que vous avez récemment soumise au Programme canadien de surveillance des effets indésirables des médicaments. Les renseignements sur les effets indésirables sont maintenus dans une base de données informatisée et servent à l'évaluation continue des produits de santé commercialisés.

Votre notification pour le produit de santé suivant : Salvia avec l'identifiant KD a reçu le numéro de référence [REDACTED]. Si des informations supplémentaires sur ce cas deviennent disponibles, veuillez s'il vous plaît les faire parvenir à notre centre en mentionnant ce numéro de référence.

Nous profitons aussi de l'occasion pour vous inviter à vous abonner à la liste d'envoi "Info\_Prod\_Santé" afin de recevoir, par courriel, les mises à jour de la Direction des produits de santé commercialisés (DPSC), de la Direction des produits thérapeutiques (DPT) et de la Direction des produits biologiques et des thérapies génétiques (DPBTG) et la plus récente publication du Bulletin canadien des effets indésirables des médicaments, ainsi que les avis destinés aux professionnels de la santé ou les mises en garde aux consommateurs concernant les produits de santé. Le Bulletin canadien des effets indésirables des médicaments est une source fiable de renseignements sur les effets indésirables. Il s'agit d'une publication trimestrielle. Pour s'y abonner, il suffit d'aller à l'adresse suivante :

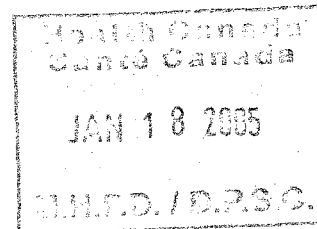
[http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe\\_f.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_f.html)

Votre contribution et votre engagement à l'égard de la surveillance de l'innocuité des produits de santé sont grandement appréciés.

Veillez agréer nos sincères salutations.

[REDACTED]

/lp



Les centres régionaux des EI oeuvrent en partenariat avec la Direction des produits de santé commercialisés

98  
21/19/05

FofR ABUSE  
C.R.S.  
R.

DISSEMINATION  
CONDITIONS  
HANDLING OF

126544  
Santé Health  
Canada Canada

Programme canadien de surveillance  
des effets indésirables des médicaments

Direction générale des produits de  
santé et des aliments  
Health Products and Food Branch

• Voir au verso pour l'adresse de retour.  
• The english version of this document is available upon request.  
See reverse for list of centres.

Notification concernant un effet indésirable présumé dû à un produit pharmaceutique commercialisé au Canada (Vaccins exclus)

s.19(1)

PROTÉGÉ

**A. Données relatives au patient**

1. Identification	2. Âge au moment de la réaction	3. Sexe	4. Taille	5. Poids
	ou	<input type="checkbox"/> Homme	pi	lb
Numéro de dossier	Date de naissance	<input type="checkbox"/> Femme	ou	ou
JJ MM AAAA	JJ MM AAAA		cm	kg

**B. Effet indésirable**

1. Suites de l'effet indésirable (cocher toutes les cases pertinentes)

Décès (jj / mm / aaaa)  Incapacité

Met la vie en danger  Malformation congénitale

Hospitalisation  Besoin d'intervention pour prévenir lésions / invalidités permanentes

Hospitalisation prolongée  Autre :

2. Date et heure de l'effet JJ MM AAAA

3. Date de la présente notification JJ MM AAAA

4. Description de l'effet ou du problème

eucius que se trouve disponible dans magasin en vente libre. Après 1 puff pendant 5-10 minutes = pas capable de se lever, ne reconnaît rien, ni son mari, ni elle-même. Ne savait plus où elle était, qui elle était. Hallucinations incroyables de lumières de couleur elle avait 100 maux

5. Données (tests, analyses de laboratoire) pertinentes (avec les dates (jj / mm / aaaa))

et pieds. Durée environ 10 minutes puis intensité durée totale 30 minutes. (sa fille a rapporté le même effet voir )

6. Histoire médicale pertinente, y compris les facteurs préexistants (p. ex. allergies, grossesse, consommation de tabac et d'alcool, dysfonctionnement hépatique / rénal)

**C. Produit(s) pharmaceutique(s) suspect(s)**  
(Voir section «Comment déclarer un EIM» au verso)

1. Nom (préciser la teneur indiquée sur l'étiquette et le nom du fabricant, si connus)

N° 1 Al SASIA eucius special

N° 2 SANTA DE VINORUM

2. Dose, fréquence et voie d'administration N° 1

3. Dates du traitement (si inconnues, donner la durée) N° 1 Du (jj / mm / aaaa) - Au (jj / mm / aaaa)

N° 2

4. Indications relatives au produit pharmaceutique suspect N° 1

5. Effet disparu après arrêt de l'administration ou réduction de la dose N°1  Oui  Non  ne s'applique pas

N° 2 N°2  Oui  Non  ne s'applique pas

6. N° de lot (si connu) N° 1

7. Date d'exp. (si connue) N° 1 (jj / mm / aaaa)

8. Effet réapparu après réadministration N°1  Oui  Non  ne s'applique pas

N° 2 N° 2 N°2  Oui  Non  ne s'applique pas

9. Médication concomitante (nom, dose, fréquence et voie d'administration) et dates du traitement (jj / mm / aaaa) (exclure le traitement de l'effet)

Health Canada  
Santé Canada

MAR 17 2005

M.H.P.D. / D.P.S.C.

10. Traitement de l'effet indésirable (médicaments et / ou traitement), avec les dates (jj / mm / aaaa)

~~pas~~ pas repris et elle a fait plainte à Santé Canada au bureau de pour faire interdire ce produit.

**D. Déclarant (voir section «Confidentialité» au verso)**

1. Nom, adresse et numéro de téléphone

2. Professionnel de la santé?  Oui  Non

3. Profession

4. Également déclaré au fabricant?  Oui  Non

Une déclaration n'équivaut pas à reconnaître que le personnel médical ou le produit a causé ou contribué à causer l'effet indésirable.

Canada

COPIE



s.19(1)

RIM                      Demandeur [REDACTED]                      Profession RIM - Patients                      Departement RIM  
 Bureau 1-(418) 647-1452                      Poste                      Fax - ( ) -                      Autre - ( ) -                      Lotus Notes/Email  
 Reçu    GL    2005-01-11    13:16:40    Modifié    VCP    2005-02-23    14:11:09    Fermé    VCP    2005-02-23    14:11:09    Réouverture? - -

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ATTEND SON APPEL  
 Elle a appelé à SC pour faire une plainte et on lui a dit de nous appeler (répondeur)

Statut de l'appel

Closed

Priorité - Délai de réponse

Mots clé

n/a

Nature de la question    RIM\_Suivi

Indexation dans FLS

Si non, raison:

R \* 11-1-05 13h15 GL il n'y a personne, je laisse message sur la boite vocale.

É \* 17-2-05 10:30 VP j'ai pris en note sa notification concernant un encens special à fumer Alsasia. Voir [REDACTED]  
 P c'est [REDACTED] qui a rapporté [REDACTED] et [REDACTED]

O \* Elle a rapelé pour dire qu'elle avait reçu lettre de confirmation avec formulaire vierge. Elle voulait savoir pourquoi un formulaire ? Je lui ai  
 N expliqué que c'était pour un usage futur si besoin. Il se demandait ou en était rendue la plainte qu'elle avait fait à santé Canada à [REDACTED]  
 S alors je lui ai expliqué que ce n'était pas le même département et je lui ai suggéré de rappeler à [REDACTED]

Type de réf:

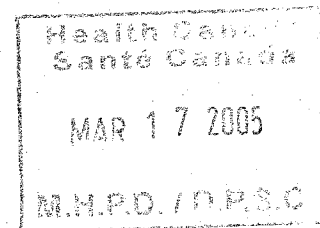
No Classe:

FS Titre de réf:

GL

FS

Facture





Health Canada Santé Canada

Programme canadien de surveillance des effets indésirables (EI) des médicaments

Le 18 février 2005.

**Objet : Numéro de référence de l'effet indésirable :** [REDACTED]

Madame,

Nous vous remercions pour la notification que vous avez récemment soumise au Programme canadien de surveillance des effets indésirables des médicaments. Les renseignements sur les effets indésirables sont maintenus dans une base de données informatisée et servent à l'évaluation continue des produits de santé commercialisés.

Votre notification pour le produit de santé suivant : Alasia<sup>MD</sup> avec l'identifiant CB a reçu le numéro de référence [REDACTED]. Si des informations supplémentaires sur ce cas deviennent disponibles, veuillez s'il vous plaît les faire parvenir à notre centre en mentionnant ce numéro de référence.

Nous profitons aussi de l'occasion pour vous inviter à vous abonner à la liste d'envoi "Info\_Prod\_Santé" afin de recevoir, par courriel, les mises à jour de la Direction des produits de santé commercialisés (DPSC), de la Direction des produits thérapeutiques (DPT) et de la Direction des produits biologiques et des thérapies génétiques (DPBTG) et la plus récente publication du Bulletin canadien des effets indésirables des médicaments, ainsi que les avis destinés aux professionnels de la santé ou les mises en garde aux consommateurs concernant les produits de santé. Le Bulletin canadien des effets indésirables des médicaments est une source fiable de renseignements sur les effets indésirables. Il s'agit d'une publication trimestrielle. Pour s'y abonner, il suffit d'aller à l'adresse suivante :

[http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe\\_f.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_f.html)

Votre contribution et votre engagement à l'égard de la surveillance de l'innocuité des produits de santé sont grandement appréciés.

Veuillez agréer nos sincères salutations.

/lp

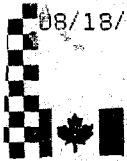
Les centres régionaux des EI oeuvrent en partenariat avec la Direction des produits de santé commercialisés

2005-04-06 REP/

ASTHENIA  
Confusion  
Hallucination

Eam  
Feb 28/05

08/18/2005 09:16



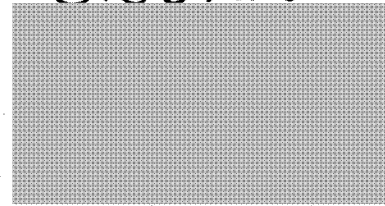
Health Canada Santé Canada

0185128

129517

FU #2

s.19(1)



**Canadian Adverse Drug Reaction Monitoring Program**

If you receive this fax in error, please advise the sender immediately.

**TO:** Karen Pilon

Date: August 18, 2005

**Fax:** 613-957-0335

No. of Pages, including this page: 2

**FROM:**

Tel:

Fax:

**MESSAGE:**

As requested, follow-up for

Health Canada  
Santé Canada

AOUT 18 2005

M.H.P.D. / D.P.S.C.

Health Professionals and consumers may use the following toll-free numbers to report adverse reactions, or request further information about the Adverse Reaction program. Calls will be automatically routed to the appropriate Regional or the National Adverse Reaction Centre, based on the area code from which the call originates.

Toll-free telephone: 1-866-234-2345 Toll-free fax: 1-866-678-6789

Canada

000044

08/18/2005 09:16

s.19(1)

Faxed to Karen F  
August 18/05

Regional Adverse Reaction Centre  
Adverse Reaction Report Followup/Clarification Form

Case #: [redacted]

Follow-up/clarification requested by: Karen Pilon

Follow-up requested from: [redacted] (Reporter.)

Home: [redacted] Work: [redacted]

Date of follow-up request: August 16, 2005

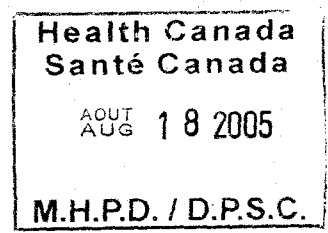
Data elements requested/clarified:

6. "Has taken Salvia in the past on its own with no reaction  
- How did he take it? Was it an oral pill or smoked?  
What was the dose?"

Response: Yes it was an oral pill, same dose, obtained from the same place. He has always taken the \$30 pill. The only difference between this occasion and the others is that he had alcohol with it on this occasion. All previous occasions, he did not have alcohol.

~~Attachments if applicable (e.g. letter, e-mail)~~

Note: Could not confirm dose of 72mg. Reporter did state there were 2 pills available  
- \$30 pill  
- \$40 pill



I:/HPSID/ARInfo/Stiver/RegionalCentres/Standard letters  
March/04

[redacted]

AUG 17/05

0185128

129517 fu

**Adverse Reaction Information Section  
Adverse Reaction Report Followup Request Summary**

s.19(1)

**CADRIS No:** 0185128

**Specialist:** Karen Pilon

**Market Authorization Holder (MAH) or Regional Centre No:** [REDACTED]

**MHPD staff requesting followup:** Thérèse Desjarlais-Renaud  
Marketed Natural Health Products

**Follow-up requested from (i.e. name of MAH or RC contact, physician etc.):**  
[REDACTED] - Candice Fisher to contact reporter

**Date of follow-up request:** July 28, 2005

**Data elements requested:**

Where was the product (tablet) purchased?  
How was the tablet ingested?

**Response:** July 28, 2005

Reporter confirmed that the tablet was purchased from [REDACTED]  
The 72 mg tablet was packaged in a small black box with no label. It was "behind the counter" and had to be asked for.

**Attachments if applicable (i.e. letter, e-mail, MAH follow-up report):**

129517

s.19(1)

0185128

RECEIVED

MAY 17 2005

Canadian Adverse Drug Reaction Monitoring Program

Health Products and Food Branch  
Direction générale des produits de santé et des aliments

Report of suspected adverse reaction due to health products\* marketed in Canada

PROTECTED B\*\*  
(when completed)

The form should be printed and faxed toll free to: 1 866 678-6789 or mailed as per instructions below.  
La version française de ce document est disponible à: [http://www.hc-sc.gc.ca/hpfs/dapsa/gpd-dpa/adverse\\_f.pdf](http://www.hc-sc.gc.ca/hpfs/dapsa/gpd-dpa/adverse_f.pdf)

A. Patient Information  
(See "Confidentiality" section below)

1. Identifier	3. Sex <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	4. Height _____ feet or _____ cm	5. Weight 150 lbs or _____ kgs
2. Age at time of reaction 16			

B. Adverse Reaction

1. Outcome attributed to adverse reaction (check all that apply)

Death (dd/mm/yyyy)     Disability  
 Life-threatening     Congenital malformation  
 Hospitalization     Required intervention to prevent damage/permanent impairment  
 Hospitalization - prolonged     Other: \_\_\_\_\_

2. Date of reaction DD MM YYYY 29 03 2005	3. Date of this report DD MM YYYY 17 05 2005
---	--

4. Describe reaction or problem

- Drug induced psychosis  
 - incoherent  
 - suicidal  
 - restrained  
 - threatened to kill police officers  
 - amnesia (does not remember any of these events.)  
 - jailed

5. Relevant tests / laboratory data (including dates (dd/mm/yyyy))

Nil

6. Other relevant history, including pre-existing medical conditions (e.g. allergies, pregnancy, smoking and alcohol use, hepatic / renal dysfunction)

ADD - not being treated.  
 Has taken Salvia on its own previously → no reaction.

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the adverse reaction.

\* Use this form to report suspected adverse reactions to pharmaceuticals, biologics (including fractionated blood products, as well as therapeutic and diagnostic vaccines), natural health products or radiopharmaceuticals.  
\*\* As per the Treasury Board of Canada Secretariat Government Security Policy.

C. Suspected Health Product(s)  
(See "How to report" section below)

1. Name (give labeled strength & manufacturer, if known)

#1 Salvia (aka Maria Pastora)  
 #2 Alcohol

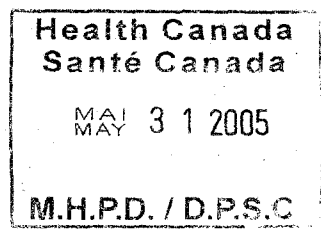
2. Dose, frequency & route used #1 Single oral tablet	3. Therapy dates (if unknown, give duration) #1 From (dd/mm/yyyy) - To (dd/mm/yyyy) March 29/05
#2 few drinks/Alcohol	#2 March 29/05

4. Indication for use of suspected health product #1	5. Reaction abated after use stopped or dose reduced #1 <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply
#2	#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply

6. Lot # (if known) #1	7. Exp. date (if known) #1 (dd/mm/yyyy)	8. Reaction reappeared after reintroduction #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply
#2	#2	#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply

9. Concomitant health products (name, dose, frequency and route used), and therapy dates (dd/mm/yyyy) (exclude treatment of reaction)

Nil



10. Treatment of adverse reaction (medications and / or other therapy), include dates (dd/mm/yyyy)

Nil

D. Reporter Information  
(See "Confidentiality" section below)

1. Name, address & phone number

2. Health professional? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	3. Occupation (Parent) Consumer	4. Also reported to manufacturer? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	------------------------------------	---

Verbal Report  
taken by

May 17/05



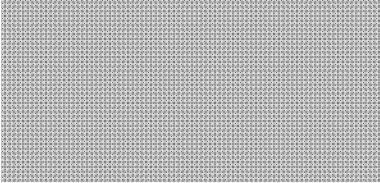
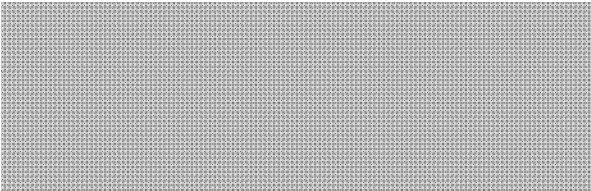
000047



Health Canada / Santé Canada

Canadian Adverse Drug Reaction Monitoring Program

s.19(1)



2005-05-17

**Re: Adverse Reaction Tracking Number 60015**

Dear [Redacted]

Thank you for the recent case report submitted to the Canadian Adverse Drug Reaction Monitoring Program. Suspected adverse reaction reports are submitted on a voluntary basis and maintained in a computerized database. Adverse reaction information is used for the monitoring of marketed health products, and may contribute to the detection of potential product-related safety issues as well as to the benefit-risk assessments of these products.

The case report for the health product(s):

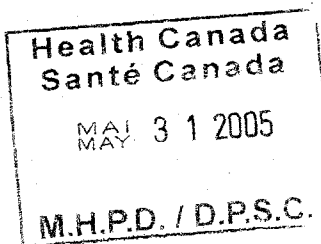
**ALCOHOL  
SALVIA**

with identifier [Redacted] has been assigned the tracking number [Redacted]. If further information becomes available regarding this case, please forward it to our centre citing the tracking number. For your convenience, please find enclosed an adverse reaction reporting form for your future use.

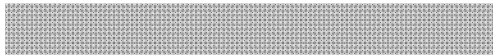
Any information related to the identity of the patient and/or the reporter of the adverse reaction is kept strictly confidential. For more details with regards to personal information collected under this program, visit the Personal Information Bank; Health Canada; Health Products and Food Branch; Branch Incident Reporting System; PIB # PPU 088 at: [http://infosource.gc.ca/inst/shc/fed07\\_e.asp](http://infosource.gc.ca/inst/shc/fed07_e.asp)

We would also like to take this opportunity to invite you to join Health Canada's Health\_Prod\_Info mailing list to receive the Canadian Adverse Reaction Newsletter and health products advisories by e-mail. To subscribe, please visit: [http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index\\_adverse\\_e.htm](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_e.htm)

Your contribution and commitment to health product safety monitoring are appreciated.



Yours sincerely,



Canadian Adverse Drug Reaction Monitoring Program

Health professionals and consumers may use the following toll-free numbers to report adverse reactions, or request further information about the Adverse Reaction program. Calls will be automatically routed to the appropriate Regional or the National Adverse Reaction Centre, based on the area code from which the call originates.  
Toll-free telephone: 1-866-234-2345 Toll-free fax: 1-866-678-6789



F/u 2005-07-28 KCP/

2005-06-08 KCP/

(psychosis)  
confusion  
thoughts of self-harm  
aggressive reaction  
amnesia

REPORT ISR51

**s.19(1)** Incident number: M IV 4 625

\*Date Received: 10-JAN-05 Inquiry : N Incident Nature: VENTE PSN - RISQUE A LA SANTE Inc.Type: D DRUGS  
 Source: C CONSUMER COMPLAINT Source System Id: N/A Priority : REGULAR  
 REPORTED?: \*ILLNESS: N \*ALLERGY: N \*SABOTAGE/TAMPER: N \*Summary: N FOR PICK-UP?: \*SPECIMEN: N Opened by : STEPHANE GELINAS

PART A. CLIENT INFORMATION: ID #: 12851 Correspondence : FRENCH

Type Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
						CANADA

PART B. PRODUCT INFORMATION

Code	Product Name	Brand Name	Size	Lot#	Purchased
ZZZZ	UNKNOWN	SALVIA DIVINORUM	SACHET	n/a	n/a

Common Name	Distribution	DIN/GP	MAN PROD NO.	Model#	Serial#	Lot Size
SALVINORIN A	N/A			N/A	N/A	N/A

UPC	Expiry Date
N/A	N/A

Enterprise associated with the product

9092 V VENDOR/RETAILER

Type Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
						CANADA

ACTION(S) TAKEN

Product	Enterprise	Action Date/Comment	Code Compliance Action	Depth Of Recall	Effectiveness
ZZZZ	9092	03-NOV-05 achat echantillon	F Classification request	NA NOT APPLICABLE	NA NOT APPLICABLE

Enterprise associated with the product

9093 V VENDOR/RETAILER

Type Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
						CANADA

ACTION(S) TAKEN

Product	Enterprise	Action Date/Comment	Code Compliance Action	Depth Of Recall	Effectiveness
---------	------------	---------------------	------------------------	-----------------	---------------

INCIDENT STATUS HISTORY

Code	Status	Effective Date	Expiry Date	User Name
OP	OPEN INCIDENT	10-JAN-05	18-FEB-05	STEPHANE GELINAS
IA	INVESTIGATOR ASSIGNED	18-FEB-05	30-NOV-05	STEPH000050
CL	CLOSE INCIDENT	13-JAN-06	13-JAN-06	F. ME

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08-FEB-07

INCIDENT DETAIL REPORT

REPORT ISR51

Incident number: M IV 4 625

INCIDENT STATUS HISTORY

Code	Status	Effective Date	Expiry Date	User Name
RV	REVIEW	13-JAN-06	13-JAN-06	F. MENARD

WORK ASSIGNMENT INFORMATION

Reg/Dis	Started	Completed	Work Spec Code	Gm Unit	Negotiated Unit	Time	Region	Organizational Unit
M IV	10-JAN-05	13-JAN-06	DDOC	DILA				INVESTIGATIONS UNIT

Type	User Name	Date Assigned	Date Complete
I	STEPHANE GELINAS	18-FEB-05	30-NOV-05

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08-FEB-07

INCIDENT DETAIL REPORT

C - 1

REPORT ISR51

s.19(1)

Incident number: M IV 4 625

INCIDENT TEXT

03-MAY-05 09:07:21 O OPEN INCIDENT STEPHANE GELINAS

10-Jan-05: Ouverture incident

L'inspectorat a reçu une plainte téléphonique de la part de [REDACTED]. Elle nous informe qu'elle et sa mere ont vu la semaine precedente, une emission a TQS-Quebec qui parlait de la Salvia Divinorum comme etant benefique contre les chaleurs provoques par la menopause mais qui aurait aussi des proprietes hallucinogenes.

Le vendredi 7 janvier 2005, sa mere, [REDACTED] a achete le produit pour verifier ses effets. Elle s'est rendue a [REDACTED] au [REDACTED] a [REDACTED]. Elle a demande a la vendeuse si elle pouvait avoir de la Salvia. La vendeuse lui a dit qu'elle avait de la Salvia "forte", "moyenne" et "douce". Elle a demande a avoir 4 sachets de force "moyenne". La vendeuse a pris les sachets derriere son comptoir. Les sachets sont identifies comme etant de "1'Encens Special One Puff". Il n'y aucune mention de Salvia Divinorum sur l'etiquette du sachet, ni aucune reclame.

[REDACTED] et leurs conjoints ont fume le produit a l'aide d'une pipe a hasch. [REDACTED] n'aurait pris qu'une seule inhalation. Tous auraient eu des reactions adverses importantes. Aucune des quatre personnes n'a consulte un medecin. Etant donne qu'ils ont fume les quatre sachets, elle ne peut nous fournir d'echantillon, ni l'emballage.

[REDACTED] aurait communique avec TQS-Quebec pour les informer de la vente de ce produit qu'elle considere dangereux. Elle leur aurait montre les sachets vides.

[REDACTED] a une autre succursale situee au [REDACTED]. [REDACTED] a ete avise de communiquer avec le Bureau des reactions indesirables de Sante Canada pour rapporter cet incident.

03-MAY-05 09:07:43 I INVESTIGATIVE STEPHANE GELINAS

20-AVR-05: Recherche sur site Web

L'Inspectorat du Centre Operationnel [REDACTED] a deja refuse une importation commerciale de 100 Kg de Salvia Divinorum destinee a [REDACTED] sise au [REDACTED].

Une recherche a l'aide du site WhitePages.com, en utilisant cette adresse, nous donne le nom de [REDACTED].

Une seconde recherche sur le site de CIDREQ, en utilisant le nom de [REDACTED], nous donne le nom de [REDACTED] comme etant l'actionnaire majoritaire des 2 etablisements de [REDACTED] soit:

03-MAY-05 09:07:59 I INVESTIGATIVE STEPHANE GELINAS

25-AVR-05: Courriel a Jenny et Marie

J'ai envoye un courriel a Jenny McLaughlin et Maire Morrissey afin de savoir si une evaluation du danger a la sante (HHE) a ete faite et si oui, quel etait le niveau de risque. Une demande de classification du produit a ete faite le 26 mai 2004 et la Salvia Divinorum ainsi que son principe actif Salvinorin A sont classifies comme etant un PSN.

03-MAY-05 09:08:12 I INVESTIGATIVE STEPHANE GELINAS

02-Mai-05: Reponse de Jenny

Jenny m'a repondu par courriel et m'avise qu'il n'y a pas eu de HHE de fait.

30-NOV-05 03:54:34 I INVESTIGATIVE STEPHANE GELINAS

06-Mai-05: BSC avise

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000052

08-FEB-07

INCIDENT DETAIL REPORT

C - 2

REPORT ISRS1

Incident number: M IV 4 625

INCIDENT TEXT

Jenny a rapporte au Bureau des Substances Controlees (BSC OCS) a Ottawa que le centre operationnel [redacted] a ete informe de la vente de Salvia Divinorum dans 2 boutiques de la ville [redacted]

30-NOV-05 03:54:51 I INVESTIGATIVE STEPHANE GELINAS

11-Mai-05: Courriel de Jenny  
Jenny nous informe qu'elle veut organiser une rencontre avec BSC/Inspectorat/NHPD et Services legaux pour determiner comment le produit devrait etre reglemente et les actions appropriees a prendre dans ce dossier.

30-NOV-05 03:55:09 I INVESTIGATIVE STEPHANE GELINAS

08-Sep-05: Courriel a Jenny  
J'ai envoye un courriel a Jenny pour savoir s'il y a du nouveau dans ce dossier.  
Jenny m'informe qu'il n'y a pas de mis a jour pour le statut de la Salvia Divinorum. Cependant, BSC / OCS a place la Salvia Divinorum sur sa "Watch list" et suit de pres l'utilisation de la Salvia au Canada.

30-NOV-05 03:55:55 I INVESTIGATIVE STEPHANE GELINAS

03-Nov-05: Achat de Salvia  
Le 3 novembre 2005, j'ai fait un achat incognito de Salvia Divinorum a [redacted] situee au [redacted]. Apres avoir demande s'il avait de la Salvia a vendre, le prepose au comptoir m'a demande si je voulais de la 5X, 10X, 15X ou 20X et quel poids que je desirais. J'ai demande au prepose de m'expliquer ce que veut dire 5X, par exemple. Il m'a repondu que la 5X est 5 fois plus forte que la plante mere qui est consideree 1X.  
Le prepose m'a indique que 0,1 gramme de Salvia equivaut a 1 "trip" et que je devais essayer la 5X ou 10X mais pas plus fort que ca puisque c'est la premiere fois que je vais l'essayer. Il m'a mentionne que la matiere premiere est importee du Mexique. Rendu [redacted] il extrait le principe actif de la plante et l'ajoute a des feuilles sechees de la plante qui sert de substrat.  
J'ai procede a l'achat de 0,1 gramme de Salvia 5X au cout de 5,00 dollars (taxable) et de 0,1 gramme de Salvia 10X au cout de 10,00 dollars (taxable).  
Sur le coupon de caisse, il est indique "Encens". Sur l'etiquette des sachets, il est indique: <<Salvia Divinorum Encens naturel non destinee a la consommation / Not for human consumption>>. Une adresse internet est egalement indiquee sur l'etiquette du produit: [redacted]

30-NOV-05 03:56:16 G GENERAL STEPHANE GELINAS

30-Nov-05: Fermeture dossier  
Puisque que la Salvia Divinorum rencontre seulement la partie "substance" de la definition d'un produit de sante naturel (la partie "fonction" n'est pas rencontree puisque "hallucinogene" n'est pas acceptable pour un PSN), que le Bureau des substances controlees a ete avise du fait de la vente de Salvia dans la region de la ville de [redacted] que le BSC a place la substance sur sa "watch list", que la Salvia n'est pas une substance controlee, et que le produit n'est pas represente pour consommation humaine et ne fait aucune reclame therapeutique, aucune autre action n'est jugee necessaire pour le moment dans ce dossier. [redacted] a ete avisee par courrier du resultat de sa plainte.

\*\*\*\*\* END OF REPORT ISRS1 \*\*\*\*\*

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## Plainte Salvia Divinorum

10 janvier 2005

J'ai reçu un téléphone de [REDACTED] de la sécurité des produits, me demandant de téléphoner une dame qui désire se plaindre de la vente de Salvia Divinorum. Elle m'a fait suivre un résumé de la conversation qu'elle a eue un peu plus tôt avec la dame:

Bonjour [REDACTED] voici les informations recueillies.

[REDACTED]

Émission regardée à TQS Québec la semaine dernière, qui parlait de ce produit naturel qui s'apparentait à la sauge et avait des propriétés quelconque (elle ne se souvient pas). [REDACTED] se sont dit qu'ils essaieraient ces herbes pour voir l'effet.

[REDACTED] veut faire une plainte parce qu'elle considère ce produit comme très dangereux car il est en vente libre et que même des jeunes en achètent :

- Son mari ainsi que sa mère en ont fait l'essai. Son époux s'est retrouvé avec "de la broue sur le bord de la bouche" et au bord d'un "bad trip". Selon [REDACTED] elle et son conjoint ont déjà consommé d'autres substances et selon eux ces herbes sont très néfastes et devraient être retiré du marché car trop dangereuse.

- Sachet vendu 6 \$ + taxe. Inscription : Puff Encens Spécial. Herbe hachée, brun foncé, se fume à l'aide d'une pipe. [REDACTED] me mentionne que le produit avait été acheté à [REDACTED]

[REDACTED]

Le produit est vendu en concentration douce, moyenne et forte.

La mère de [REDACTED] a contacté les gens de TQS ce matin.

Bonne fin de journée

[REDACTED]

J'ai communiqué avec [REDACTED] en après-midi. Elle m'a informé qu'elle avait vu en compagnie de sa mère, la semaine dernière, une émission à TQS qui parlait de la Salvia Divinorum comme étant bénéfique contre les chaleurs provoquées par la ménopause mais qui avait aussi des propriétés hallucinogènes. Le vendredi 7 janvier 2005, [REDACTED] a décidé d'aller en acheter pour vérifier. Elle s'est rendue à [REDACTED]. Elle a demandé à la vendeuse si elle pouvait avoir de la Salvia. La vendeuse lui a dit qu'elle avait de la Salvia "forte", "moyenne" et "douce". Elle a demandé à avoir 4 sachets de force "moyenne". La vendeuse a pris les sachets derrière son comptoir. Les sachets sont identifiés comme étant de l'Encens Spécial One Puff. Il n'y a aucune mention de Salvia Divinorum sur le sachet.

.../2

Plainte Salvia Divinorum  
10 janvier 2005

s.19(1)

/2

[REDACTED] de celles-ci ont fumé le produit à l'aide d'une pipe à hasch. [REDACTED] n'aurait pris qu'une seule inhalation. Tous auraient eu des réactions adverses importantes. Aucune des quatre personnes n'a consulté le médecin. Étant donné qu'ils ont fumé les quatre sachets, elle ne peut me fournir d'échantillon. Sa mère aurait communiqué avec TQS pour les informer de la vente de ce produit qu'elle considère dangereux. Elle leur aurait montré les sachets vides.

J'ai demandé à [REDACTED] de communiquer avec le Bureau des réactions indésirables de Santé Canada pour rapporter cet incident.

[REDACTED] a une autre succursale au [REDACTED]  
J'ai également inclus une copie de refus d'entrée datée de juillet 2003 signé par Paul Hébert dont l'importateur est [REDACTED]

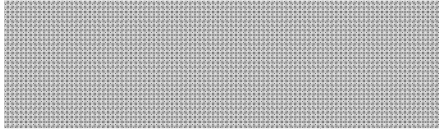
[REDACTED]



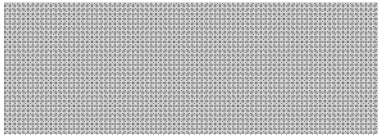
s.19(1) Loi sur l'accès à l'information

**À CLASSER**

DOSSIER #

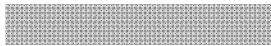


Le 1 décembre 2005



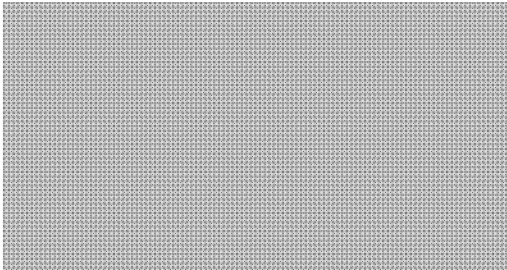
**Objet: Salvia Divinorum**

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Par la présente, nous vous informons qu'après étude de la plainte que vous nous avez soumise concernant le produit ci-haut mentionné, l'Inspectorat de la Direction générale des produits de santé et des aliments a pris les mesures jugées nécessaires dans ce dossier.

Nous vous remercions d'avoir porté ce cas à notre attention et nous vous prions d'accepter l'expression de nos sentiments les meilleurs.





08-FEB-07

INCIDENT DETAIL REPORT

REPORT ISR51

Incident number: M IV 4 626

\*Date Received: 12-JAN-05 Inquiry : N Incident Nature: VENTE PSN - RISQUE A LA SANTE

Inc.Type: D DRUGS

Source: C CONSUMER COMPLAINT Source System Id: N/A

Priority : REGULAR

REPORTED?: \*ILLNESS: N \*ALLERGY: N \*SABOTAGE/TAMPER: N \*Summary: N FOR PICK-UP?: \*SPECIMEN: N

Opened by : STEPHANE GELINAS

PART A. CLIENT INFORMATION: ID #: 12852

Correspondence : FRENCH

Type Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
						CANADA

PART B. PRODUCT INFORMATION

Code	Product Name	Brand Name	Size	Lot#	Purchased
ZZZZ	UNKNOWN	SALVIA DIVINORUM	SACHET	n/a	n/a

Common Name	Distribution	DIN/GP	MAN PROD NO.	Model#	Serial#	Lot Size
SALVINORIN A	N/A			N/A	N/A	N/A

UPC	Expiry Date
N/A	N/A

Enterprise associated with the product

9092

V VENDOR/RETAILER

Type Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
						CANADA

ACTION(S) TAKEN

Product	Enterprise	Action Date/Comment	Code Compliance Action	Depth Of Recall	Effectiveness
ZZZZ	9092	03-NOV-05 achat echantillon	F Classification request	NA NOT APPLICABLE	NA NOT APPLICABLE

Enterprise associated with the product

9093

V VENDOR/RETAILER

Type Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
						CANADA

ACTION(S) TAKEN

Product	Enterprise	Action Date/Comment	Code Compliance Action	Depth Of Recall	Effectiveness
---------	------------	---------------------	------------------------	-----------------	---------------

INCIDENT STATUS HISTORY

Code	Status	Effective Date	Expiry Date	User Name
OP	OPEN INCIDENT	12-JAN-05	18-FEB-05	STEPHANE GELINAS
IA	INVESTIGATOR ASSIGNED	18-FEB-05	30-NOV-05	STEPH000057
CL	CLOSE INCIDENT	13-JAN-06	13-JAN-06	F. MEI

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INCIDENT STATUS HISTORY

Code	Status	Effective Date	Expiry Date	User Name
RV	REVIEW	13-JAN-06	13-JAN-06	F. MENARD

WORK ASSIGNMENT INFORMATION

Reg/Dis	Started	Completed	Work Spec Code	Gm Unit	Negotiated Unit	Time	Region	Organizational Unit
M IV	12-JAN-05	13-JAN-06	DDOC	DILA				INVESTIGATIONS UNIT

Type	User Name	Date Assigned	Date Complete
I	STEPHANE GELINAS	18-FEB-05	30-NOV-05

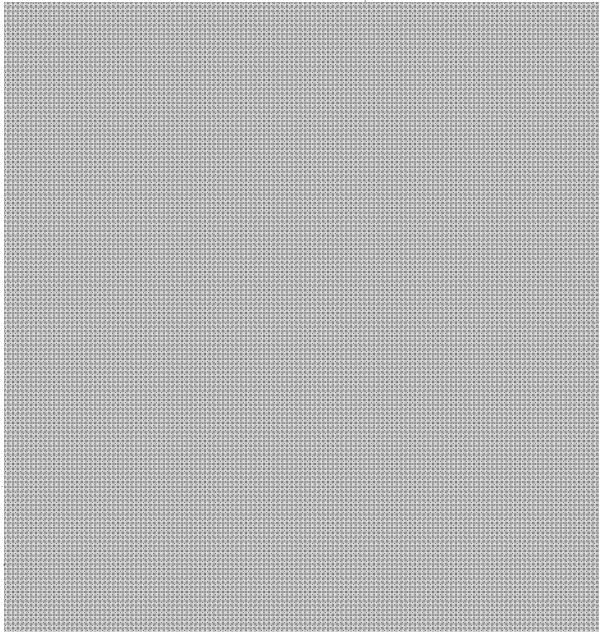
s.19(1)

Plainte Salvia Divinorum  
11 janvier 2005

[REDACTED] a téléphoné pour se plaindre à son tour de la vente de Salvia Divinorum. (Voir plainte du 10 janvier 2005 sur le même sujet.)

[REDACTED], s'inquiète pour ses petits-enfants. Elle m'a rapporté sensiblement la même chose que [REDACTED] concernant la vente d'Encens Spécial One Puff contenant de la Salvia Divinorum ainsi que les réactions adverses importantes; complètement perdue, ne reconnaissait plus son conjoint. Même choses pour sa fille et les deux conjoints.

J'ai demandé à [REDACTED] de communiquer avec le Bureau des effets indésirables de Santé Canada pour rapporter cet incident.



JAN 2005

s.19(1)

12 janvier 2005

à qui de droit  
— au sous de [redacted]

je fais une plainte pour (Saluscia)

J'ai été en chercher plusieurs jeunes etant dans le magasin pour en acheter des jeunes de 13 ans 14. la vendeuse nous a offert une pipe à eau pour fumer j'ai demandé la plus forte elle ma dit que je reconnaîtrais plus mon mari alors j'ai pris la main forte sur le sac cest marquer encen specials 1 puff

L'effet est horrible la main forte je ne reconnais plus mon mari je reconnais plus ma maison

Les hallucinations sont tellement forte on avait mis des petite lumiere elle sont devenu horriblement forte j'étais plus capable de parler je me voyais comme un dessin animé j'avais peur j'étais pas capable de penser seulement que c'était passé que j'avais fumer que j'étais comme ça et j'avait comme des éclats dans mon cerveau tout ça a duré 5 minute après j'étais comme si j'avais pris de l'acide pendant 20 minutes pareille pour mon mari

SVP entriez ça avant que un de nos jeunes en meurt

[redacted] accuse l'écriture  
[redacted] j'ai fait ça vite



Santé  
Canada Health  
Canada

**À CLASSER**

DOSSIER #

s.19(1)

[REDACTED]

Le 1 décembre 2005

[REDACTED]

**Objet: Salvia Divinorum**

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[REDACTED]

Par la présente, nous vous informons qu'après étude de la plainte que vous nous avez soumise concernant le produit ci-haut mentionné, l'Inspectorat de la Direction générale des produits de santé et des aliments a pris les mesures jugées nécessaires dans ce dossier.

Nous vous remercions d'avoir porté ce cas à notre attention et nous vous prions d'accepter l'expression de nos sentiments les meilleurs.

[REDACTED]

10 janvier 05

Reception d'une plainte téléphonique concernant la Salvia divinorum.

→ Plaignant dit que le produit est dangereux et doit être retiré du marché.

→ 2

→ TQS a été informé

01 mars 2005

[redacted] m'a contacté et m'a donné les renseignements suivants :

→ [redacted] vend la Salvia dans des sachets avec comme étiquette "Encens Special" au prix d'environ \$ 5.00.

→ dans la boutique, on retrouve des pipes pour fumer, linge indien, produit de sexe.

→ au moment où [redacted] a acheté de la Salvia, c'est une vendeuse qui l'a servi.

→ [redacted] est travailleuse de rue (pendant 10 ans) et a déjà consommé du pot, acide, LSD. et prétend que Salvia produit des effets s

2

→ TQS, l'aurait contacté afin de savoir si Santé Canada a pris des actions dans ce dossier.

→ [redacted] (Lon-Mer,

→ [redacted] (Mar-Jew-Ven,

20 avril 2005

→ j'ai fait des recherches sur le Web avec l'adresse du refus douanier de Paul pour importation de 100 Kg de Salvia.

A l'adresse

[redacted]

c'est [redacted] qui apparaît comme étant la personne qui demeure à cette adresse.

→ Recherche dans C.DREQ sur [redacted] et c'est [redacted] qui apparaît comme étant propriétaire.

25 avril 2005

Courriel envoyé à Jimmy + Marie Morissette pour savoir si un HHE a été fait. Si oui, quel est le niveau de risque.

Courriel de Jenny McLaughlin

02 mai 2005

- pas de HHE de fait
- me demande s'il y a des réclames sur l'emballage. ?
- OCS intéressé ?

02 mai 2005

Appel plaignant

- [redacted], elle me mentionne que sa mère n'a pas conservé l'emballage.
  - la seule mention sur l'emballage est "Encens Special One puff"
  - Aucune autre indication sur l'emballage.
- ↳ À la fin, elle me mentionne que de plus en plus de jeunes personnes en achète puisque l'info a été diffusée auprès des jeunes.

06 mai 2005

Courriel de Jenny McLaughlin

- À ce jour, il y a 2 plaintes [redacted] et 1 au [redacted] pour la vente de Solvia Divinorum
- Elle demande sous quelle autorité réglementaire est régi la Solvia

NHP Reg / CDSA / FADR ?  
000064



4  
Counil de Jenny McLaughlin

11 mai 2005

⇒ Elle informe [redacted] qu'elle veut rééduler un meeting avec OCS / inspectat / NHPS et services légers pour déterminer les actions appropriées à prendre en regard à la vente de Salvia Divinorum.

08 sept 2005

J'ai demandé à Jenny s'il y avait de nouveau concernant la Salvia.

Elle me mentionne que pour le moment OCS a placé la Salvia Divinorum sur sa "watch list".

03 NOV 2005

J'ai fait un achat incognito à [redacted] au [redacted], [redacted] de Salvia Divinorum.

Le préposé m'a demandé si je voulais 0,1 / 0,5 ou 1 gramme de Salvia. De plus, il m'a demandé si je voulais de la 5x, 10x, 15x ou 20x. Je lui ai demandé ce que cela signifiait et il m'a répondu que, par exemple, la 5x est 5 fois plus fort que la plante-mère qui est 1x.

Le préposé m'a mentionné que 0,1 gr. équivaut à "1 trip" et que je devrais essayer la 5x ou 10x ~~pour~~ puisque c'est la première fois.

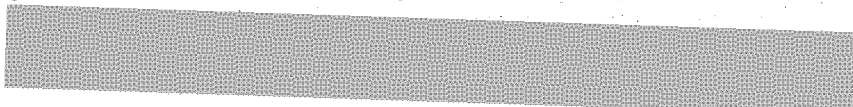
Il m'a indiqué qu'il importait la matière première du Mexique. Rendre il extrait le principe actif de la plante et l'additionne à la plante séchée qui sert de substrat.

j'ai acheté 0,1 gr de Salvia 5X au coût de \$5.00 + TX.

et 0,1 gr de Salvia 10X au coût de \$10.00 + TX.

Sur le coupon de caisse, il est indiqué "Encens".

Sur les sachets, il est indiqué « Salvia Divinorum - Encens Naturel Non destiné à la consommation ». Une adresse internet est également indiquée sur le sachet



## CAUSALITY ASSESSMENTS OF ADVERSE REACTIONS

Updated September 9, 2005  
Draft Subject to revision

**Natural Health Product: *Salvia divinorum***

### **Purpose of the assessment:**

To review the adverse reactions associated with the use of *Salvia divinorum*. (Domestic case reports are reviewed with respect to causality<sup>1</sup> and seriousness<sup>2</sup>.)

### **Date of review commenced:**

May 2005

### **Search Strategy:**

Adverse reactions suspected to be associated with *Salvia divinorum* were sought, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to May 31, 2005)

### **Executive summary:**

There are 4 domestic Canadian case reports of psychological adverse effect associated with the use of *Salvia divinorum* (3 inhaled and 1 oral).

In the one 'serious' case, oral usage was associated with psychosis but alcohol was as significant confounder and the causality was assessed as 'possible'.

One of the inhaled case was assessed as 'probable' but the reaction was not 'serious'.

**Conclusion:** In the serious case, *Salvia* was sold in a drug form, a tablet containing 57 or 72 mg of Salvinorin-A. In this case concomitant use of *Salvia* and alcohol most likely suggests a combined effect.

In the 3 non serious cases, there was disorientation and hallucination after taking one "puff" of *Salvia divinorum*.

**Reviler's comment:** As a clinician, I find it worrisome that *Salvia divinorum* is so readily available for use and misuse by the Canadian public.

*Salvia* is also used in tablet form making it a drug, and is not authorized for sale by Health Canada.

Further evaluation/categorization is needed to regulate *Salvia divinorum*.

### **Medical evaluator(s):**

Dr. T. Desjarlais-Renaud

Dr. M. Murty

Peer reviewed

<sup>1</sup> Based on the WHO causality algorithm unless otherwise specified.

<sup>2</sup> Internal Health Canada document. *Guidelines for reviewing Adverse Drug Reaction Reports*. Date of Revision August 2000.

*A serious adverse drug reaction is defined as: A noxious and unintended response to a drug, which occurs at any dose and requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above may also be considered serious.*

000067

Dr. T. Hall

Source of ADRs	# of cases report	route		psychosis	hallucination disorientation	Causality certain	Causality probable	Causality possible	Serious	Fatal outcome
CADRMP	4	oral	1	1				1	1	0
		inhalation	3		3		1	2	0	0

Summary of Causality Assessment of reaction associated with the use of *Salvia divinorum*

Case ID reporter	Age/gender	Date/Adverse reaction (AR)	Suspect drug/Product name	Route/Dose/Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177866 consumer Jan 12, 2005	27yr/F	-Unknown - Disorientation, hallucination, not recognizing people around her.	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No	Recovered (Effect lasted 5 minutes)	Probable	No

Case summary no 0177866

A 27 year old woman experienced disorientation, not recognizing people in the room, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. Patient reported prior use of mescaline and LSD and that the effect of those were not as bad ("moins pires"). The patient was on no other medications. This is not an unexpected reaction to *Salvia divinorum*. There is no evidence from the case report that she had recently taken other hallucinogenic substances. The causality was assigned as probable. The adverse reaction judged as not serious.

s.19(1)

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Case ID reporter date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177865 consumer Jan 12, 2005	28yr/M	-Unknown -Disorientation, hallucination, - foaming at the mouth	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No -no other medications -past med history - unknown	Recovered (Effect lasted 5 minutes)	Possible	No

Case summary no 0177865

A 28 year old man experienced disorientation, foaming at the mouth, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. There was no concomitant medication. Past medical history is unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.  
The adverse reaction judged as not serious.

s.19(1)

Case ID reporter date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
179969  consumer Feb. 17, 2005	56yr/F	-Unknown -Disorientation, hallucination, does not recognize husband	<i>Salvia divinorum</i> Al sasia encens special	Inhalation	1 puff taken	Unknown	Recovered (total effect 30 minutes)	Possible	No

Case summary no 0179969

A 56 year old woman experienced 30 minutes of disorientation and vivid hallucination after taking 1 puff of *Salvia divinorum*. The reaction was very intense for 10 minutes and then decrease in intensity. The past medical history, concomitant medication and NHP usage are unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.  
The adverse reaction judged as not serious.

Case ID reporter date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
0185128  Consumer (parent)  May 31, 2005	16/M  150lbs	March 29, 2005/ -drug induce psychosis -incoherent -suicidal -restrained -threatened to kill police officers -amnesia (does not remember any of these events) -jailed	Salvia/ aka Maria Pastora	oral/ 1 tablet "the 30\$ pill" 57mg*	single dose	Yes  <u>Concomitant intake of:</u> Alcohol ("few drinks")  <u>Concomitant condition:</u> ADD	Recovered	Possible	Yes

**Case summary no 0185128:**

On March 23, 2005, a 16 year old male experienced drug induced psychosis: was incoherent, was suicidal, needed to be restrained, threatened to kill police officers, was jailed and had amnesia of these events after taking a single tablet of Salvia ( aka Maria Pastra). He had also consume a few drinks of alcohol. He has a underlying ADD but not receiving medication for this. He had previously taken Salvia "on its own" (route of administration unknown) with no adverse reaction.

Additional information obtained through the ADR specialist:

\* Follow up request for more information obtained July 28 2005, confirmed that the tablet was oral "30 \$ pill" purchased "behind the counter" at [REDACTED] in [REDACTED]

This place sells a Salvia 10x containing 57 mg of Salvinorin-A for 29.98\$ and a Salvia 20x containing 72 mg of Salvinorin-A for 39.98\$.

Further information received August 18 2005: When Salvia taken before, it was the same dose (30\$ pill orally). The only thing different was that on previous occasions he did not have alcohol wit it.

This is a case where there was no adverse reaction with previous use of Salvia (same dosage, same distributer, same route of administration) but when associated with alcohol had a severe reaction.

The causality was assigned as possible with alcohol as a confounder.

The adverse reaction was judged as serious because it required intervention.

s.19(1)

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ORIGINAL



# CAUSALITY ASSESSMENTS OF ADVERSE REACTIONS

Updated December 1, 2005  
Draft Subject to revision

**Natural Health Product: *Salvia divinorum***

**Purpose of the assessment:**

To review the adverse reactions associated with the use of *Salvia divinorum*. (Domestic case reports are reviewed with respect to causality<sup>1</sup> and seriousness<sup>2</sup>.)

**Date of review commenced:**

May 2005

**Search Strategy:**

Adverse reactions suspected to be associated with *Salvia divinorum* were sought, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to May 31, 2005)

**Executive summary:**

There are 4 domestic Canadian case reports of psychological adverse effect associated with the use of *Salvia divinorum* (3 inhaled and 1 oral). In the one 'serious' case, oral usage was associated with psychosis but alcohol was as significant confounder and the causality was assessed as 'possible'. The 3 inhaled case were judged to be 'non serious'<sup>3</sup>. One of the inhaled cases was assessed as 'probable'.

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<sup>1</sup> Based on the WHO causality algorithm unless otherwise specified.

<sup>2</sup> Internal Health Canada document. *Guidelines for reviewing Adverse Drug Reaction Reports*. Date of Revision August 2000.

*A serious adverse drug reaction is defined as: A noxious and unintended response to a drug, which occurs at any dose and requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above may also be considered serious.*

<sup>3</sup>\*These 3 reactions could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems is used: "d. concern for misuse or dependence".  
World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

**Conclusion:** In the serious case, Salvia was sold in a drug form, a tablet containing 57 or 72 mg of Salvinorin-A. In this case concomitant use of Salvia and alcohol most likely suggests a combined effect.

In the 3 non serious<sup>3</sup> cases, there was disorientation and hallucination after taking one "puff" of Salvia divinorum.

**Reviewer's comment:**

As a clinician, I find it worrisome that Salvia divinorum is so readily available for use and misuse by the Canadian public.

Salvia is also use in tablet form making it a drug, and is not authorized for sale by Health Canada.

Further evaluation/categorization is needed to regulate Salvia divinorum.

**Medical evaluator(s):**

Dr. T. Desjarlais-Renaud

Dr. M. Murty

Peer reviewed

Dr. T. Hall

Source of ADRs	# of cases report	route		psychosis	hallucination disorientation	Causality certain	Causality probable	Causality possible	Not serious	Serious	Fatal outcome
CADRMP	4	oral	1	1				1		1	0
		inhalation	3		3		1	2	3 <sup>3</sup>	0	0

Summary of Causality Assessment of reaction associated with the use of *Salvia divinorum*

Case ID date received reporter	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177866  consumer  Jan 12, 2005	27yr/F	-Unknown - Disorientation, hallucination, not recognizing people around her.	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No	Recovered (Effect lasted 5 minutes)	Probable	No*

## Case summary no 0177866

A 27 year old woman took *Salvia divinorum* for the purpose of experiencing hallucinations. She experienced disorientation, not recognizing people in the room, hallucinations for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial*, obtained from a boutique called [REDACTED] was inhaled through a pipe. The patient reported prior use of mescaline and LSD and that the effect of those were not as bad. ("moins pires"). The patient was on no other medications nor natural health products. This is not an unexpected reaction to *Salvia divinorum*. In this case there is a concern for misuse.

There is no evidence from the case report that she had recently taken other hallucinogenic substances.

The causality was assigned as 'probable'.

The adverse reaction was judged as 'not serious'.\*

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems<sup>4</sup> is used: "d. concern for misuse or dependence".

<sup>4</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Case ID reporter  date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177865 consumer  Jan 12, 2005	28yr/M	-Unknown -Disorientation, hallucination, - foaming at the mouth	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No -no other medications -past med history - unknown	Recovered (Effect lasted 5 minutes)	Possible	No*

Case summary no 0177865

A 28 year old man took *Salvia divinorum* for the purpose of experiencing hallucinations. He experienced disorientation, foaming at the mouth, and hallucinations for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial*, obtained from a boutique called [REDACTED] was inhaled through a pipe. There was no concomitant medication. Past medical history is unknown. This is not an unexpected reaction to *Salvia divinorum*. In this case there is a concern for misuse.

The causality was assigned as 'possible'.

The adverse reaction judged as 'not serious'.\*

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems<sup>5</sup> is used: "d. concern for misuse or dependence".

<sup>5</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Case ID reporter date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
179969  consumer Feb. 17, 2005	56yr/F	-Unknown -Disorientation, hallucination, does not recognize husband	<i>Salvia divinorum</i> Al sasia encens special	Inhalation	1 puff taken	Unknown	Recovered (total effect 30 minutes)	Possible	No*

Case summary no 0179969

A 56 year old woman experienced 30 minutes of disorientation and vivid hallucinations after taking 1 puff of *Salvia divinorum*. The reaction was very intense for 10 minutes and then decreased in intensity. The past medical history, concomitant medication and NHP usage are unknown. This is not an unexpected reaction to *Salvia divinorum*.

In this case there is a concern for misuse

The causality was assigned as 'possible'.

The adverse reaction was judged as not serious'.

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems<sup>6</sup> is used: "d. concern for misuse or dependence".

<sup>6</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Case ID reporter date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
0185128  Consumer (parent)  May 31, 2005	16/M  150lbs	March 29, 2005/ -drug induce psychosis -incoherent -suicidal - restrained -threatened to kill police officers -amnesia (does not remember any of these events) -jailed	Salvia/ aka Maria Pastora	oral/ 1 tablet "the 30\$ pill" 57mg*	single dose	Yes  <u>Concomitant intake of:</u> Alcohol ("few drinks")  <u>Concomitant condition:</u> ADD	Recovered	Possible	Yes

Case summary no 0185128:

On March 23, 2005, a 16 year old male experienced drug induced psychosis: was incoherent, was suicidal, needed to be restrained, threatened to kill police officers, was jailed and had amnesia of these events after taking a single tablet of Salvia ( aka Maria Pastra). He had also consume a few drinks of alcohol. He has a underlying ADD but not receiving medication for this. He had previously taken Salvia "on its own" (route of administration unknown) with no adverse reaction.

Additional information obtained through the ADR specialist:

\* Follow up request for more information obtained July 28 2005, confirmed that the tablet was oral "30 \$ pill" purchased "behind the counter" at [redacted] in [redacted]. This place sells a Salvia 10x containing 57 mg of Salvinorin-A for 29.98\$ and a Salvia 20x containing 72 mg of Salvinorin-A for 39.98\$.

Further information received August 18 2005: When Salvia taken before, it was the same dose (30\$ pill orally). The only thing different was that on previous occasions he did not have alcohol wit it.

This is a case where there was no adverse reaction with previous use of Salvia (same dosage, same distributor, same route of administration) but when associated with alcohol had a severe reaction.

The causality was assigned as 'possible' with alcohol as a confounder.

The adverse reaction was judged as 'serious' because it required intervention.

[redacted]

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**Original**

## MHPD Risk Management (MHPD-RM)

### Issues Summary Report

[*Salvia divinorum* - a potential drug for abuse]

Date: December 16, 2005

Updated: November 22, 2006

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#### DIVISION:

- |  |   |
|--|---|
| <input type="checkbox"/> Marketed Biologicals & Biotechnology Products               | <input type="checkbox"/> Director General's Office              |
| <input type="checkbox"/> Marketed Health Products Safety & Effectiveness Information | <input type="checkbox"/> Marketed Pharmaceuticals               |
| <input type="checkbox"/> Marketed Medical Devices                                    | <input type="checkbox"/> Policy and Partnerships                |
| <input checked="" type="checkbox"/> Marketed Natural Health Products                 | <input type="checkbox"/> Therapeutic Effectiveness Surveillance |
- 

- Date of presentation at BEC-RM:
- Proposed date to present at BEC-RM:

#### Subject matter:

- Product's trade/generic names- *Salvia divinorum*
- Product class: Natural Health Products
- Main indication(s): used as a hallucinating agent
- Therapeutic class: Natural Health Products
- Status -  marketed  
           not marketed-authorized

#### Early Warning statement:

- *Salvia divinorum* is a plant from the mint family that has been used in traditional and spiritual practices by the Mazatec Indians of Oaxaca, Mexico to produce "mystical" or hallucinogenic experiences. Health Canada has received four reports of adverse reactions associated with the use of *Salvia divinorum*. In addition, there have been several reports (scientific articles, media enquiry/reports) which indicate that *Salvia divinorum* has a potential for abuse, and is being used by adolescents and young adults for its hallucinogenic properties. MHPD of Health Canada will share the issue summary report (ISR), summarizing all the information concerning the health risk associated with *Salvia divinorum* in Canada as well as recommendations for mitigating the risk with other directorates (NHPD, OCS, HPPFBI) and will develop appropriate risk mitigation strategies, if deemed necessary.

#### Background provided by which Officer/Directorate:

- Shahid Perwaiz, MNHPD, MHPD

#### What is the issue?

- The Canadian Adverse Reaction Information System (CADRIS) has received four reports of adverse reactions (ARs) associated with the use of *Salvia divinorum* or its active constituents. All of these ARs involved psychotropic effects.



- A recently published article (Dennehy et al., 2005) has reported *Salvia divinorum* to be one of the most prevalent marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults.
- Recently, the media has shown interest in the issue of *Salvia divinorum*, specifically its presence on the market as a legal alternative to illicit drugs (<http://www.radio-canada.ca/radio/sansfrontieres/66659.shtml>).
- This information (case reports, media interest and publications) triggered MNHPD to review the safety of *Salvia divinorum*, and to provide recommendations to mitigate the potential risk of abuse associated with *Salvia divinorum* use.

#### Why is this an issue?

- Salvinorin A is a constituent of *Salvia divinorum*, and is a powerful naturally-occurring non-nitrogenous hallucinogen that stimulates kappa-opioid receptors (KOR) (Chavkin et al., 2004). A minimum dose of 200-500 µg of purified salvinorin A, or 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled (Bucheler et al., 2005).
- *Salvia divinorum*, or its active constituents, are neither listed in any schedule to the *Controlled Drugs and Substances Act*, nor any schedule of the *Food and Drugs Act and Regulations*. Therefore, some on-line botanical companies and drug promotional sites ([www.salviasupply.com](http://www.salviasupply.com) , [www.wellcoolstuff.com](http://www.wellcoolstuff.com) , [www.salvia-divinorum.com](http://www.salvia-divinorum.com) , [www.sagewisdom.com](http://www.sagewisdom.com) , etc.) have advertised *Salvia divinorum* as a legal alternative to illicit drugs.
- In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long-term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the uniform Schedule of Drugs & Poisons. (TGA, 2002). In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of a psychoactive drug (Bucheler et al., 2005). The American Drug Enforcement Agency (DEA) has also placed *Salvia divinorum* on a list of drugs and chemicals "of concern," without legal implications (US DEA, 2002).
- Out of the 4 ARs reported to Health Canada, 3 cases involving inhalation were associated with hallucinogenic effects, and were considered to be non-serious reactions. The fourth case, however, was considered serious, and was associated with the oral use of the chemical constituent salvinorin A. As well, it should be noted that in this case-report, salvinorin A was consumed in a drug form (tablets containing 57 or 72 mg of salvinorin A) which now potentially becomes an unapproved health product offered for sale on the Canadian market.

Total number of cases	4
Route of exposure	Oral (1) & Inhalation (3)
Age range	16 yrs - 56 yrs
Gender	2 male, 2 female

Causality	oral - 1 possible; inhalation - 2 possible, 1 probable
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**Please see Appendix B for the detailed causality assessment report.**

- Recently, an international case report of *Salvia divinorum* poisoning was published in a scientific journal, in which a young man (19 years of age) described his perceptions after inhaling *Salvia divinorum*. The peak of psychotropic effects, including prickling of the skin, fever-like hot flashes, muscular tremor, and depersonalization, were reached in less than five minutes after inhalation of dried leaves of *Salvia divinorum* (Bucheler et al., 2005).
- Various studies have claimed that the psychotropic effects of *Salvia divinorum* closely resemble the symptoms of schizophrenia induced by other drugs such as LSD, phencyclidine or ketamine. Open field testing has also indicated that salvinorin A has a potency equivalent to that of mescaline (Hansen et al., 1988; Javitt and Zukin, 1991; Valdes, 1994).
- There has been a growing trend of cultivation of *Salvia divinorum* observed in South and North America as well as in Europe. Recently, several authors warned that *Salvia divinorum* might become a new recreational drug (Bucheler et al., 2005; Giroud et al., 2000; Halpern, 2004).
- On November 16, 2006, Le Journal de Montréal published a report entitled “Un hallucinogène légal Santé Canada a cependant la *Salvia divinorum* à l'oeil” which indicated that Health Canada is evaluating the possibility of imposing restrictions over the sale and use of *Salvia divinorum*, similar to those of certain countries. Given that *Salvia* does not have long-term adverse effects or the risk of dependence, the article suggests that Health Canada does not consider the short-term hallucinogenic effects to be sufficiently significant health risks to impose restrictions over its sale. In fact, according to the article, *Salvia divinorum* has been sold in certain Quebec retail outlets since 2000, as a hallucinogen. The article quotes an RCMP officer in saying that prevention of *Salvia divinorum*'s use is necessary. Additionally, the article quotes Jean-Sébastien Roy, in saying that Quebec's law enforcers' hands are tied because Health Canada has not categorized *Salvia divinorum* as a controlled substance, despite its effects being comparable to the illicit drugs cannabis and LSD. Additionally, he indicated that if an individual were stopped for erratic driving under *Salvia divinorum*'s influence, they would be charged for driving while impaired.
- On October 6, 2006, the HPFBI Ontario Region received an enquiry from MP Joe Preston's office (Elgin-Middlesex, London, Ontario riding). A constituent inquired why the hallucinogenic product, *Salvia divinorum*, was available as an over-the-counter product.

#### **Who is involved?**

- MNHPD, NHPD, HPFBI and the Office of Controlled Substances (OCS, HECS Branch)

#### **What action has been taken?**

- Neither *Salvia divinorum* nor its active constituent (Salvinorin A) have been authorised for sale in Canada, as confirmed by the Natural Health Products Directorate (NHPD) and TPD's Submission & Information Policy Division (SIPD).

- CADRIS has confirmed four case reports of poisoning associated with *Salvia divinorum* in Canada.
- HC has drafted an issue analysis summary (IAS) on the issue of health risks associated with the use of *Salvia divinorum* and its regulation in Canada (see Appendix A).
- Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, Health Canada will work with its partners, including law enforcement agencies and international counterparts to collect relevant information on this herb".
- A Customs Lookout is already in place to restrict the importation of *Salvia divinorum* .
- Additionally, HC has conducted causality assessments on the four Canadian ADRs associated with *Salvia divinorum* use. There are 4 domestic Canadian case reports of psychological adverse effect associated with the use of *Salvia divinorum* (3 inhaled and 1 oral). In the one 'serious' case, oral usage was associated with psychosis but alcohol was as significant confounder and the causality was assessed as 'possible'. The 3 inhaled case were judged to be 'non serious. One of the inhaled cases was assessed as 'probable' (see Appendix B).

#### **What are the key activities and time line?**

- Health Canada will continue to monitor the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the internet, as well as through contacts with other Regulatory organizations and will share this information with OCS for their further regulatory actions.
- Based on all information received, Health Canada will assess the potential for regulatory control of *Salvia divinorum* and will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its sale and use
- An anticipatory QP note on this issue has been finalized on November 22, 2006.

#### **MNHPD's recommendation:**

Health Canada has received four domestic case reports of adverse reactions (ARs) associated with the use of *Salvia divinorum* (3 inhaled and 1 oral). Out of 4 ARs, one oral case was assessed as serious reaction, and other 3 inhaled cases were judged to be non serious. Since the 4 Canadian reports of adverse reaction associated with the *Salvia divinorum* use are all recent, this may further confirm a new trend in the use of this hallucinogenic plant in Canada. Although it is important to note that accumulated case reports cannot be used to determine the incidence of a reaction nor the risk of a product, since the total number of reactions, occurring and the number of people taking the product, is unknown

The Health Products and Food Branch of Health Canada will continue to collect relevant information concerning these, and other potential signals to determine whether or not risk mitigation strategies are required. This issue will be brought to the attention of the OCS, HECS Branch, for potential action. The OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada.

Although *Salvia divinorum* is on the watch list of the OCS, it may be appropriate to restrict *Salvia divinorum* and its active constituents by adding these to appropriate schedules under the *Controlled Drugs and Substances Act*.

**Additional information/attachment (specify):**

Appendix A: IAS prepared by NHPD and MHPD.

Appendix B: Causality Assessments of Adverse Reactions associated with use of *Salvia divinorum*, conducted by MHPD.

**Peer-reviewed By:** Dr. Scott Jordan, MHPD

Date: Nov. 28, 2005.

Date: Dec. 7, 2005.

Date: Dec. 14, 2005.

**Peer-reviewed By:** Dr. Jenna Griffiths, MHPD

Date: Nov. 29, 2005.

**Approved By:** Dr. Mano Murty

**Date:** December 16, 2005

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## **APPENDIX A:**

### **NHPD AND MHPD ISSUE ANALYSIS SUMMARY** ***Salvia divinorum* Regulatory Authority and Health Risks**

**Prepared by:** Jacinta Roberts and Robin Marles, NHPD, and Shahid Perwaiz, MHPD

**Draft Date:** June 24, 2004

**Draft Revised:** July 15, 2004

**Finalized:** July 15, 2004

**Updated:** October 17, 2006

#### **ISSUES**

1. Which regulatory authority is most appropriate for *Salvia divinorum* under various conditions of use?
2. What are the risks to consumers of this substance?

#### **BACKGROUND AND ISSUE ANALYSIS**

##### ***Salvia divinorum* as a Health Product**

*Salvia divinorum* Epling & Játiva is an herb in the mint family (Lamiaceae), native to Mexico, that is smoked as a hallucinogen. As a substance it falls under Item 1 of Schedule 1 (inclusion list) to the *Natural Health Products Regulations*, which includes: "a plant or plant material, an alga, a bacterium, a fungus or a non-human animal material."

The main active ingredient of *Salvia divinorum* is a neoclerodane diterpene compound called salvinorin A, which currently falls under Schedule 1, item 2: "an extract or isolate of a substance described in item 1, the primary molecular structure of which is identical to that which it had prior to its extraction or isolation."

In Canada neither the herb, *Salvia divinorum*, nor its active ingredients, such as salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* (CDSA), nor any Schedule of the *Food and Drugs Act* or its Regulations that would remove it from the purview of the *Natural Health Products Regulations*.

*Salvia divinorum* and its active constituents therefore meet the substance aspect of the regulatory definition of a natural health product.

Whether or not *Salvia divinorum* products meet the function aspect of the regulatory definition of a natural

health product depends on the purpose for which the product is being manufactured, sold, or represented for use. According to Section 1(1) of the *Natural Health Products Regulations*, a natural health product means a substance that is manufactured, sold, or represented for use in:

- (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- (b) restoring or correcting organic functions in humans; or
- (c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

*Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/ constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1982).

With respect to potential modern uses, there is one human case study from Australia suggesting a possible antidepressant effect (Hanes 2001).

Since *Salvia divinorum* and salvinorin A under some conditions of use meet both the functional and substance portions of the definition of a natural health product and are not currently subject to any regulatory exclusions, if associated with a health claim finished products containing these substances could be considered to be natural health products (NHPs).

Until such time as the herb and its active constituent are scheduled under the CDSA or Schedule F to the *Food and Drug Regulations*, the NHPD has jurisdiction to receive a Product Licence Application for a therapeutic use. However, the safety assessment will be sufficiently rigorous to protect consumers' health, particularly with respect to the following safety factors:

- "Does the medicinal ingredient or product have a demonstrated potential for addiction, abuse or severe dependency that is likely to lead to harmful non-medicinal use?"
- "Does the medicinal ingredient or product have known adverse effects at the recommended or therapeutic dosage level?"
- "Does the medicinal ingredient or product have a therapeutic effect based on recently established pharmacological concepts, the consequences of which have not yet been fully established?"
- "Does the medicinal ingredient or product possess a high level of risk relative to expected benefits?"

The answers to these questions are as follows:

- Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in way that is quite different from other hallucinogens such as heroin or LSD.
- Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions.
- It is subject to abuse as a street drug.
- It acts on the brain in a way that is quite novel and for which the consequences have not yet been fully established.

For all those reasons, the risks of *Salvia divinorum* use compared to any expected benefits suggest that if it were to be regulated as a health product, it should require a prescription under the *Food and Drug Regulations*, rather than being regulated as an over-the-counter natural health product.

### ***Salvia divinorum as a Hallucinogen***

As with many other NHP substances, there are other uses for the herb that may in future be more

appropriately regulated under a different framework.

*Salvia divinorum* is used as a hallucinogen in traditional divination rituals (Valdés et al. 1982) and is being widely touted on internet sites aimed at young adults and adolescents as a “legal” alternative street drug.

The current use and advertising of *Salvia divinorum* as a recreational hallucinogen does not meet the intent of the function component of the *Natural Health Products Regulations*' definition of a natural health product. Nevertheless, even if it is being sold without labelled claims as leaf material in a plastic baggy, it is being represented for use in “modifying organic functions in humans” so from a compliance perspective *Salvia divinorum* falls under the jurisdiction of the *Food and Drugs Act*.

As a hallucinogen and drug of abuse, Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances will collect relevant information specific to this herb and its active constituents.

### ***Salvia divinorum in Other Regulatory Jurisdictions***

In the U.S. Congress, *Salvia divinorum* was the subject of a bill (H.R.5607) entitled “To amend the Controlled Substances Act to place Salvinorin A in Schedule I” introduced on October 10, 2002, seeking to place the herb and its active constituent salvinorin A onto U.S. Controlled Substances Act Schedule 1 (drugs or other substances with a high potential for abuse, with no currently accepted medical use in treatment in the United States, and with respect to which there is a lack of accepted safety for use under medical supervision). Since November 11, 2002, the bill has been referred to the Subcommittee on Crime, Terrorism, and Homeland Security (<http://thomas.loc.gov/cgi-bin/bdquery/z?d107:HR05607:@@@L&summ2=m&>, accessed June 24, 2004). Currently, the FDA considers street drug alternatives such as *Salvia divinorum* to be unapproved new drugs and misbranded drugs under sections 505 and 502 of the Act (<http://www.fda.gov/cder/guidance/3602fnl.pdf>, accessed May 26, 2004) and has issued warning letters to a number of firms. Thus it appears that the U.S. has sufficient regulatory authority already to achieve the necessary level of control.

Both the herb and the active ingredient are listed on Schedule 9 of Australia's Standard for the Uniform Scheduling of Drugs and Poisons on the basis of “high potential for abuse and risk to public health and safety,” but no substantiation of this risk was provided (<http://www.tga.health.gov.au/ndpsc/record/rr200111upd8.pdf>, accessed May 26, 2004). They are both also in Category B of the Danish list of controlled substances (<http://www.retsinfo.dk/delfin/html/b2003/0071405.htm>, accessed May 26, 2004).

### ***Scientific Details of the Potential of Salvia divinorum for Abuse***

*Salvia divinorum* is smoked to induce visual hallucinations, the diversity of which are described by its users to be similar to those induced by other hallucinogens such as mescaline or psilocybin. Since neither *Salvia divinorum* nor any of its active ingredients are specifically listed in the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act* or its Regulations in Canada, some on-line botanical companies and drug promotional sites have advertised the herb as a legal alternative to other plant hallucinogens like mescaline. The objective of this section is to provide background on whether or not *Salvia divinorum* has the potential to induce dependence effects.

Salvinorin A (there are B and C forms) is a hallucinogen when vaporized and inhaled. Salvinorin A is a highly efficacious  $\kappa$ -opioid receptor agonist of clinical interest for treatment and etiological studies of

depression, dementia, bipolar disorder, and schizophrenia (Chavkin et al. 2004, Roth et al. 2002). Chemically, salvinorin A is a psychotropic diterpenoid.

Other plants with similar properties include *Cannabis sativa*, which contains the phenolic active principle, tetrahydrocannabinol (THC), and *Artemisia absinthium*, also known as wormwood and used to make the liqueur asbinthe, which contains the monoterpene active principle, thujone.

A dose of 200 to 500 micrograms of salvinorin A produces profound hallucinations when smoked. Its effects in the open field test in mice and locomotor activity tests in rats are similar to those of mescaline. A large body of evidence links the action of hallucinogenic agents (LSD, mescaline) to effects at serotonin (5-HT) receptor sites in the central nervous system (Aghajanian and Marek 1999). Salvinorin A's actions in the brain are not well elucidated. However, recent tissue testing (in vitro assays) have suggested that salvinorin A acts at the kappa opiate receptor site (Chavkin et al. 2004; Valdes 1994; Roth et al. 2002). Effects associated with kappa opioid receptor activation include analgesia, sedation, and dysphoria (Barker et al. 2002). Using in vitro methods, Margolis et al. (2003) have found evidence that the mechanism of action of kappa opiate receptor agonists may involve direct inhibition of midbrain (ventral tegmental area) dopaminergic neurons that play a critical role in motivation and reinforcement of goal-directed behaviours, and have also been implicated in the addictive process initiated by drugs such as morphine.

Drug dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal; it can be of two types, physical and/or psychological dependence. The existence of three major groups of opioid receptors (mu, delta and kappa) in the central nervous system is well documented (Suzuki and Misawa 1997). There are complicated interactions among opioid receptor types. The activation of the kappa opioid receptor suppresses physical and psychological dependence on mu and delta opioid receptor agonists, but the activation of the delta opioid receptor potentiates the dependence on mu opioid receptor agonists. Various studies provide arguments to support substantial roles for mu-opioid receptors and the possible involvement of delta-opioid receptors in the development of physical and psychological dependence on morphine (Narita et al. 2001; Suzuki and Misawa 1997).

Most of the drugs used clinically that are mu-opioid analgesics are habit-forming. While both receptor types (delta and mu) provide analgesia, only the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dextromethorphan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor (Gaveriaux-Ruff and Kieffer 2002; Narita et al. 2001; Pasternak 2003; Suzuki and Misawa 1997). From behavioural, biochemical and molecular biological studies, it is suggested so far that development of physical dependence on morphine results predominantly from an activation of mu 1 and mu 2 opioid receptors which cause functional changes in Gi/o, adenylate cyclase, protein kinases A and C, beta-adrenoceptor and NMDA receptor in the locus coeruleus. However, activation of the mesolimbic dopamine system may lead to psychological dependence on opioids (Narita et al. 2001; Suzuki and Misawa 1997).

It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect, i.e. dysphoria rather than euphoria (Kumor et al. 1986; Rothman et al. 2000). Recently, there have been significant advances in studies on the role of kappa opioid receptor agonists in producing an aversive effect of other stimulants such as morphine, cocaine, THC, alcohol, and in other non-opioid addictions (Cui et al. 2000; Hahn et al. 2000; Collins et al. 2001; Mori et al. 2002; Raffa et al. 2003; Rosin et al. 1999; Rothman et al. 2000; Schenk et al. 1999; Tao et al. 1994). The activation of kappa-receptors also leads to the suppression of unpleasant mu/delta-mediated



side effects such as dependence and respiratory depression. Considering the functional interaction between opioid receptor types, the co-administration of morphine-like compounds with kappa-receptor agonists may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

Salvinorin A is unique in that it is a potent, non-nitrogenous, selective kappa opioid agonist distinct in its actions from other known opioid agonists. Therefore, it appears to be devoid of the mainly mu receptor-mediated side effects such as dependence and respiratory depression associated with morphine and its other analogues. It may thus be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, depression, and even excessive marijuana use. Being defined by its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

In conclusion, on the basis of available scientific literature, the potential addiction or dependence effects of *Salvia divinorum* are expected to remain very low because of the following:

- Most of the drugs which cause dependence and addiction are mu-opioid agonists, while salvinorin A acts as a full agonist at kappa opioid receptors and appears to possess no mu opioid receptor activity.
- Kappa opioid receptor agonists are characterized as being able to modulate dependence-related behavioural effects of drugs like morphine and cocaine rather than causing dependence.
- There have been no cases of dependence on *Salvia divinorum* or salvinorin A reported in the scientific literature.
- The precise mechanism of interaction between salvinorin A and the brain to produce its hallucinogenic effects remains unclear.
- The toxicity of salvinorin A is relatively low, even at doses many times greater than what humans are exposed to (Mowry et al., 2003).
- Many individuals have reported experiencing negative effects (bitter taste, unpredictable and occasionally disturbing short-term mental effects) during their first experience with *Salvia divinorum* and indicate that they would not use it a second time.

#### ***Canadian Reports of Adverse Reactions to Salvia divinorum Products***

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with products said to contain *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum* products. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of tablets said to contain *Salvia divinorum* and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

#### **PRESENT HEALTH CANADA ACTIONS:**

1. Adverse reactions to *Salvia divinorum* or salvinorin A reported through the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) and those reported in the United States and other jurisdictions are being monitored continuously, recognizing that it is unlikely that adverse reaction reports for these

substances will be adequately documented due to *Salvia divinorum*'s use primarily as an hallucinogen. Some information might also be available from Poison Control Centres but there is apparently no uniform means for communication between Poison Control Centres at this time.

2. Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances is collecting relevant information specific to this herb and its active constituents.

3. A Customs Lookout is already in place and should be continued to restrict importation.

4. *Salvia divinorum* and its active principles are being represented for use in modifying organic functions in humans and are therefore classified as health products that fall under the jurisdiction of the *Food and Drugs Act*. To protect the health of Canadians, they are subject to compliance actions by the Health Products and Food Branch Inspectorate in accordance with their Policy 0001.

#### NEXT STEPS:

1. If the information collected warrants further action, the Office of Controlled Substances will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedule of the *Controlled Drugs and Substances Act*. These criteria include:

- international requirements and trends in control/scheduling;
- chemical and pharmacological similarity to other drugs listed in the CDSA;
- dependence potential;
- likelihood of abuse/misuse;
- extent of abuse/misuse in Canada;
- danger to public health and safety, and
- legitimate use in Canada.

2. If *Salvia divinorum* is added to one of the Schedules to the *Controlled Drugs and Substances Act* it will become subject to compliance actions by the federal, provincial, and municipal police forces instead of the HPFB Inspectorate.

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## APPENDIX B

### *Salvia divinorum* and Adverse Drug Reactions: Causality Assessments:

#### CAUSALITY ASSESSMENTS OF ADVERSE REACTIONS

Updated December 1, 2005

#### Draft Subject to revision

Natural Health Product: *Salvia divinorum*

#### Purpose of the assessment:

To review the adverse reactions associated with the use of *Salvia divinorum*. (Domestic case reports are reviewed with

respect to causality<sup>1</sup> and seriousness<sup>2</sup>.) **Date of review commenced:**  
May 2005

**Search Strategy:**

Adverse reactions suspected to be associated with *Salvia divinorum* were sought, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to May 31, 2005)

**Executive summary:**

There are 4 domestic Canadian case reports of psychological adverse effect associated with the use of *Salvia divinorum* (3 inhaled and 1 oral).

In the one 'serious' case, oral usage was associated with psychosis but alcohol was as significant confounder and the causality was assessed as 'possible'.

The 3 inhaled case were judged to be 'non serious'<sup>3</sup>. One of the inhaled cases was assessed as 'probable'.

**Conclusion:** In the serious case, *Salvia* was sold in a drug form, a tablet containing 57 or 72 mg of Salvinorin-A. In this case concomitant use of *Salvia* and alcohol most likely suggests a combined effect.

In the 3 non serious<sup>3</sup> cases, there was disorientation and hallucination after taking one "puff" of *Salvia divinorum*.

**Reviewer's comment:**

As a clinician, I find it worrisome that *Salvia divinorum* is so readily available for use and misuse by the Canadian public.

*Salvia* is also use in tablet form making it a drug, and is not authorized for sale by Health Canada.

Further evaluation/categorization is needed to regulate *Salvia divinorum*.

**Medical evaluator(s):**

Dr. T. Desjarlais-Renaud

Dr. M. Murty

Peer reviewed

Dr. T. Hall

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<sup>1</sup> Based on the WHO causality algorithm unless otherwise specified.

<sup>2</sup> Internal Health Canada document. *Guidelines for reviewing Adverse Drug Reaction Reports*. Date of Revision August 2000.

*A serious adverse drug reaction is defined as: A noxious and unintended response to a drug, which occurs at any dose and requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above may also be considered serious.*

<sup>3</sup>\*These 3 reactions could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems is used: "d. concern for misuse or dependence".

World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Source of ADRs	# of cases reported	route		psychosis	hallucination disorientation	Causality certain	Causality probable	Causality possible	Not serious	Serious	Fatal outcome
		oral									
CADRMP	4	oral	1	1				1		1	0
		inhalation	3		3		1	2	33	0	0

**Summary of Causality Assessment of reaction associated with the use of *Salvia divinorum***

Case ID date received reported	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177866  consumer  Jan 12, 2005	27yr/F	-Unknown - Disorientation, hallucination, not recognizing people around her.	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No	Recovered (Effect lasted 5 minutes)	Probable	No*

Case summary no 0177866

A 27 year old woman took *Salvia divinorum* for the purpose of experiencing hallucinations. She experienced disorientation, not recognizing people in the room, hallucinations for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial*, obtained from a boutique called [REDACTED], was inhaled through a pipe. The patient reported prior use of mescaline and LSD and that the effect of those were not as bad ("moins pires"). The patient was on no other medications nor natural health products. This is not an unexpected reaction to *Salvia divinorum*. In this case there is a concern for misuse.

There is no evidence from the case report that she had recently taken other hallucinogenic substances.

The causality was assigned as 'probable'.

The adverse reaction was judged as 'not serious'.\*

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal

medicines in pharmacovigilance systems<sup>4</sup> is used: “d. concern for misuse or dependence”.

---

<sup>4</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.



Case ID reporter date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177865 consumer Jan 12, 2005	28yr/ M	-Unknown -Disorientation, hallucination, - foaming at the mouth	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No -no other medications -past med history - unknown	Recovered (Effect lasted 5 minutes)	Possible	No*

Case summary no 0177865

A 28 year old man took *Salvia divinorum* for the purpose of experiencing hallucinations. He experienced disorientation, foaming at the mouth, and hallucinations for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial*, obtained from a boutique called [REDACTED] was inhaled through a pipe. There was no concomitant medication. Past medical history is unknown. This is not an unexpected reaction to *Salvia divinorum*. In this case there is a concern for misuse.

The causality was assigned as 'possible'.  
The adverse reaction judged as 'not serious'.\*

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal

medicines in pharmacovigilance systems<sup>5</sup> is used: “d. concern for misuse or dependence”.

---

<sup>5</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Case ID reporter date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
179969  consumer Feb. 17, 2005	56yr/F	-Unknown -Disorientation, hallucination, does not recognize husband	<i>Salvia divinorum</i> Al sasia encens special	Inhalation	1 puff taken	Unknown	Recovered (total effect 30 minutes)	Possible	No*

Case summary no 0179969

A 56 year old woman experienced 30 minutes of disorientation and vivid hallucinations after taking 1 puff of *Salvia divinorum*. The reaction was very intense for 10 minutes and then decreased in intensity. The past medical history, concomitant medication and NHP usage are unknown. This is not an unexpected reaction to *Salvia divinorum*.

In this case there is a concern for misuse

The causality was assigned as 'possible'.

The adverse reaction was judged as not serious'.

\*This reaction could be judged as 'serious' if the definition for 'serious adverse event' suggested in WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems<sup>6</sup> is used: "d. concern for misuse or dependence".

<sup>6</sup>World Health Organization. Part II Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (The Uppsala Monitoring Centre, Uppsala, Sweden, 2000). In *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. France: World Health Organization; 2004:15.

Case ID reporter date received	Age/ gender	Date/Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
0185128  Consumer (parent)  May 31, 2005	16/M  150lbs	March 29, 2005/ -drug induce psychosis -incoherent -suicidal - restrained -threatened to kill police officers -amnesia (does not remember any of these events) -jailed	Salvia/ aka Maria Pastora	oral/ 1 tablet "the 30\$ pill" 57mg*	single dose	Yes  <u>Concomitant intake of:</u> Alcohol ("few drinks")  <u>Concomitant condition:</u> ADD	Recovered	Possible	Yes

Case summary no 0185128:

On March 23, 2005, a 16 year old male experienced drug induced psychosis: was incoherent, was suicidal, needed to be restrained, threatened to kill police officers, was jailed and had amnesia of these events after taking a single tablet of Salvia ( aka Maria Pastra). He had also consume a few drinks of alcohol. He has a underlying ADD but not receiving medication for this. He had previously taken Salvia "on its own" (route of administration unknown) with no adverse reaction.

Additional information obtained through the ADR specialist:

\* Follow up request for more information obtained July 28 2005, confirmed that the tablet was oral "30 \$ pill" purchased "behind the counter" at [redacted] in [redacted]. This place sells a Salvia 10x containing 57 mg of Salvinorin-A for 29.98\$ and a Salvia 20x containing 72 mg of Salvinorin-A for 39.98\$. Further information received August 18 2005: When Salvia taken before, it was the same dose (30\$ pill orally). The only thing different was that on previous occasions he did not have alcohol with it.

This is a case where there was no adverse reaction with previous use of Salvia (same dosage, same distributor, same route of administration) but when associated with alcohol had a severe reaction.

The causality was assigned as 'possible' with alcohol as a confounder.

The adverse reaction was judged as 'serious' because it required intervention.

[redacted]

C:\WINNT\Temp\notes26B5FA\ISR- Salvia divinorum- Nov 22, (updated), 2006 .wpd



**Shahid Perwaiz**  
2005-11-28 10:57 AM

To: Robin Marles/HC-SC/GC/CA  
cc: Duc Vu/HC-SC/GC/CA, Jenna Griffiths/HC-SC/GC/CA, Scott  
Jordan/HC-SC/GC/CA, Mano Murty/HC-SC/GC/CA  
Subject: Re: Silvia divinorum-Fw: FYI - Q.P. Transcripts - November 25

Good morning Dr. Robin,  
Would it be possible for you to send us the most recent version of the IAS prepared on the *Salvia*  
*divinorum* issue?  
Thank you in advance!  
shahid  
Jenna Griffiths



**Jenna Griffiths**  
2005-11-28 09:48 AM

To: Robin Marles/HC-SC/GC/CA@HWC  
cc: Patricia Maynard/HC-SC/GC/CA@HWC, Marie  
Morrisey/HC-SC/GC/CA@HWC, Chris Turner/HC-SC/GC/CA@HWC,  
Duc Vu/HC-SC/GC/CA@HWC, Julia Hill/HC-SC/GC/CA@HWC, Mano  
Murty/HC-SC/GC/CA@HWC, Mark Korchinski/HC-SC/GC/CA@HWC,  
Ouassim Meguellati/HC-SC/GC/CA@HWC, Patrice  
Lemyre/HC-SC/GC/CA@HWC, "Scott Jordan"  
<scott\_jordan@hc-sc.gc.ca>, "Shahid Perwaiz"  
<shahid\_perwaiz@hc-sc.gc.ca>, Thérèse  
Desjarlais-Renaud/HC-SC/GC/CA@HWC, Trudy  
Hall/HC-SC/GC/CA@HWC  
Subject: Re: Silvia divinorum-Fw: FYI - Q.P. Transcripts - November 25

Thanks Robin.

Shahid will finish his ISR (which we'll circulate shortly), and then he'll formulate an anticipatory QP.

Thanks.  
Jenna  
Robin Marles

**Robin Marles**  
11/26/2005 12:36 PM

To: Mano Murty/HC-SC/GC/CA@HWC  
cc: Chris Turner/HC-SC/GC/CA@HWC, Duc Vu/HC-SC/GC/CA@HWC,  
"Jenna Griffiths" <jenna\_griffiths@hc-sc.gc.ca>, Mark  
Korchinski/HC-SC/GC/CA@HWC, "Scott Jordan"  
<scott\_jordan@hc-sc.gc.ca>, "Shahid Perwaiz"  
<shahid\_perwaiz@hc-sc.gc.ca>, Thérèse  
Desjarlais-Renaud/HC-SC/GC/CA@HWC, Trudy  
Hall/HC-SC/GC/CA@HWC, Julia Hill/HC-SC/GC/CA@HWC, Patrice  
Lemyre/HC-SC/GC/CA@HWC, Ouassim  
Meguellati/HC-SC/GC/CA@HWC  
Subject: Re: Silvia divinorum-Fw: FYI - Q.P. Transcripts - November 25

Actually the Office of Controlled Substances has the lead on the *Salvia* *divinorum* issue since it is not a  
health product but a street drug.

Although we are NOT the lead, since MHPD and NHPD were coauthors of the original issue analysis, we  
will be happy to cooperate with MHPD on any necessary revisions to your ISR.

Robin.  
Mano Murty



**Mano Murty**

To: Duc Vu/HC-SC/GC/CA@HWC



11/25/2005 02:47 PM

cc: Chris Turner/HC-SC/GC/CA@HWC, "Jenna Griffiths" <jenna\_griffiths@hc-sc.gc.ca>, Mark Korchinski/HC-SC/GC/CA@HWC, "Robin Marles" <robin\_marles@hc-sc.gc.ca>, "Scott Jordan" <scott\_jordan@hc-sc.gc.ca>, "Shahid Perwaiz" <shahid\_perwaiz@hc-sc.gc.ca>, Trudy Hall/HC-SC/GC/CA@HWC, Thérèse Desjarlais-Renaud/HC-SC/GC/CA@HWC  
Subject: Re: Silvia divinorum-Fw: FYI - Q.P. Transcripts - November 25

Hi Duc

Just a note to let you know that Shahid is working on this and formatting into an ISR. I am informed that NHPD has the lead on this. I will check if there are QP notes on this issue and if not, proceed in this direction.  
Mano

Duc Vu

Duc Vu  
2005-11-25 01:48 PM

To: "Jenna Griffiths" <jenna\_griffiths@hc-sc.gc.ca>, "Mano Murty" <mano\_murty@hc-sc.gc.ca>, "Shahid Perwaiz" <shahid\_perwaiz@hc-sc.gc.ca>, "Scott Jordan" <scott\_jordan@hc-sc.gc.ca>, Mark Korchinski/HC-SC/GC/CA@HWC, Trudy Hall/HC-SC/GC/CA@HWC, "Robin Marles" <robin\_marles@hc-sc.gc.ca>  
cc: Chris Turner/HC-SC/GC/CA@HWC  
Subject: Silvia divinorum-Fw: FYI - Q.P. Transcripts - November 25

Hi colleagues

Please note there was a Question related to *salvia divinorum* at QP

Hi Shahid

What is the status of the updated document on *salvia divinorum*? We need to share with our colleagues in NHPD, Office of Controlled Substances, and HPFB-I on new information received (ie AR of *salvia divinorum* "pills" in Canada, recent articles indicated that *salvia divinorum* is one of the most abused herb etc.)

-----  
Sent from my BlackBerry Wireless Handheld  
Louise Carriere

**From:** Louise Carriere  
**Sent:** 11/25/2005 01:25 PM  
**To:** MHPD\_DPSC\_Management  
**Cc:** MHPD\_DPSC\_MC\_Assistants  
**Subject:** FYI - Q.P. Transcripts - November 25

----- Forwarded by Louise Carriere/HC-SC/GC/CA on 2005-11-25 01:24 PM -----




Murielle Weiler  
2005-11-25 01:04 PM

To: HPFB\_QP\_Coordinators  
cc:  
Subject: Q.P. Transcripts - November 25

FYI

Murielle Weiler  
HPFB/ADMO  
952-6161

----- Forwarded by Murielle Weiler/HC-SC/GC/CA on 2005-11-25 01:04 PM -----

 **Nicholas R Brown**  
2005-11-25 12:34 PM

To: PRO-QP Transcripts  
CC:  
Subject: Q.P. Transcripts - November 25



During today's Question Period proceedings, four health-related questions were raised.  
Please find attached today's Q.P. transcripts.

- **Larry Miller (CPC)** raised a question dealing with Aboriginal Health Services.  
The question was taken by the **Parliamentary Secretary, Robert Thibault.**



Miller to Thibault (Aboriginal Health Services) NOV 2

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Fletcher to Thibault (Health Care Services X2) NOV 2

- **Denise Poirier-Rivard (BQ)** raised a question dealing with **Salvia Divinorum**.  
The question was taken by the **Parliamentary Secretary, Robert Thibault.**



Poirier-Rivard to Thibault (Salvia Divinorum) NOV 2

Bonne journée!

Thank you,

Nicholas R. Brown  
Parliamentary Relations Officer / Agent des relations parlementaires  
Parliamentary Relations Office / Bureau des relations parlementaires  
Health Canada / Santé Canada  
Tel: 952-6956  
Fax: 941-0608





Robin Marles  
2006-10-17 04:30 PM

To: Julie Desrosiers/HC-SC/GC/CA@HWC  
cc:  
Subject: Re: FOR URGENT DG APPROVAL: MEDIA RESPONSES ON SALVIA DIVINORUM

Here is my edited version.



Media Response - Salvia Divinorum (CBC Sudbury) - October 2006 - draft v06 ed by Julie Desrosiers

Julie Desrosiers  
10/17/2006 03:35 PM

To: Robin Marles/HC-SC/GC/CA@HWC  
cc:  
Subject: FOR URGENT DG APPROVAL: MEDIA RESPONSES ON SALVIA DIVINORUM

I have some concerns with these lines- I think you will too.  
----- Forwarded by Julie Desrosiers/HC-SC/GC/CA on 10/17/2006 03:34 PM -----



Darrin Denne  
10/17/2006 01:11 PM

To: Chris Turner/HC-SC/GC/CA@HWC, Louise Carriere/HC-SC/GC/CA@HWC, Carole Gauthier/HC-SC/GC/CA@HWC, Grace Accettura/HC-SC/GC/CA@HWC, David Clapin/HC-SC/GC/CA@HWC, Julie Desrosiers/HC-SC/GC/CA@HWC, YVES FORTIN/HC-SC/GC/CA@HWC, Laura Stephen/HC-SC/GC/CA@HWC, Chantal Stead/HC-SC/GC/CA@HWC, Brenda Lajeunesse/HC-SC/GC/CA@HWC  
cc: Julia Hill/HC-SC/GC/CA@HWC, Brook Bertrand/HC-SC/GC/CA@HWC, Laura De Curtis/HC-SC/GC/CA@HWC, Marianne van Oosten/HC-SC/GC/CA@HWC  
Subject: FOR URGENT DG APPROVAL: MEDIA RESPONSES ON SALVIA DIVINORUM

**FOR URGENT APPROVAL: MEDIA RESPONSES ON SALVIA DIVINORUM**

Good afternoon,

Please find attached responses prepared to questions posed by CBC Radio Sudbury on *Salvia divinorum*. These response have been prepared by MHPD and by the Office of Controlled Substances in HECS, and are being sent for DG approval. **Please return your approval and/or comments to me by 3 p.m. today.**



Media Response - Salvia Divinorum (CBC Sudbury) - October 2006 - dra


Cheers,  
Darrin

---

Darrin Denne  
Senior Communications Advisor - HPFB / Conseiller principal en communications - DGPSA  
Strategic Communications Directorate / Direction des communications stratégique  
Public Affairs, Consultation and Regions Branch (PACRB) /  
Direction générale des affaires publiques, de la consultation et des régions (DGAPCR)  
Health Canada / Santé Canada  
Tel: (613) 946-0648  
Cel: ( )

Fax: (613) 957-8805

**Marie Morrisey**  
2005-11-28 10:50 AM

To: Jenna Griffiths/HC-SC/GC/CA@HWC  
cc: Chris Turner/HC-SC/GC/CA@HWC, Duc Vu/HC-SC/GC/CA@HWC,  
Julia Hill/HC-SC/GC/CA@HWC, Mano Murty/HC-SC/GC/CA@HWC,  
Mark Korchinski/HC-SC/GC/CA@HWC, Ouassim  
Subject: Re: Silvia divinatorum-Fw: FYI - Q.P. Transcripts - November 25 

Hi to all,

The Insp has been discussing the issue of SD with OCS for years. OCS has advised that:

- SD is on their "Watch List"
- everytime the Insp encounters products containing SD or pure SD on the market, we are to alert them - which is what we have been doing (we encounter it often)

I have asked many times re: what takes a substance off the Watch List and places it on a schedule - the answer: depends on how widely it is used / abused. M

Marie Morrisey  
Natural Health Products Compliance Coordinator  
Coordinatrice de conformité des produits de santé naturels  
Health Products and Food Branch Inspectorate / Inspectorat de la Direction générale des produits de santé et des aliments  
Health Canada / Santé Canada  
Tel: 613-957-6712  
Cell: [REDACTED]  
Fax: 613-946-5636  
Jenna Griffiths



**Jenna Griffiths**  
11/28/2005 09:48 AM

To: Robin Marles/HC-SC/GC/CA@HWC  
cc: Patricia Maynard/HC-SC/GC/CA@HWC, Marie Morrisey/HC-SC/GC/CA@HWC, Chris Turner/HC-SC/GC/CA@HWC, Duc Vu/HC-SC/GC/CA@HWC, Julia Hill/HC-SC/GC/CA@HWC, Mano Murty/HC-SC/GC/CA@HWC, Mark Korchinski/HC-SC/GC/CA@HWC, Ouassim Meguellati/HC-SC/GC/CA@HWC, Patrice Lemyre/HC-SC/GC/CA@HWC, "Scott Jordan" <scott\_jordan@hc-sc.gc.ca>, "Shahid Perwaiz" <shahid\_perwaiz@hc-sc.gc.ca>, Thérèse Desjarlais-Renaud/HC-SC/GC/CA@HWC, Trudy Hall/HC-SC/GC/CA@HWC

Subject: Re: Silvia divinorum-Fw: FYI - Q.P. Transcripts - November 25 [1]

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11/26/2005 12:36 PM

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Subject: Re: Silvia divinorum-Fw: FYI - Q.P. Transcripts - November 25 [1]

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Mano Murty



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11/25/2005 02:47 PM

To: Duc Vu/HC-SC/GC/CA@HWC  
cc: Chris Turner/HC-SC/GC/CA@HWC, "Jenna Griffiths" <jenna\_griffiths@hc-sc.gc.ca>, Mark Korchinski/HC-SC/GC/CA@HWC, "Robin Marles" <robin\_marles@hc-sc.gc.ca>, "Scott Jordan" <scott\_jordan@hc-sc.gc.ca>, "Shahid Perwaiz" <shahid\_perwaiz@hc-sc.gc.ca>, Trudy Hall/HC-SC/GC/CA@HWC, Thérèse Desjarlais-Renaud/HC-SC/GC/CA@HWC  
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Duc Vu

**Duc Vu**  
2005-11-25 01:48 PM

To: "Jenna Griffiths" <jenna\_griffiths@hc-sc.gc.ca>, "Mano Murty" <mano\_murty@hc-sc.gc.ca>, "Shahid Perwaiz" <shahid\_perwaiz@hc-sc.gc.ca>, "Scott Jordan" <scott\_jordan@hc-sc.gc.ca>, Mark Korchinski/HC-SC/GC/CA@HWC, Trudy Hall/HC-SC/GC/CA@HWC, "Robin Marles" <robin\_marles@hc-sc.gc.ca>  
cc: Chris Turner/HC-SC/GC/CA@HWC  
Subject: Silvia divinorum-Fw: FYI - Q.P. Transcripts - November 25

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-----  
Sent from my BlackBerry Wireless Handheld  
Louise Carriere

**From:** Louise Carriere  
**Sent:** 11/25/2005 01:25 PM  
**To:** MHPD\_DPSC\_Management  
**Cc:** MHPD\_DPSC\_MC\_Assistants  
**Subject:** FYI - Q.P. Transcripts - November 25

----- Forwarded by Louise Carriere/HC-SC/GC/CA on 2005-11-25 01:24 PM -----



**Murielle Weiler**  
2005-11-25 01:04 PM

To: HPFB\_QP\_Coordinators  
cc:  
Subject: Q.P. Transcripts - November 25

FYI

Murielle Weiler  
HPFB/ADMO  
952-6161

----- Forwarded by Murielle Weiler/HC-SC/GC/CA on 2005-11-25 01:04 PM -----



**Nicholas R Brown**  
2005-11-25 12:34 PM

To: PRO-QP Transcripts  
CC:  
Subject: Q.P. Transcripts - November 25

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Poirier-Rivard to Thibault (Salvia Divinorum) NOV 2

Bonne journée!

Thank you,

Nicholas R. Brown  
Parliamentary Relations Officer / Agent des relations parlementaires  
Parliamentary Relations Office / Bureau des relations parlementaires  
Health Canada / Santé Canada  
Tel: 952-6956  
Fax: 941-0608

---

## TRANSCRIPT

---

**DATE:** *Friday November 25, 2005*

**QUESTION:** *Denise Poirier-Rivard (BQ):  
Châteauguay—Saint-Constant*

**RESPONSE:** *Robert Thibault (Lib): West Nova*

---

**QUESTION:**

Mr. Speaker, a hallucinogenic plant is being sold legally across the country. This plant is prohibited in Australia, Italy, Denmark and Finland. It causes hallucinations and can create mental health problems among users. Can the Minister of Health tell us how it is that this hallucinogenic substance is still not controlled in Canada, it is sold freely and accessible to everyone in businesses that are on the street?

**ANSWER:**

I'm sorry, Mr. Speaker. I did not hear the beginning of the question. There was so much noise here. As soon as we are clear on the question, the Minister of health will be pleased to respond

\*\*\*\*\*



Dorota Bidas  
2006-11-17 11:28 AM

To: Robin Marles/HC-SC/GC/CA@HWC  
cc: Laura Cooney/HC-SC/GC/CA@HWC, Nancy Richards/HC-SC/GC/CA@HWC  
Subject: URGENT - QP Salvia D

Laura, can you please bring it to Robin the moment he is available; in case any addition/changes to be made. I believe he was consulted on this QP.  
thanks, Dorota

----- Forwarded by Dorota Bidas/HC-SC/GC/CA on 2006-11-17 11:23 AM -----



Louise Carriere  
2006-11-17 10:40 AM

To: Brenda Lajeunesse/HC-SC/GC/CA@HWC, Helene Amyot/HC-SC/GC/CA@HWC, Carole Laberge/HC-SC/GC/CA@HWC, Stephanie Szick/HC-SC/GC/CA@HWC  
cc: Chris Cadieux/HC-SC/GC/CA@HWC, Nancy Richards/HC-SC/GC/CA@HWC, MHPD\_DPSC DGO Division, MBBNHPB Support Staff, MBBNHPB Management, Hannah Kahn/HC-SC/GC/CA@HWC  
Subject: URGENT - QP Salvia D

Hi all,

ADMO\_HPFB is requesting this QP asap. Our QP was previously updated (Oct 20th) and sent to ADMO, but from my understanding was never moved to the ADM approved database, hence the reason why all the different colors, highlights and strikout. MHPD's latest changes are in pink.

In any case, please advise - if this version below is approved by :

- HPFBI (Brenda Lajeunesse) (if making changes - please use orange font)
- HECS-OCS (Carole Laberge/Stephanie Szick) (if making changes - please use green font)
- NHPD (Helene Amyot) (if making changes - please use purple font)

Reply via email. Thank you.

Louise Carrière  
Director General's Office/Bureau du directeur général  
Marketed Health Products Directorate (MHPD)/ A.L. 0701B  
Direction des produits de santé commercialisés (DPSC)  
Tel./Tél.: 613-948-6136  
Fax/Télécopieur: 613-952-7738

----- Forwarded by Louise Carriere/HC-SC/GC/CA on 2006-11-17 10:08 AM -----

*Working Draft / Document de travail*

QUESTION PERIOD NOTE  
NOTES POUR LA PÉRIODE DE QUESTIONS

Classification: HPFB PROTECTED/PROTÉGÉ DGPSA

Requested/Demandée

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**



## MEDIA ANALYSIS - ANALYSE DES MÉDIAS

English:

*Salvia divinorum* is a herb which belongs to the mint family that has been used in traditional and spiritual practices by the Aboriginal peoples of Mexico to produce hallucinogenic experiences. It is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of *Salvia divinorum*. In addition, there have been several reports from scientific and media sources, which indicate that *Salvia divinorum* has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating this issue in light of the risks of *Salvia divinorum* to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of *Salvia divinorum*?

## KEY MESSAGES - MESSAGES CLÉS

English:

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level.

*Salvia divinorum* has not been authorized for sale in Canada. ~~If marketed, *Salvia divinorum* would pose a risk for~~ is abused, is likely to lead subject to harmful non-medicinal use, and thus, ~~would be~~ is subject to immediate compliance action by the Health Products and Food Branch Inspectorate.

- Health Canada is assessing the potential for regulatory control of *Salvia divinorum* and will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its availability and use.

Français:

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## BACKGROUND / CONTEXTE

On November 16, 2006, Le Journal de Montréal published a report entitled "Un hallucinogène légal Santé Canada a cependant la *Salvia divinorum* à l'oeil" which indicated that Health Canada is evaluating the possibility of imposing restrictions over the sale and use of *Salvia divinorum*, similar to those of certain countries. Given that *Salvia* does not have long-term adverse effects or the risk of dependence, the article suggests that Health Canada does not consider the short-term hallucinogenic effects to be sufficiently significant health risks to impose restrictions over its sale. In fact, according to the article, *Salvia divinorum* has been sold in certain Quebec retail outlets since 2000, as a legal hallucinogen. The article quotes an RCMP officer in saying that prevention of *Salvia divinorum*'s use is necessary. Additionally, the article quotes Jean-Sébastien Roy, in saying that Quebec's law enforcers' hands are tied because Health Canada has not categorized *Salvia divinorum* as a controlled substance, despite its effects being comparable to the illicit drugs cannabis and LSD. Additionally, he indicated that if an individual were stopped for erratic driving under *Salvia divinorum*'s influence, they would be considered driving while impaired. On October 6, 2006, the Health Products and Food Branch Inspectorate (HPFBI), Ontario Region received an enquiry from MP Joe Preston's office (Elgin-Middlesex, London, Ontario riding). A constituent had inquired why the hallucinogenic product, *Salvia divinorum*, was available as an over-the-counter product.

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* has traditional medicinal uses among the Aboriginal peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1983). *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious kappa-opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*, that would remove it from the purview of the *Natural Health*

## Products Regulations .

Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act* , although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

## Current Situation in Canada

~~*Salvia divinorum* and salvinorin A meet both the functional and substance portions of the definition of a natural health product and are not currently subject to any regulatory exclusions, and therefore, they would be considered natural health products in Canada. However, since *Salvia divinorum* and salvinorin A are subject to the *Natural Health Products Regulations* and the *Food and Drugs Act* , and present a risk for abuse that is likely to lead to harmful non-medicinal use, they are subject to immediate compliance action by the HPFBI according to the Compliance Policy for Natural Health Products.~~

In July of 2005 Health Canada completed a review of the information currently available on the potential risks and benefits of *Salvia divinorum* use in humans. *Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico where it grows naturally, so a product with such health claims could meet the definition of a natural health product and therefore be subject to the *Food and Drugs Act* and the *Natural Health Products Regulations* . One of the advantages of these Regulations is the mandatory assessment of every product for its safety, effectiveness with regard to the claims on the label, and quality issues such as ensuring that it is the correct herb and that it is free of contamination by pesticides, toxic metals such as lead, bacteria and molds.

However, it is highly unlikely that a *Salvia divinorum* product would be licensed as a natural health product due to its safety issues. Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in way that is quite different from other hallucinogens such as heroin or LSD. Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions, it is subject to abuse as a street drug, and it acts on the brain in a ways that are is quite novel and for which the consequences have not yet been fully established. For all these these reasons, the risks of *Salvia divinorum* use compared to any expected benefits suggest that if it were to be regulated as a health product, it should require a prescription under the *Food and Drug Regulations* , rather than being regulated as an over-the-counter natural health product.

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia*

*divinorum* , used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum* . All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS has placed *Salvia divinorum* on their 'watch list', meaning, they will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and international regulatory status as monitored by MHPD. Additionally, if the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

#### Health Canada Actions

HPFBI has requested that a complaint be submitted to the HPFBI office in Toronto for the product identified by MP Joe Preston's constituent, identifying the location of the retailer and the product. HPFBI will take appropriate compliance and enforcement actions per Compliance and Enforcement Policy (POL-0001).

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

#### Remarks/ Remarques:

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother*. Oct;39(10):1634-9. Epub 2005 Sep 13.

Díaz JL. 1976. Propiedades Terapéuticas Atributas a Plantas Mexicanas, Primera Parte: Nombre Botánico y Usos. Instituto Mexicano para el Estudio de las Plantas Medicinales, Mexico.

Valdés LJ, Díaz JL, Paul AG. 1983. Ethnopharmacology of *Ska María Pastora* (*Salvia divinorum*), Epling and Játiva-M.). J. Ethnopharmacology 7(3): 287-312.

\* HECS-OCS was consulted on this QP - Oct 11, 2006

\* NHPD was consulted on this QP - Oct 13, 2006

**Contact Information / Personnes-Ressource**

<b>*Primary/Primaire:</b> Dr. Shahid Perwaiz	<b>*Telephone/Téléphone:</b> (613)-948-8540 <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b>  <b>Title/Titre:</b> Director General	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b> [REDACTED]
<b>Secondary/Secondaire:</b> Dr. Jenna Griffiths	<b>Telephone/Téléphone:</b> (613)-946-6507 <b>Mobile/Cellulaire:</b>		

**\*Date Prepared/**  
**Date préparé:** 2006-10-12

**\*Director-Contact/**  
**Directeur-personne** Hans Yu **\*Phone Number/** 613-952-8301  
**ressource:** **Téléphone:**

**\*Directorate & Bureau/** Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits b  
**Direction et bureau:** biotechnologiques et de santé naturels commercialisés

**Contact Signed/**  
**Signature par la**  
**personne-ressource:**  Contact Signed/Signature de la personne ressource

**Date Signed/ Date signé:** 2006-10-13

Date will be entered automatically when signed and saved.

**D.G. Approved/**  
**Approuvé par le DG:**

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/**  
**Date de l'approbation du DG:**

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé  
Commercialisés

**ADM Approved/** Neil Yeates - HPFB/DGPSA (957-1804)  
**Approbation par le SMA :**

**Branches/** HPFB/ DGPSA

**Directions générale:**

**Departments/ Ministères:** Health Canada / Santé Canada

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**Edit History:**

Jenna Griffiths	Nov 16, 2006 - 04:37:50 PM	updating
Shahid Perwaiz	Nov 16, 2006 - 02:54:52 PM	updating
Louise Carriere	Oct 20, 2006 - 12:33:01 PM	DG approval
Jenna Griffiths	Oct 18, 2006 - 03:52:20 PM	editing
Shahid Perwaiz	Oct 18, 2006 - 03:36:50 PM	Updating
Hannah Kahn	Oct 18, 2006 - 02:53:45 PM	for update
Louise Carriere	Oct 16, 2006 - 07:25:15 AM	DG approval
Jenna Griffiths	Oct 13, 2006 - 01:33:08 PM	updating
Shahid Perwaiz	Oct 13, 2006 - 11:31:49 AM	revision
Jenna Griffiths	Oct 12, 2006 - 04:28:17 PM	updating
Jenna Griffiths	Oct 12, 2006 - 03:47:13 PM	updating
Shahid Perwaiz	Oct 12, 2006 - 10:32:39 AM	editing

**Created By:** Louise Carriere/HC-SC/GC/CA  
**Modified By:** Jenna Griffiths/HC-SC/GC/CA

**Date Created:** October 12, 2006  
**Date Modified:** November 16, 2006



Nancy Richards  
2006-11-17 04:52 PM

To: Robin Marles/HC-SC/GC/CA@HWC  
cc:  
Subject: Re: URGENT - QP Salvia D

FYI -- Robin -- here is the response that went up to the QP note coordinator in ADMO re the NHPD input for the QP note attached at the bottom dated October 12th.

I went into the QP database and there is no updated note posted in the working QP database at this time nor is there a final note but the MHPD folks have the lead as far as I can see since the Oct 12th note indicates it is to be signed off by the DG of MHPD.

Nancy

----- Forwarded by Nancy Richards/HC-SC/GC/CA on 2006-11-17 04:46 PM -----



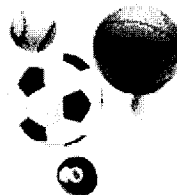
Nancy Richards  
Sent by: Dorota Bidas  
2006-11-17 01:40 PM

To: Louise Carriere/HC-SC/GC/CA@HWC  
cc: Helene Amyot/HC-SC/GC/CA@HWC, Nancy  
Richards/HC-SC/GC/CA@HWC, Brook Bertrand/HC-SC/GC/CA@HWC  
Subject: Re: URGENT - QP Salvia D

Hi Louise, following your request please note :NHPD - no changes, ok with the content.

thank you,

Louise Carriere



Louise Carriere  
2006-11-17 10:40 AM

To: Brenda Lajeunesse/HC-SC/GC/CA@HWC, Helene  
Amyot/HC-SC/GC/CA@HWC, Carole Laberge/HC-SC/GC/CA@HWC,  
Stephanie Szick/HC-SC/GC/CA@HWC  
cc: Chris Cadieux/HC-SC/GC/CA@HWC, Nancy  
Richards/HC-SC/GC/CA@HWC, MHPD\_DPSC DGO Division,  
MBBNHPB Support Staff, MBBNHPB Management, Hannah  
Kahn/HC-SC/GC/CA@HWC  
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- NHPD (Helene Amyot) (if making changes - please use **purple font**)

Reply via email. Thank you.

Louise Carrière  
Director General's Office/Bureau du directeur général  
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Tel./Tél.: 613-948-6136  
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----- Forwarded by Louise Carriere/HC-SC/GC/CA on 2006-11-17 10:08 AM -----

Working Draft / Document de travail

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Requested/Demandée

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**KEY MESSAGES - MESSAGES CLÉS**

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## Health Products and Food Branch Inspectorate.

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product identified by MP Joe Preston's constituent, identifying the location of the retailer and the product. HPFBI will take appropriate compliance and enforcement actions per Compliance and Enforcement Policy (POL-0001).

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13.

Díaz JL. 1976. *Propiedades Terapéuticas Atributas a Plantas Mexicanas, Primera Parte: Nombre Botánico y Usos.* Instituto Mexicano para el Estudio de las Plantas Medicinales, Mexico.

Valdés LJ, Días JL, Paul AG. 1983. *Ethnopharmacology of Ska María Pastora (Salvia divinorum)*, Epling and Játiva-M.). *J. Ethnopharmacology* 7(3): 287-312.

**\* HECS-OCS was consulted on this QP - Oct 11, 2006**

**\* NHPD was consulted on this QP - Oct 13, 2006**

<b>Contact Information / Personnes-Ressource</b>
--

<b>*Primary/Primaire:</b> Dr. Shahid Perwaiz	<b>*Telephone/Téléphone:</b> (613)-948-8540 <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b>	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b> [REDACTED]
<b>Secondary/Secondaire:</b> Dr. Jenna Griffiths	<b>Telephone/Téléphone:</b> (613)-946-6507 <b>Mobile/Cellulaire:</b>	<b>Title/Titre:</b> Director General	

**\*Date Prepared/**

**Date préparé:** 2006-10-12

**\*Director-Contact/  
Directeur-personne  
ressource:**

Hans Yu

**\*Phone Number/  
Téléphone:** 613-952-8301

**\*Directorate & Bureau/  
Direction et bureau:**

Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits biotechnologiques et de santé naturels commercialisés

**Contact Signed/  
Signature par la  
personne-ressource:**

Contact Signed/Signature de la personne ressource

**Date Signed/ Date signé:** 2006-10-13

Date will be entered automatically when signed and saved.

**D.G. Approved/**

**Approuvé par le DG:**

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/**

**Date de l'approbation du DG:**

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/ Approbation par le SMA :** Neil Yeates - HPFB/DGPSA (957-1804)

**Branches/ Directions générale:** HPFB/ DGPSA

**Departments/ Ministères:** Health Canada / Santé Canada

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**Edit History:**

Jenna Griffiths	Nov 16, 2006 - 04:37:50 PM	updating
Shahid Perwaiz	Nov 16, 2006 - 02:54:52 PM	updating
Louise Carriere	Oct 20, 2006 - 12:33:01 PM	DG approval
Jenna Griffiths	Oct 18, 2006 - 03:52:20 PM	editing
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Shahid Perwaiz	Oct 13, 2006 - 11:31:49 AM	revision
Jenna Griffiths	Oct 12, 2006 - 04:28:17 PM	updating
Jenna Griffiths	Oct 12, 2006 - 03:47:13 PM	updating
Shahid Perwaiz	Oct 12, 2006 - 10:32:39 AM	editing

**Created By:** Louise Carriere/HC-SC/GC/CA

**Date Created:** October 12, 2006

**Modified By:** Jenna Griffiths/HC-SC/GC/CA

**Date Modified:** November 16, 2006



Robin Marles  
2006-11-17 01:03 PM

To: Nancy Richards/HC-SC/GC/CA@HWC  
cc: Dorota Bidas/HC-SC/GC/CA@HWC  
Subject: Re: URGENT - QP Salvia D

This captures the essential points that I raised earlier. It is not worth delaying submission to tweak it further. I recommend it for NHPD DG approval.

Robin  
Dorota Bidas

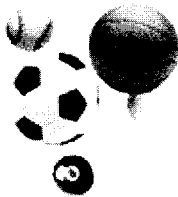


Dorota Bidas  
11/17/2006 11:28 AM

To: Robin Marles/HC-SC/GC/CA@HWC  
cc: Laura Cooney/HC-SC/GC/CA@HWC, Nancy  
Richards/HC-SC/GC/CA@HWC  
Subject: URGENT - QP Salvia D

Laura, can you please bring it to Robin the moment he is available; in case any addition/changes to be made. I believe he was consulted on this QP.  
thanks, Dorota

----- Forwarded by Dorota Bidas/HC-SC/GC/CA on 2006-11-17 11:23 AM -----



Louise Carriere  
2006-11-17 10:40 AM

To: Brenda Lajeunesse/HC-SC/GC/CA@HWC, Helene  
Amyot/HC-SC/GC/CA@HWC, Carole Laberge/HC-SC/GC/CA@HWC,  
Stephanie Szick/HC-SC/GC/CA@HWC  
cc: Chris Cadieux/HC-SC/GC/CA@HWC, Nancy  
Richards/HC-SC/GC/CA@HWC, MHPD\_DPSC DGO Division,  
MBBNHPB Support Staff, MBBNHPB Management, Hannah  
Kahn/HC-SC/GC/CA@HWC  
Subject: URGENT - QP Salvia D

Hi all,

ADMO\_HPFBI is requesting this QP asap. Our QP was previously updated (Oct 20th) and sent to ADMO, but from my understanding was never moved to the ADM approved database, hence the reason why all the different colors, highlights and strikethrough. MHPD's latest changes are in pink.

In any case, please advise - if this version below is approved by :

- HPFBI (Brenda Lajeunesse) (if making changes - please use orange font)
- HECS-OCS (Carole Laberge/Stephanie Szick) (if making changes - please use green font)
- NHPD (Helene Amyot) (if making changes - please use purple font)

Reply via email. Thank you.

Louise Carrière  
Director General's Office/Bureau du directeur général  
Marketed Health Products Directorate (MHPD)/ A.L. 0701B  
Direction des produits de santé commercialisés (DPSC)  
Tel./Tél.: 613-948-6136  
Fax/Télécopieur: 613-952-7738

----- Forwarded by Louise Carriere/HC-SC/GC/CA on 2006-11-17 10:08 AM -----

*Working Draft / Document de travail*

QUESTION PERIOD NOTE

000126

English:

## **DRUGS - SALVIA DIVINORUM**

Français:

## **DROGUES - SALVIA DIVINORUM**

### **MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

*Salvia divinorum* is a herb which belongs to the mint family that has been used in traditional and spiritual practices by the Aboriginal peoples of Mexico to produce hallucinogenic experiences. It is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of *Salvia divinorum*. In addition, there have been several reports from scientific and media sources, which indicate that *Salvia divinorum* has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating this issue in light of the risks of *Salvia divinorum* to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of *Salvia divinorum*?

### **KEY MESSAGES - MESSAGES CLÉS**

English:

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level.

*Salvia divinorum* has not been authorized for sale in Canada. ~~If marketed, *Salvia divinorum* would pose a risk for~~ is abused, is likely to lead subject to harmful non-medicinal use, and thus, ~~would be~~ is subject to immediate compliance action by the Health Products and Food Branch Inspectorate.

- Health Canada is assessing the potential for regulatory control of *Salvia divinorum* and will take necessary actions to safeguard

Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its availability and use.

Français:

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#### BACKGROUND / CONTEXTE

On November 16, 2006, Le Journal de Montréal published a report entitled "Un hallucinogène légal Santé Canada a cependant la *Salvia divinorum* à l'oeil" which indicated that Health Canada is evaluating the possibility of imposing restrictions over the sale and use of *Salvia divinorum*, similar to those of certain countries. Given that *Salvia* does not have long-term adverse effects or the risk of dependence, the article suggests that Health Canada does not consider the short-term hallucinogenic effects to be sufficiently significant health risks to impose restrictions over its sale. In fact, according to the article, *Salvia divinorum* has been sold in certain Quebec retail outlets since 2000, as a legal hallucinogen. The article quotes an RCMP officer in saying that prevention of *Salvia divinorum*'s use is necessary. Additionally, the article quotes Jean-Sébastien Roy, in saying that Quebec's law enforcers' hands are tied because Health Canada has not categorized *Salvia divinorum* as a controlled substance, despite its effects being comparable to the illicit drugs cannabis and LSD. Additionally, he indicated that if an individual were stopped for erratic driving under *Salvia divinorum*'s influence, they would be considered driving while impaired. On October 6, 2006, the Health Products and Food Branch Inspectorate (HPFBI), Ontario Region received an enquiry from MP Joe Preston's office (Elgin-Middlesex, London, Ontario riding). A constituent had inquired why the hallucinogenic product, *Salvia divinorum*, was available as an over-the-counter product.

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* has traditional medicinal uses among the Aboriginal peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1983). *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious *kappa*-opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia,



bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*, that would remove it from the purview of the *Natural Health Products Regulations*.

Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act*, although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

### Current Situation in Canada

~~*Salvia divinorum* and salvinorin A meet both the functional and substance portions of the definition of a natural health product and are not currently subject to any regulatory exclusions, and therefore, they would be considered natural health products in Canada. However, since *Salvia divinorum* and salvinorin A are subject to the *Natural Health Products Regulations* and the *Food and Drugs Act*, and present a risk for abuse that is likely to lead to harmful non-medicinal use, they are subject to immediate compliance action by the HPFBI according to the Compliance Policy for Natural Health Products.~~

In July of 2005 Health Canada completed a review of the information currently available on the potential risks and benefits of *Salvia divinorum* use in humans. *Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico where it grows naturally, so a product with such health claims could meet the definition of a natural health product and therefore be subject to the *Food and Drugs Act* and the *Natural Health Products Regulations*. One of the advantages of these Regulations is the mandatory assessment of every product for its safety, effectiveness with regard to the claims on the label, and quality issues such as ensuring that it is the correct herb and that it is free of contamination by pesticides, toxic metals such as lead, bacteria and molds.

However, it is highly unlikely that a *Salvia divinorum* product would be licensed as a natural health product due to its safety issues. Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in way that is quite different from other hallucinogens such as heroin or LSD. Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions, it is subject to abuse as a street drug, and

it acts on the brain in a ways that are is quite novel and for which the consequences have not yet been fully established. For all these these-reasons, the risks of *Salvia divinorum* use compared to any expected benefits suggest that if it were to be regulated as a health product, it should require a prescription under the *Food and Drug Regulations* , rather than being regulated as an over-the-counter natural health product.

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum* , used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum* . All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non- serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS has placed *Salvia divinorum* on their 'watch list', meaning, they will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and international regulatory status as monitored by MHPD. Additionally, if the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

#### Health Canada Actions

HPFBI has requested that a complaint be submitted to the HPFBI office in Toronto for the product identified by MP Joe Preston's constituent, identifying the location of the retailer and the product. HPFBI will take appropriate compliance and enforcement actions per Compliance and Enforcement Policy (POL-0001).

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13.

Díaz JL. 1976. Propiedades Terapéuticas Atributas a Plantas Mexicanas, Primera Parte: Nombre Botánico y Usos. Instituto Mexicano para el Estudio de las Plantas Medicinales, Mexico.

Valdés LJ, Díaz JL, Paul AG. 1983. Ethnopharmacology of *Ska María Pastora* (*Salvia divinorum* , Epling and Játiva-M.). *J. Ethnopharmacology* 7(3): 287-312.

\* HECS-OCS was consulted on this QP - Oct 11, 2006

\* NHPD was consulted on this QP - Oct 13, 2006

**Contact Information / Personnes-Ressource**

<b>*Primary/Primaire:</b> Dr. Shahid Perwaiz	<b>*Telephone/Téléphone:</b> (613)-948-8540 <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b> Title/Titre: Director General	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b> [REDACTED]
<b>Secondary/Secondaire:</b> Dr. Jenna Griffiths	<b>Telephone/Téléphone:</b> (613)-946-6507 <b>Mobile/Cellulaire:</b>		

**\*Date Prepared/**

Date préparé: 2006-10-12

**\*Director-Contact/  
Directeur-personne  
ressource:**

Hans Yu

**\*Phone Number/  
Téléphone:** 613-952-8301

**\*Directorate & Bureau/  
Direction et bureau:**

Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits b  
biotechnologiques et de santé naturels commercialisés

**Contact Signed/  
Signature par la  
personne-ressource:**

Contact Signed/Signature de la personne ressource

**Date Signed/ Date signé:** 2006-10-13

Date will be entered automatically when signed and saved.

**D.G. Approved/  
Approuvé par le DG:**

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/  
Date de l'approbation du DG:**

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/  
Approbation par le SMA :** Neil Yeates - HPFB/DGPSA (957-1804)

**Branches/  
Directions générale:** HPFB/ DGPSA

**Departments/ Ministères:** Health Canada / Santé Canada

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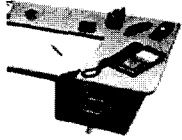
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**Edit History:**

Jenna Griffiths	Nov 16, 2006 - 04:37:50 PM	updating
Shahid Perwaiz	Nov 16, 2006 - 02:54:52 PM	updating
Louise Carriere	Oct 20, 2006 - 12:33:01 PM	DG approval
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Shahid Perwaiz	Oct 12, 2006 - 10:32:39 AM	editing

**Created By:** Louise Carriere/HC-SC/GC/CA  
**Modified By:** Jenna Griffiths/HC-SC/GC/CA

**Date Created:** October 12, 2006  
**Date Modified:** November 16, 2006



Robin Marles  
2006-10-17 06:47 PM

To: Jenna Griffiths/HC-SC/GC/CA@HWC  
cc: Ana Mayorga/HC-SC/GC/CA@HWC, Barbara Bartlett/HC-SC/GC/CA@HWC, Hans Yu/HC-SC/GC/CA@HWC, Julie Desrosiers/HC-SC/GC/CA@HWC, Nathalie  
Subject: Re: QP on Salvia divinorum

Sorry but I was out of the office most of last week. Here are my suggested revisions, in blue.

Robin  
Jenna Griffiths



Jenna Griffiths  
10/13/2006 04:47 PM

To: Robin Marles/HC-SC/GC/CA@HWC  
cc: Julie Desrosiers/HC-SC/GC/CA@HWC, Barbara Bartlett/HC-SC/GC/CA@HWC, Nathalie Lalonde/HC-SC/GC/CA@HWC, Hans Yu/HC-SC/GC/CA@HWC, Ana Mayorga/HC-SC/GC/CA@HWC, Shahid Perwaiz/HC-SC/GC/CA@HWC  
Subject: QP on Salvia divinorum

Hi Robin,

Could you kindly advise if you're ok with the QP note below which we have revised with input from OCS and HPFBI?

Thanks in advance.  
Jenna

*Working Draft / Document de travail*

QUESTION PERIOD NOTE  
NOTES POUR LA PÉRIODE DE QUESTIONS

Classification: HPFB PROTECTED/PROTÉGÉ DGPSA

Requested/Demandée

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

**MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Salvia divinorum is a herb which belongs to the mint family that has been used in traditional and spiritual practices by the Aboriginal peoples of Mexico to produce hallucinogenic experiences. It is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating this issue in light of the risks of Salvia divinorum to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate

the risk.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of *Salvia divinorum*?

## KEY MESSAGES - MESSAGES CLÉS

English:

- Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level.

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- Health Canada is assessing the potential for regulatory control of *Salvia divinorum* and will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its availability and use.

Français:

---

### BACKGROUND / CONTEXTE

On October 6, 2006, the Health Products and Food Branch Inspectorate (HPFBI), Ontario Region received an enquiry from MP Joe Preston's office (Elgin-Middlesex, London, Ontario

riding). A constituent had inquired why the hallucinogenic product, *Salvia divinorum*, was available as an over-the-counter product.

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#### Regulatory Control of *Salvia divinorum*

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Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act*, although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

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In July of 2005 Health Canada completed a review of the information currently available on the

potential risks and benefits of *Salvia divinorum* use in humans. *Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico where it grows naturally, so a product with such health claims could meet the definition of a natural health product and therefore be subject to the *Food and Drugs Act* and the *Natural Health Products Regulations*. One of the advantages of these Regulations is the mandatory assessment of every product for its safety, effectiveness with regard to the claims on the label, and quality issues such as ensuring that it is the correct herb and that it is free of contamination by pesticides, toxic metals such as lead, bacteria and molds.

However, it is highly unlikely that a *Salvia divinorum* product would be licensed as a natural health product due to its safety issues. Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in way that is quite different from other hallucinogens such as heroin or LSD. Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions, it is subject to abuse as a street drug, and it acts on the brain in a way that is quite novel and for which the consequences have not yet been fully established. For all those reasons, the risks of *Salvia divinorum* use compared to any expected benefits suggest that if it were to be regulated as a health product, it should require a prescription under the *Food and Drug Regulations*, rather than being regulated as an over-the-counter natural health product.

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS has placed *Salvia divinorum* on their 'watch list', meaning they will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and international regulatory status as monitored by MHPD. Additionally, if the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;



- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada Actions

HPFBI has requested that a complaint be submitted to the HPFBI office in Toronto for the product identified by MP Joe Preston's constituent, identifying the location of the retailer and the product. HPFBI will take appropriate compliance and enforcement actions per Compliance and Enforcement Policy (POL-0001).

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

Remarks/ Remarques:

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13.

Díaz JL. 1976. Propiedades Terapéuticas Atributas a Plantas Mexicanas, Primera Parte: Nombre Botánico y Usos. Instituto Mexicano para el Estudio de las Plantas Medicinales, Mexico.

Valdés LJ, Días JL, Paul AG. 1983. Ethnopharmacology of *Ska María Pastora* (*Salvia divinorum* , Epling and Játiva-M.). *J. Ethnopharmacology* 7(3): 287-312.

**\* HECS-OCS was consulted on this QP - Oct 11, 2006**

<b>Contact Information / Personnes-Ressource</b>
--

<p><b>*Primary/Primaire:</b> Louise Carriere Dr. Shahid Perwaiz</p>	<p><b>*Telephone/Téléphone:</b> (613) 948-6136 (613)-948-8540</p> <p><b>Mobile/Cellulaire:</b></p>	<p><b>Approved by/Approuvé par:</b></p>	<p><b>Telephone/Téléphone:</b> 613-941-8889</p>
<p><b>Secondary/Secondaire:</b> Dr. Jenna Griffiths</p>	<p><b>Telephone/Téléphone:</b> (613)-946-6507</p> <p><b>Mobile/Cellulaire:</b></p>	<p><b>Title/Titre:</b> Director General</p>	<p><b>Mobile/Cellulaire:</b></p>

**\*Date Prepared/**  
**Date préparé:** 2006-10-12

**\*Director-Contact/**  
**Directeur-personne** Hans Yu **\*Phone Number/** 613-952-8301  
**ressource:** **Téléphone:**

**\*Directorate & Bureau/** Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits b  
**Direction et bureau:** biotechnologiques et de santé naturels commercialisés

**Contact Signed/  
Signature par la  
personne-ressource:**

**Date Signed/ Date signé:**

Date will be entered automatically when signed and saved.

**D.G. Approved/  
Approuvé par le DG:**

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/  
Date de l'approbation du DG:**

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/  
Approbation par le SMA :** Neil Yeates - HPFB/DGPSA (957-1804)

**Branches/  
Directions générale:** HPFB/ DGPSA

**Departments/ Ministères:** Health Canada / Santé Canada

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**Edit History:**

Jenna Griffiths	Oct 13, 2006 - 01:33:08 PM	updating
Shahid Perwaiz	Oct 13, 2006 - 11:31:49 AM	revision
Jenna Griffiths	Oct 12, 2006 - 04:28:17 PM	updating
Jenna Griffiths	Oct 12, 2006 - 03:47:13 PM	updating
Shahid Perwaiz	Oct 12, 2006 - 10:32:39 AM	editing

**Created By:** Louise Carriere/HC-SC/GC/CA  
**Modified By:** Jenna Griffiths/HC-SC/GC/CA

**Date Created:** October 12, 2006  
**Date Modified:** October 13, 2006



Jenna Griffiths  
2006-10-13 04:47 PM

To: Robin Marles/HC-SC/GC/CA@HWC  
cc: Julie Desrosiers/HC-SC/GC/CA@HWC, Barbara Bartlett/HC-SC/GC/CA@HWC, Nathalie Lalonde/HC-SC/GC/CA@HWC, Hans Yu/HC-SC/GC/CA@HWC, Ana  
Subject: QP on Salvia divinorum

Hi Robin,

Could you kindly advise if you're ok with the QP note below which we have revised with input from OCS and HPFBI?

Thanks in advance.  
Jenna

*Working Draft / Document de travail*

QUESTION PERIOD NOTE  
NOTES POUR LA PÉRIODE DE QUESTIONS

Classification: HPFB PROTECTED/PROTÉGÉ DGPSA

Requested/Demandée

English:

## **DRUGS - SALVIA DIVINORUM**

Français:

## **DROGUES - SALVIA DIVINORUM**

### **MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Salvia divinorum is a herb which belongs to the mint family that has been used in traditional and spiritual practices by the Aboriginal peoples of Mexico to produce hallucinogenic experiences. It is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating this issue in light of the risks of Salvia divinorum to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

## **KEY MESSAGES - MESSAGES CLÉS**

English:

- Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level.

*Salvia divinorum* has not been authorized for sale in Canada. If marketed, *Salvia divinorum* would pose a risk for abuse, likely to lead to harmful non-medicinal use, and thus, would be subject to immediate compliance action by the Health Products and Food Branch Inspectorate.

- Health Canada is assessing the potential for regulatory control of *Salvia divinorum* and will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its availability and use.

Français:

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#### BACKGROUND / CONTEXTE

On October 6, 2006, the Health Products and Food Branch Inspectorate (HPFBI), Ontario Region received an enquiry from MP Joe Preston's office (Elgin-Middlesex, London, Ontario riding). A constituent had inquired why the hallucinogenic product, *Salvia divinorum*, was available as an over-the-counter product.

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* has traditional medicinal uses among the Aboriginal peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1983). *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious *kappa*

-opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

#### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*, that would remove it from the purview of the *Natural Health Products Regulations*.

Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act*, although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

#### Current Situation in Canada

*Salvia divinorum* and salvinorin A meet both the functional and substance portions of the definition of a natural health product and are not currently subject to any regulatory exclusions, and therefore, they would be considered natural health products in Canada. However, since *Salvia divinorum* and salvinorin A are subject to the *Natural Health Products Regulations* and the *Food and Drugs Act*, and present a risk for abuse that is likely to lead to harmful non-medicinal use, they are subject to immediate compliance action by the HPFBI according to the Compliance Policy for Natural Health Products.

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as

well as through contacts with other regulatory organizations. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS has placed *Salvia divinorum* on their 'watch list', meaning, they will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and international regulatory status as monitored by MHPD. Additionally, if the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

#### Health Canada Actions

HPFBI has requested that a complaint be submitted to the HPFBI office in Toronto for the product identified by MP Joe Preston's constituent, identifying the location of the retailer and the product. HPFBI will take appropriate compliance and enforcement actions per Compliance and Enforcement Policy (POL-0001).

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

#### Remarks/ Remarques:

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother*. Oct;39(10):1634-9. Epub 2005 Sep 13.

Díaz JL. 1976. *Propiedades Terapéuticas Atributas a Plantas Mexicanas, Primera Parte: Nombre Botánico y Usos*. Instituto Mexicano para el Estudio de las Plantas Medicinales, Mexico.

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**\* HECS-OCS was consulted on this QP - Oct 11, 2006**

Contact Information / Personnes-Ressource

<b>*Primary/Primaire:</b> Louise Carriere Dr. Shahid Perwaiz	<b>*Telephone/Téléphone:</b> (613) 948-6136 (613)-948-8540 <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b>	<b>Telephone/Téléphone:</b> 613-941-8889
<b>Secondary/Secondaire:</b> Dr. Jenna Griffiths	<b>Telephone/Téléphone:</b> (613)-946-6507 <b>Mobile/Cellulaire:</b>	<b>Title/Titre:</b> Director General	<b>Mobile/Cellulaire:</b> [REDACTED]

**\*Date Prepared/**  
**Date préparé:** 2006-10-12

**\*Director-Contact/**  
**Directeur-personne** Hans Yu **\*Phone Number/** 613-952-8301  
**ressource:** **Téléphone:**

**\*Directorate & Bureau/** Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits b  
**Direction et bureau:** biotechnologiques et de santé naturels commercialisés

**Contact Signed/**  
**Signature par la**  
**personne-ressource:**

**Date Signed/ Date signé:**

Date will be entered automatically when signed and saved.

**D.G. Approved/**  
**Approuvé par le DG:**

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/**  
**Date de l'approbation du DG:**

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé  
Commercialisés

**ADM Approved/** Neil Yeates - HPFB/DGPSA (957-1804)  
**Approbation par le SMA :**

**Branches/** HPFB/ DGPSA  
**Directions générale:**

**Departments/ Ministères:** Health Canada / Santé Canada

<b>Edit History:</b>		
Jenna Griffiths	Oct 13, 2006 - 01:33:08 PM	updating
Shahid Perwaiz	Oct 13, 2006 - 11:31:49 AM	revision
Jenna Griffiths	Oct 12, 2006 - 04:28:17 PM	updating
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Shahid Perwaiz	Oct 12, 2006 - 10:32:39 AM	editing

Created By: Louise Carriere/HC-SC/GC/CA  
Modified By: Jenna Griffiths/HC-SC/GC/CA

Date Created: October 12, 2006  
Date Modified: October 13, 2006



Joan Kennedy/HC-SC/GC/CA

2008-02-05 04:26 PM

To HPFB\_QP\_MHPD\_DGO

cc HPFB\_QP\_NHPD\_DGO, Pat Corbett/HC-SC/GC/CA@HWC, Diane Laplante/HC-SC/GC/CA@HWC, Liliane Brazeau/HC-SC/GC/CA@HWC

bcc

Subject QP Note on DRUGS - SALVIA DIVINORUM

Please see request from PRO below. Please update the QP on Salvia Divinorum, prepared by MHPD in November 2006. Please consult with NHPD and HECS in the preparation of this QP.

Due in ADMO Wednesday, February 6 at 10:00am.

If you have any questions, please do not hesitate to consult me.

Thank you.

Joan Kennedy  
ADMO/HPFB  
948-3205

----- Forwarded by Joan Kennedy/HC-SC/GC/CA on 2008-02-05 04:20 PM -----

Marianne  
DeVito/HC-SC/GC/CA

2008-02-05 03:26 PM

To Diane Laplante/HC-SC/GC/CA@HWC, Pat Corbett/HC-SC/GC/CA@HWC, Joan Kennedy/HC-SC/GC/CA@HWC, Liliane Brazeau/HC-SC/GC/CA@HWC, Marie Morrisey/HC-SC/GC/CA@HWC

cc Helene Landers/HC-SC/GC/CA@HWC, Geoff Barrett/HC-SC/GC/CA@HWC, Bob Houston, Julien Clavel/HC-SC/GC/CA@HWC

Subject QP Note on DRUGS - SALVIA DIVINORUM



Hello all :

Sounds like the Montreal Gazette is working on an investigative piece regarding Salvia Divinorum. (*see media inquiry below*)

The last QP Note that was drafted on this issue dates back to November 2006 ->

As such, it would be wise to ensure it is updated in the event that this issue needs to be addressed by the Minister.

Would suggest updated key messages that read **something** like this:

- *Salvia divinorum* meets the definition of a natural health product, which means its importation and sale can be restricted under the *Food and Drugs Act's regulations*.
- One of the advantages of these Regulations is the mandatory assessment of every product for its safety, label claim effectiveness, and quality issues such as ensuring that the herb is free of contamination by pesticides, toxic metals, bacteria and moulds.

- Health Canada is currently collecting information about the plant and its active ingredient, Salvinorin A from both national and international sources, and assessing the risk that the unrestricted sale of the plant poses to public health and safety, its pharmacological and chemical similarity to other substances scheduled under the CDSA, and its abuse and dependence potential.
- Health Canada collects relevant information specific to this herb and its active constituents and monitors the trend of its use at the national/international level. If the information collected warrants further action, Health Canada will assess the potential for regulatory control and take all necessary actions to safeguard Canadians against its potential health risks.

Bonne fin de journée!

-Marianne DeVito-

Question Period & Private Members' Business Coordinator /  
Coordinatrice de la Période des questions & des affaires émanant des députés  
Parliamentary Relations Office / Bureau des relations parlementaires  
Tél.: (613) 952-7108 Cél: [REDACTED]

----- Forwarded by Marianne DeVito/HC-SC/GC/CA on 2008-02-05 02:32 PM -----



Health Santé  
Canada Canada

### Media Enquiry - Demande médiatique

Name/Nom : [REDACTED]

Media/Média : Montreal Gazette

Email/Courriel : [REDACTED]@thegazette.canwest.com

Date and Time Received

Date Completed

Date et Heure de réception : 2008-02-05 11:36:57 AM

Date d'achèvement : 2008-02-05

Subject/Objet : Controlled Substances/Substances contrôlées

#### Question:

2008-02-05 11:36:58 AM (Paul Duchesne)

[REDACTED] (Montreal Gazette)" [REDACTED]@thegazette.canwest.com>

2008-02-05 11:22 AM

To

<Jean\_Tessier@hc-sc.gc.ca>, <paul\_duchesne@hc-sc.gc.ca>, <carole\_saindon@hc-sc.gc.ca>

cc

Subject

Salvia: Following up on phone messages just now

Hi:

I need \*\*\*everything\*\*\* you've got on salvia divinorum, a hallucinogen that apparently has hit Montreal and is said to be not illegal.

Full fact sheets (effects, legal status, reports by users, Health Canada position on, possible deleterious effects of course..... Everything ASAP!) by e-mail, svp, and I'll study. We'll follow up by phone with Health Canada's top authority on this svp, of whom I expect to be able to ask intelligent questions by early or mid-afternoon.

Contact details below.

Thanks!

[Redacted]

-----

[Redacted]

The Gazette  
Montréal

Phone: [Redacted]  
E-mail: [Redacted]@thegazette.canwest.com  
Fax: [Redacted]

**Response/Réponse :**

2008-02-05 2:12:35 PM (Paul Duchesne)  
Hi [Redacted]

As requested:

**-What is Salvia Divinorum?**

*Salvia divinorum* is a species of sage which belongs to the mint family. It is found in the form of dried leaves, extract and plant cuttings.

**-Is it legal?**

*Salvia divinorum* meets the definition of a natural health product, and this means that its importation and sale can be restricted under the *Food and Drugs Act*.  
*Salvia divinorum* is not controlled under the *Controlled Drugs and Substances Act*.

**-What are the health effects?**

Reliable, systematic and controlled observations on the psychotropic activities of *Salvia divinorum* are scarce. The following effects have been reported by *Salvia* users: dissociative effects, laughter, sense of well-being, sedation/calmness, confusion/anxiety, lack of coordination, chills/sweating, increased urination.

**-What is Health Canada doing about salvia?**

Health Canada is currently collecting information about the plant and its active ingredient, Salvinorin A from both national and international sources, and assessing the risk that the unrestricted sale of the plant poses to public health and safety, its pharmacological and chemical similarity to other substances scheduled under the CDSA, and its abuse and dependence potential. This information is hard to obtain because much of the information about the effects of *Salvia divinorum* and/or the incidence of its use in Canada is anecdotal in nature.

**-Will HC control salvia under the Controlled Drugs and Substances Act?**

Health Canada has not yet elected to regulate *Salvia divinorum* as a controlled substance under the *Controlled Drugs and Substances Act*.

When considering whether to add a substance to one of the schedules to the CDSA, Health Canada considers a range of factors including the pharmacological and chemical similarity of the substance in question to other substances already scheduled under the CDSA, the substance's abuse and dependence potential, the risk to public health and safety, etc. In the case of *Salvia divinorum*, Health Canada has only anecdotal information about many of these factors and in fact, has no specific information about actual usage in Canada.

Regards,

Paul Duchesne  
A/Senior Media Relations Advisor/Conseiller supérieur int., Relations avec les médias  
Health Canada / Santé Canada  
Tel:/Tél: (613) 954-4807  
Fax:/Télec: (613) 952-7747  
www.healthcanada.gc.ca / www.santecanada.gc.ca  
Government of Canada / Gouvernement du Canada

**Action Taken/Mesures prises :**

2008-02-05 11:45:57 AM (Paul Duchesne)  
Spoke to reporter. Sent request to Stephanie Szick and Christina Daly.

2008-02-05 12:08:37 PM (Paul Duchesne)  
Sent to Laryssa Waler in MO for approval.

2008-02-05 12:12:36 PM (Paul Duchesne)  
MO approved. Sent to Giselle Robichaud at PCO for approval.

2008-02-05 2:11:47 PM (Paul Duchesne)  
PCO approved.

2008-02-05 2:12:38 PM (Paul Duchesne)  
Sent response above to reporter via e-mail. Call completed.

Interview with spokesperson granted/Entrevue avec porte-parole accordé: N

Branch/Direction générale : HECS - Controlled Substances & Drug Analysis/DGSESC - Direction de la sécurité des substances  
chimiques et des produits de consommation

Spokesperson/Porte-parole :  
Reporter's Deadline  
Heure de tombée du journaliste :  
Priority/Priorité : Regular

Telephone/Téléphone :  
Story Run Date  
Date de parution de l'article :  
Status/Rapport de situation : Completed

**Comment/Commentaire :**

Marianne  
DeVito/HC-SC/GC/CA  
2008-02-06 08:23 AM

To PRO-QP Requests  
cc Luc Fournier/HC-SC/GC/CA@HWC, Cassie  
MacAndrew/HC-SC/GC/CA@HWC, Erik Waddell, David  
Pierce/HC-SC/GC/CA@HWC, Laryssa  
bcc

Subject REQUIRED QP Notes - February 6

\* TITLE (SUBJECT), MEDIA ANALYSIS and QUESTION fields should appear on the QP Note AS PROVIDED BELOW \*  
PLEASE ENSURE THAT ALL INFORMATION RELATED TO THE IDENTIFIED TEXT (below) IS CLEARLY ADDRESSED IN THE QP NOTE

**Due to PRO-QP Requests**  
Please cc: Julien\_Clavel@hc-sc.gc.ca on all submissions.

**HPB Lead**

**1. CANADA HEALTH ACT - PRIVATIZATION OF HEALTH CARE SERVICES**

http://206.75.155.80/health/newbook/tdsearch.asp?Lang=E&cmd=getdoc&maxSize=200000&DocId=4037&index=d%3a%5cdsearch%5cUserData%5cToday&HitCount=5&hits=cc+cd+e8+e9+ea+&hc=312&req=%28%22Health+Canada%22+or+%22Sante+Canada%22+or+%22Public+Health+Agency%22+or+%22Agence+de+sante+publique%22+or+%22Tony+Clement%22+or+%22Canada+Health+Act%22+or+%22Cardyn+Bennett%22+or+%22Pat+Martin%22+or+%22Penny+Priddy%22%29+AND+stiller%28date+%22M02%2FD08%2FY2008%7E%7EM02%2FD08%2FY2008%22%29

What concrete actions is the Minister of Health prepared to take to stop the creeping privatisation of health care services in Canada? Is he prepared to hire a Health Act Ombudsman and initiative an appeal process that would operate in the best interest of all Canadians?

Update existing QP Note to address situation in PEI ->

**MEDIA ANALYSIS :** The Guardian (Charlottetown), DATE: 2008.02.06, PAGE: A1 -> The state of Prince Edward Island's health-care system was front and centre in the House of Commons in Ottawa yesterday (Feb 5) as Judy Wasylycia-Leis, the NDP MP for Winnipeg North, raised alarm bells about the privatization of the Island's health-care system.

- "There is something wrong when we cannot get the government to stand up and defend medicare. I would suggest that this minister of Health start listening to P.E.I. health coalition activists who say that Islanders are getting ripped off at the hospitals," Wasylycia-Leis said during question period. "Residents of P.E.I. must pay for ambulance service, physiotherapy, medically necessary cosmetic surgery, diagnostic tests, new medications not yet approved. The prime minister's so-called wait-time guarantee has not made wait times in P.E.I. go down at all. Does the minister at least agree with the suggestion that Canada needs a health act ombudsman and an appeal process?"
- Health Minister Tony Clement defended his Conservative government's handling of health care, adding he is standing up for medicare. He said his government supports the five pillars of the Canada Health Act, including universality, accessibility and affordability. "We do take this seriously. That is why our focus has been on the patients. That is why we have been working with the provinces and territories to ensure that health care is a priority for this government and our future governments as well," Clement said from the floor of the House of Commons.
- Islanders are being forced to pay for ambulance services, physiotherapy and even parking at the Queen Elizabeth Hospital in Charlottetown as just three examples. Wasylycia-Leis said there are growing waiting lists and growing privatization in the health-care system across Canada.

**ANTICIPATORY QP NOTES DUE TO PRO**

- (HECSB) DRUGS - SALVIA DIVINORUM

**OVERVIEW INFORMATION EXPECTED IN PRO**

- **(Manitoba Region) MOBILE MEDICAL SERVICES**  
<http://206.75.155.80/health/newlook/showfile.asp?Lang=E&URL=/health/summary/080206/#0060AF.htm>
- **(HPFB) SAFETY OF COTTON SWABS (LABELLING) - HC'S ROLE**  
<http://206.75.155.80/health/newlook/showfile.asp?Lang=E&URL=/health/summary/080206/#0070AP.htm>

Merci.

**-Marianne DeVito-**

Question Period & Private Members' Business Coordinator /  
Coordinatrice de la Période des questions & des affaires émanant des députés  
Parliamentary Relations Office / Bureau des relations parlementaires

Tél.: (613) 952-7108

Céll: 



Kathleen  
Lafleur/HC-SC/GC/CA  
2008-02-06 08:54 AM

To Patrice Milord/HC-SC/GC/CA@HWC, Helene  
Landers/HC-SC/GC/CA@HWC  
cc Carole Bouchard/HC-SC/GC/CA@HWC, Jocelyn  
Kula/HC-SC/GC/CA@HWC, Kyra  
Paterson/HC-SC/GC/CA@HWC, Nancy  
bcc  
Subject VERY URGENT!!! Fw: QP REQUEST - Fw: QP Note on  
DRUGS - SALVIA DIVINORUM

Hi

On behalf of Dr. Scott Jordan, could you please review the anticipated QP note hereunder and send your comments to Scott asap. Please be advised that we need your input by 9:15, so that we can get this to our DGO by 9:30.

Thank you,

Kathleen Lafleur  
Administrative Assistant / Adjoint  
Marketed Biologicals, Biotechnology & Natural Health Products Bureau  
Bureau des produits biologiques, biotechnologiques et de santé naturels commercialisés  
(ph) 613 - 948-6011 - (fax) 613 - 954-2354

----- Forwarded by Kathleen Lafleur/HC-SC/GC/CA on 2008-02-06 08:48 AM -----

Scott Jordan/HC-SC/GC/CA

2008-02-06 08:41 AM



To Kathleen Lafleur/HC-SC/GC/CA@HWC  
cc Jenna Griffiths/HC-SC/GC/CA@HWC, Shahid  
Perwaiz/HC-SC/GC/CA@HWC, Andrea  
MacTavish/HC-SC/GC/CA@HWC, MBBNHPB Support Staff  
Subject

Hi Kathleen.

For forwarding to HECS and NHPD, for comments. Please let them know we need their input by 9:15, so that we can get this to our DGO by 9:30.

Thanks!

- Scott.

----- Forwarded by Scott Jordan/HC-SC/GC/CA on 2008-02-06 08:40 AM -----

\* Indicates a Mandatory Field/ Indique un champ obligatoire

*Working Draft / Document de travail*

QUESTION PERIOD NOTE  
NOTES POUR LA PÉRIODE DE QUESTIONS

Classification: HPFB PROTECTED/PROTÉGÉ DGPSA

\*○ Anticipatory/Anticipée ● Requested/Demandée

**\*SUBJECT - SUJET**

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

**MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Salvia divinorum, a herb which belongs to the mint family, is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating these reports in light of the risks of Salvia divinorum to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

**\*ANTICIPATED QUESTION - QUESTION PRÉVUE**

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de Salvia divinorum?

**KEY MESSAGES - MESSAGES CLÉS**

A Key Message must not be longer than 300 characters (350 for French text) per bullet and a maximum of 4 bullets. Les messages clés ne devraient pas dépasser 300 caractères (350 pour le texte français) par point et un maximum de 4 points.

English:

Bullet 1:

- *Salvia divinorum* is not authorized for sale in Canada, but meets the definition of a natural health product. As such, its importation and sale could be restricted under the Food and Drugs Act. To be authorized for sale, products are required to be assessed for safety, quality and effectiveness.

Bullet 2:

- Health Canada is currently collecting information about the plant and its



active ingredient, Salvinorin A from national and international sources, and assessing the risk that the unrestricted sale of the plant poses to Canadians, including its abuse and dependence potential.

Bullet 3:

- If the information collected warrants further action, Health Canada will assess the potential for regulatory control, and take all necessary actions to safeguard Canadians from potential risks from *Salvia*. These actions may include public risk communications or restriction of availability and use.

Bullet 4:

Français:

Point 1:



Point 2:



Point 3:



Point 4:

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#### SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

English:

Français:

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#### BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a “legal” alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious *kappa* -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were

shown to produce intense psychoactive affects when inhaled.

#### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations* that would remove it from the purview of the *Natural Health Products Regulations*.

Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act*, although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

#### Current Situation in Canada

As of December, 2007, the Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. While *Salvia divinorum* meets the definition of a Natural Health Product (NHP), no products have been authorized by Health Canada, and *Salvia divinorum* does not appear to be sold as a "health product." Also, proposed use as a recreational substance would not be permitted under the *NHP Regulations*. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS has placed *Salvia divinorum* on their 'watch list', meaning, they will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and

international regulatory status as monitored by MHPD. Additionally, if the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13

**\* HECS-OCS was consulted on this QP - Oct 11, 2006**

Contact Information / Personnes-Ressource			
<b>*Primary/Primaire:</b> Joan Kennedy	<b>*Telephone/Téléphone:</b> xxx-xxxx-xxxx <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b> Dr. Chris Turner <input checked="" type="checkbox"/> <b>Title/Titre:</b> Director General	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b> [REDACTED]
<b>Secondary/Secondaire:</b>	<b>Telephone/Téléphone:</b>  <b>Mobile/Cellulaire:</b>		

**\*Date Prepared/**

**Date préparé:** 2008-02-05

**\*Director-Contact/**

**Directeur-personne  
ressource:** Hans Yu

**\*Phone Number/** 613-952-8301

**Téléphone:**

**\*Directorate & Bureau/  
Direction et bureau:**

**Contact Signed/  
Signature par la  
personne-ressource:**

**Date Signed/ Date signé:**

Date format: yyyy-mm-dd

Date will be entered automatically when signed and saved.

**D.G. Approved/  
Approuvé par le DG:**

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/  
Date de l'approbation du DG:**

Date format: yyyy-mm-dd

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/  
Approbation par le SMA :** Neil Yeates - HPFB/DGPSA (957-1804)

**Branches/  
Directions générale:** HPFB/ DGPSA

**Departments/ Ministères:** Health Canada / Santé Canada

---

**Edit History:**  
Scott Jordan

Feb 6, 2008 - 08:10:09 AM

Updating

**Created By:** Joan Kennedy/HC-SC/GC/CA  
**Modified By:** Scott Jordan/HC-SC/GC/CA

**Date Created:** February 5, 2008  
**Date Modified:** February 6, 2008



Kyra Paterson/HC-SC/GC/CA

2008-02-06 09:08 AM

To Philip Waddington, Nancy Richards/HC-SC/GC/CA@HWC

cc Robin Marles/HC-SC/GC/CA@HWC, Helene Amyot/HC-SC/GC/CA@HWC, Andrew Hrycaj/HC-SC/GC/CA@HWC, Patrice

bcc

Subject FOR APPROVAL: QP on SALVIA DIVINORUM by 9:15 am for MHPD

I am fine with this QP - MHPD (Kathleen) said it was up to NHPD whether DG sign-off is required. Please advise whether you want to review. They would like our OK by 9:15 am.

Kyra Paterson, MSc

Senior Policy Analyst/Analyste principale des politiques

Policy Development and Regulatory Affairs/Développement des politiques et affaires réglementaires

Natural Health Products Directorate/Direction des produits de santé naturels

Health Products and Food Branch/Direction générale des produits de santé et des aliments

Health Canada/ Santé Canada

tel/fax: (905)690-0900

[www.healthcanada.gc.ca/nhp](http://www.healthcanada.gc.ca/nhp)

[www.santecanada.gc.ca/psn](http://www.santecanada.gc.ca/psn)

----- Forwarded by Kyra Paterson/HC-SC/GC/CA on 2008-02-06 09:07 AM -----



Kathleen

Lafleur/HC-SC/GC/CA

2008-02-06 08:54 AM

To Patrice Milord/HC-SC/GC/CA@HWC, Helene Landers/HC-SC/GC/CA@HWC

cc Carole Bouchard/HC-SC/GC/CA@HWC, Jocelyn Kula/HC-SC/GC/CA@HWC, Kyra Paterson/HC-SC/GC/CA@HWC, Nancy Richards/HC-SC/GC/CA@HWC, Robin Marles/HC-SC/GC/CA@HWC, Scott Jordan/HC-SC/GC/CA@HWC, Jenna Griffiths/HC-SC/GC/CA@HWC, Andrea MacTavish/HC-SC/GC/CA@HWC, MHPD\_DPSC DGO Assistants, Joan Kennedy/HC-SC/GC/CA@HWC, Marianne DeVito/HC-SC/GC/CA@HWC

Subject VERY URGENT!!! Fw: QP REQUEST - Fw: QP Note on DRUGS - SALVIA DIVINORUM

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Administrative Assistant / Adjoint

Marketed Biologicals, Biotechnology & Natural Health Products Bureau

Bureau des produits biologiques, biotechnologiques et de santé naturels commercialisés

(ph) 613 - 948-6011 - (fax) 613 - 954-2354

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Scott Jordan/HC-SC/GC/CA

To Kathleen Lafleur/HC-SC/GC/CA@HWC



2008-02-06 08:41 AM

cc Jenna Griffiths/HC-SC/GC/CA@HWC, Shahid  
Perwaiz/HC-SC/GC/CA@HWC, Andrea  
MacTavish/HC-SC/GC/CA@HWC, MBBNHPB Support Staff

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*Working Draft / Document de travail*

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\*  Anticipatory/Anticipée  Requested/Demandée

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Bullet 4:

Français:

Point 1:



Point 2:



Point 3:



Point 4:

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## SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

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Français:

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### Current Situation in Canada



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- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

Remarks/ Remarques:

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marketed on the internet for recreational use. Ann Pharmacother. Oct;39(10):1634-9. Epub 2005 Sep 13

\* HECS-OCS was consulted on this QP - Oct 11, 2006

Contact Information / Personnes-Ressource			
<b>*Primary/Primaire:</b> Joan Kennedy	<b>*Telephone/Téléphone:</b> xxx-xxxx-xxxx <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b> Dr. Chris Turner <input checked="" type="checkbox"/> <b>Title/Titre:</b> Director General	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b> [REDACTED]
<b>Secondary/Secondaire:</b>	<b>Telephone/Téléphone:</b>  <b>Mobile/Cellulaire:</b>		

**\*Date Prepared/**  
**Date préparé:** 2008-02-05

**\*Director-Contact/**  
**Directeur-personne** Hans Yu **\*Phone Number/** 613-952-8301  
**ressource:** **Téléphone:**

**\*Directorate & Bureau/**  
**Direction et bureau:**

**Contact Signed/**  
**Signature par la**  
**personne-ressource:**

**Date Signed/ Date signé:** Date format: yyyy-mm-dd  
Date will be entered automatically when signed and saved.

**D.G. Approved/**  
**Approuvé par le DG:**

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/**  
**Date de l'approbation du DG:** Date format: yyyy-mm-dd  
Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/**  
**Approbation par le SMA :** Neil Yeates - HPFB/DGPSA (957-1804)

**Branches/**  
**Directions générale:** HPFB/ DGPSA

**Departments/ Ministères:** Health Canada / Santé Canada

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Edit History:  
Scott Jordan

Feb 6, 2008 - 08:10:09 AM

Updating

Created By: Joan Kennedy/HC-SC/GC/CA  
Modified By: Scott Jordan/HC-SC/GC/CA

Date Created: February 5, 2008  
Date Modified: February 6, 2008



Kyra Paterson/HC-SC/GC/CA

2008-02-06 09:38 AM

To Philip Waddington, Nancy Richards/HC-SC/GC/CA@HWC,  
Andrew Hrycaj/HC-SC/GC/CA@HWC, Robin  
Marles/HC-SC/GC/CA@HWC, Patrice  
cc Helene Amyot/HC-SC/GC/CA@HWC, Jasmin  
Eldib/HC-SC/GC/CA@HWC, Catherine  
Hone/HC-SC/GC/CA@HWC, Kyra

bcc

Subject \*\*FYI ONLY\*\* QP Note on DRUGS - SALVIA DIVINORUM

Just an FYI

I spoke to Scott Jordan and as per Phil and Nancy's recommendation, suggested the first bullet be:

- ***Salvia divinorum* is not authorized for sale in Canada. As such, its importation and sale could be restricted under the Food and Drugs Act or the Controlled Drugs and Substances Act**

Also, I stressed the point that we should take a softer line, rather than categorically stating it is an NHP (i.e., leaving room for it to fall under CDSA). Scott will make the changes and agreed with the more general approach.

Kyra Paterson, MSc

Senior Policy Analyst/Analyste principale des politiques

Policy Development and Regulatory Affairs/Développement des politiques et affaires réglementaires

Natural Health Products Directorate/Direction des produits de santé naturels

Health Products and Food Branch/Direction générale des produits de santé et des aliments

Health Canada/ Santé Canada

tel/fax: (905)690-0900

[www.healthcanada.gc.ca/nhp](http://www.healthcanada.gc.ca/nhp)

[www.santecanada.gc.ca/psn](http://www.santecanada.gc.ca/psn)

----- Forwarded by Kyra Paterson/HC-SC/GC/CA on 2008-02-06 09:36 AM -----



Kathleen

Laffleur/HC-SC/GC/CA

2008-02-06 08:54 AM

To Patrice Milord/HC-SC/GC/CA@HWC, Helene  
Landers/HC-SC/GC/CA@HWC  
cc Carole Bouchard/HC-SC/GC/CA@HWC, Jocelyn  
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Paterson/HC-SC/GC/CA@HWC, Nancy  
Richards/HC-SC/GC/CA@HWC, Robin  
Marles/HC-SC/GC/CA@HWC, Scott  
Jordan/HC-SC/GC/CA@HWC, Jenna  
Griffiths/HC-SC/GC/CA@HWC, Andrea  
MacTavish/HC-SC/GC/CA@HWC, MHPD\_DPSC DGO  
Assistants, Joan Kennedy/HC-SC/GC/CA@HWC, Marianne  
DeVito/HC-SC/GC/CA@HWC

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Kathleen Lafleur  
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(ph) 613 - 948-6011 - (fax) 613 - 954-2354

----- Forwarded by Kathleen Lafleur/HC-SC/GC/CA on 2008-02-06 08:48 AM -----

Scott Jordan/HC-SC/GC/CA

2008-02-06 08:41 AM

To Kathleen Lafleur/HC-SC/GC/CA@HWC

cc Jenna Griffiths/HC-SC/GC/CA@HWC, Shahid

Perwaiz/HC-SC/GC/CA@HWC, Andrea

MacTavish/HC-SC/GC/CA@HWC, MBBNHPB Support Staff

Subject



Hi Kathleen.

For forwarding to HECS and NHPD, for comments. Please let them know we need their input by 9:15, so that we can get this to our DGO by 9:30.

Thanks!

- Scott.

----- Forwarded by Scott Jordan/HC-SC/GC/CA on 2008-02-06 08:40 AM -----

\* Indicates a Mandatory Field/ Indique un champ obligatoire

*Working Draft / Document de travail*

QUESTION PERIOD NOTE  
NOTES POUR LA PÉRIODE DE QUESTIONS

Classification: HPFB PROTECTED/PROTÉGÉ DGPSA

\*  Anticipatory/Anticipée  Requested/Demandée

**\*SUBJECT - SUJET**

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

**MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Salvia divinorum, a herb which belongs to the mint family, is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has

received four reports of adverse reactions associated with the use of *Salvia divinorum*. In addition, there have been several reports from scientific and media sources, which indicate that *Salvia divinorum* has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating these reports in light of the risks of *Salvia divinorum* to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

#### **\*ANTICIPATED QUESTION - QUESTION PRÉVUE**

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of *Salvia divinorum*?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de *Salvia divinorum*?

#### **KEY MESSAGES - MESSAGES CLÉS**

A Key Message must not be longer than 300 characters (350 for French text) per bullet and a maximum of 4 bullets. Les messages clés ne devraient pas dépasser 300 caractères (350 pour le texte français) par point et un maximum de 4 points.

English:

Bullet 1:

- *Salvia divinorum* is not authorized for sale in Canada, but meets the definition of a natural health product. As such, its importation and sale could be restricted under the Food and Drugs Act. To be authorized for sale, products are required to be assessed for safety, quality and effectiveness.

Bullet 2:

- Health Canada is currently collecting information about the plant and its active ingredient, Salvinorin A from national and international sources, and assessing the risk that the unrestricted sale of the plant poses to Canadians, including its abuse and dependence potential.

Bullet 3:

- If the information collected warrants further action, Health Canada will assess the potential for regulatory control, and take all necessary actions to safeguard Canadians from potential risks from *Salvia*. These actions may include public risk communications or restriction of availability and use.

Bullet 4:

Français:

Point 1:



Point 2:



Point 3:



Point 4:

---

#### SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

English:

Français:

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#### BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a “legal” alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious *kappa* -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

#### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* , nor any Schedule of the *Food and Drugs Act and Regulations* that would remove it from the purview of the *Natural Health Products Regulations* .

Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act* , although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

#### Current Situation in Canada

As of December, 2007, the Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. While *Salvia divinorum* meets the definition of a Natural Health Product (NHP), no products have been authorized by Health Canada, and *Salvia divinorum* does not appear to be sold as a "health product." Also, proposed use as a recreational substance would not be permitted under the *NHP Regulations*. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS has placed *Salvia divinorum* on their 'watch list', meaning, they will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and international regulatory status as monitored by MHPD. Additionally, if the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia*



*divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13

**\* HECS-OCS was consulted on this QP - Oct 11, 2006**

<b>Contact Information / Personnes-Ressource</b>
--

<b>*Primary/Primaire:</b> Joan Kennedy	<b>*Telephone/Téléphone:</b> xxx-xxxx-xxxx <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b> Dr. Chris Turner <input type="checkbox"/>	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b>
<b>Secondary/Secondaire:</b>	<b>Telephone/Téléphone:</b>  <b>Mobile/Cellulaire:</b>	<b>Title/Titre:</b> Director General	<input type="checkbox"/>

**\*Date Prepared/**

**Date préparé:** 2008-02-05

**\*Director-Contact/  
Directeur-personne  
ressource:**

Hans Yu

**\*Phone Number/ 613-952-8301  
Téléphone:**

**\*Directorate & Bureau/  
Direction et bureau:**

**Contact Signed/  
Signature par la  
personne-ressource:**

**Date Signed/ Date signé:**

Date format: yyyy-mm-dd

Date will be entered automatically when signed and saved.

**D.G. Approved/  
Approuvé par le DG:**

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/  
Date de l'approbation du DG:**

Date format: yyyy-mm-dd

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/  
Approbation par le SMA :** Neil Yeates - HPFB/DGPSA (957-1804)

**Branches/  
Directions générale:** HPFB/ DGPSA

**Departments/ Ministères:** Health Canada / Santé Canada

---

**Edit History:**  
Scott Jordan Feb 6, 2008 - 08:10:09 AM Updating

**Created By:** Joan Kennedy/HC-SC/GC/CA **Date Created:** February 5, 2008  
**Modified By:** Scott Jordan/HC-SC/GC/CA **Date Modified:** February 6, 2008



Kyra Paterson/HC-SC/GC/CA

2008-02-06 01:40 PM

To Philip Waddington, Robin Marles/HC-SC/GC/CA@HWC,  
Nancy Richards/HC-SC/GC/CA@HWC  
cc Andrew Hrycaj/HC-SC/GC/CA@HWC, Patrice  
Milord/HC-SC/GC/CA@HWC  
bcc

Subject FYI only: ADM approved QP note on Salvia divinorum

QUESTION PERIOD NOTE  
NOTE POUR LA PÉRIODE DE QUESTIONS

Date: February 6, 2008  
Classification: HPFB PROTECTED/ PROTÉGÉ DGPSA

English:

## **DRUGS - SALVIA DIVINORUM**

Français:

## **DROGUES - SALVIA DIVINORUM**

### **MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Media interest in *Salvia divinorum* is recurrent. To date questions around this substance have always been about its legality and what, if any, regulatory actions Health Canada is taking. There have been several reports from scientific and media sources, that indicate that *Salvia divinorum* has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of *Salvia divinorum*?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de *Salvia divinorum*?

### **KEY MESSAGES - MESSAGES CLÉS**

English:

- The importation and sale of *Salvia divinorum* could either be restricted under the *Food and Drugs Act* or the *Controlled Drugs and Substances Act*. Health Canada is currently discussing the issue of *Salvia divinorum* and will take appropriate action.
- Health Canada is currently collecting information about the plant and its active ingredient, Salvinorin A from national and

international sources, and assessing the risk that the unrestricted sale of the plant poses to Canadians, including its abuse and dependence potential.

- If the information collected warrants further action, Health Canada will take all necessary actions to safeguard Canadians from potential risks from *Salvia*. These actions may include public risk communications or imposing restrictions over its sale and use.

Français:

- 
- 
- 

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#### SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

English:

Français:

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#### BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious *kappa* -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*. In addition, although *Salvia divinorum* meets the definition of a natural health product, Health Canada has not yet elected to take compliance actions under the *Food and Drugs Act* or its Regulations.

Similarly, in the United States, *Salvia Divinorum* is not regulated under the *Controlled Substances Act*, although it is included on the Drug Enforcement Administration list of Chemicals and Substances of Concern. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few other jurisdictions. In Australia, it is illegal to possess *Salvia divinorum* as both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. Other jurisdictions that have placed controls on *Salvia* are Finland, Denmark and Norway.

#### Current Situation in Canada

As of December, 2007, the Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

While *Salvia divinorum* meets the definition of a Natural Health Product (NHP), no products have been authorized by Health Canada, and *Salvia divinorum* does not appear to be sold as a "health product." *Salvia divinorum* could also be scheduled under the *Controlled Drugs and Substances Act*; however, more information and analysis is required. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on its list of substances of concern.—If the information collected warrants further action, the OCS may assess *Salvia divinorum* against for scheduling under the *Controlled Drugs and Substances Act* (CDSA) these criteria used for adding substances to the appropriate schedules of the CDSA. These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,

- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. *Epub* 2005 Sep 13

**\* HECS-OCS was consulted on this QP - Feb. 6, 2008**

**Contact Information / Personnes-Ressource**

<b>Primary/Primaire:</b> Joan Kennedy	<b>Telephone/Téléphone:</b> xxx-xxxx-xxxx <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b>	<b>Telephone/Téléphone:</b> 613-957-6660 <b>Mobile/Cellulaire:</b>
<b>Secondary/Secondaire:</b>	<b>Telephone/Téléphone:</b>	<b>Title/Titre:</b> A/Director General	
	<b>Mobile/Cellulaire:</b>		

**Director/Contact:** Chris Turner      **Phone Number/**  
**Directeur/Personne**      **Numéro de tél.:** 613-954-6522  
**Ressource:**

**Author/ Auteur:** Joan Kennedy      **Phone Number/**  
**Numéro de tél.:** xxx-xxxx-xxxx

**Directorate-Bureau/**      **Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits**  
**Direction-Bureau:**      **biologiques, biotechnologiques et de santé naturels commercialisés**

**Contact Signed/**       **Contact Signed/Signature de la personne ressource**  
**Signature de la personne**  
**ressource:**

**Date Signed /Date Signé:**      2008-02-06

**DG Approved/**       **D.G. Approved/Approbation par le D.G.**  
**Approbation par le DG:**

**DG Approved by/**  
**Approuvé par le DG:**

**Date DG Approved/**      2008-02-06  
**Date de l'approbation par le DG:**

**Directorate/ Direction:**      **Marketed Health Products Directorate/Direction des Produits de Santé**  
**Commercialisés**

**ADM Approved/**       **ADM Approved/Approbation par le SMA**  
**Approbation par le SMA:**

**ADM Approved by/  
Approuvé par le SMA:** Meena Ballantyne - HPFB/DGPSA (613-957-1804)  
**Date ADM Approved/  
Date de l'approbation  
par le SMA:** 2008-02-06  
**Branch/  
Direction générale:** HPFB/ DGPSA  
**Department/ Ministère:** Health Canada / Santé Canada

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**Edit History:**  
Joan Kennedy Feb 6, 2008 - 11:39:19 AM Moved from Working and marked "ADM Approved"  
Joan Kennedy Feb 6, 2008 - 11:38:35 AM Spellcheck  
Georgette Franklin Feb 6, 2008 - 11:02:30 AM Made changes  
Scott Jordan Feb 6, 2008 - 10:31:16 AM updates  
Scott Jordan Feb 6, 2008 - 08:10:09 AM Updating

**Created By:** Joan Kennedy/HC-SC/GC/CA **Date Created:** February 5, 2008  
**Modified By:** Joan Kennedy/HC-SC/GC/CA **Date Modified:** February 6, 2008

Kyra Paterson, MSc  
Senior Policy Analyst/Analyste principale des politiques  
Policy Development and Regulatory Affairs/Développement des politiques et affaires réglementaires  
Natural Health Products Directorate/Direction des produits de santé naturels  
Health Products and Food Branch/Direction générale des produits de santé et des aliments  
Health Canada/ Santé Canada  
tel/fax: (905)690-0900  
[www.healthcanada.gc.ca/nhp](http://www.healthcanada.gc.ca/nhp)  
[www.santecanada.gc.ca/psn](http://www.santecanada.gc.ca/psn)



Marianne  
DeVito/HC-SC/GC/CA  
2008-02-29 08:08 AM

To PRO-QP Requests  
cc Luc Fournier/HC-SC/GC/CA@HWC, Cassie  
MacAndrew/HC-SC/GC/CA@HWC, Erik Waddell, David  
Pierce/HC-SC/GC/CA@HWC, Laryssa  
bcc

Subject NO REQUIRED QP Notes - February 29

Following a thorough scan of this morning's media clippings, it appears that there are no "new" health-related issues that will need to be immediately addressed in a QP Note format.

**QP NOTES DUE TO PRO TODAY**

(HPFB/HECSB) DRUGS - SALVIA DIVINORUM  
(HPB) DRUG COVERAGE - EXPENSIVE DRUGS FOR RARE DISEASES  
(PHAC) INFECTIOUS DISEASE - HOSPITAL ACQUIRED INFECTIONS

Bonne fin de semaine!

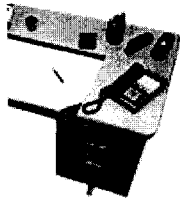
**-Marianne DeVito-**

Question Period & Private Members' Business Coordinator /  
Coordinatrice de la Période des questions & des affaires émanant des députés  
Parliamentary Relations Office / Bureau des relations parlementaires

Tél.: (613) 952-7108

Céll: 





Robin Marles/HC-SC/GC/CA  
2008-02-29 09:01 AM

To Patrice Milord/HC-SC/GC/CA@HWC, Andrew  
Hrycaj/HC-SC/GC/CA@HWC, Nancy  
Richards/HC-SC/GC/CA@HWC

cc

bcc

Subject QP input request from HECS-OCS

Jenifer Collette of HECS-OCS called me this morning looking for urgent input to a QP Note on Salvia divinorum. I forwarded to her this ADM-approved QP Note from just three weeks ago.

Robin

----- Forwarded by Robin Marles/HC-SC/GC/CA on 2008-02-29 08:59 AM -----

QUESTION PERIOD NOTE  
NOTE POUR LA PÉRIODE DE QUESTIONS

Date: February 6, 2008  
Classification: HPFB PROTECTED/ PROTÉGÉ DGPSA

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

**MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Media interest in Salvia divinorum is recurrent. To date questions around this substance have always been about its legality and what, if any, regulatory actions Health Canada is taking. There have been several reports from scientific and media sources, that indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de Salvia divinorum?

## KEY MESSAGES - MESSAGES CLÉS

English:

- The importation and sale of *Salvia divinorum* could either be restricted under the *Food and Drugs Act* or the *Controlled Drugs and Substances Act*. Health Canada is currently discussing the

issue of *Salvia divinorum* and will take appropriate action.

- Health Canada is currently collecting information about the plant and its active ingredient, Salvinorin A from national and international sources, and assessing the risk that the unrestricted sale of the plant poses to Canadians, including its abuse and dependence potential.
- If the information collected warrants further action, Health Canada will take all necessary actions to safeguard Canadians from potential risks from *Salvia*. These actions may include public risk communications or imposing restrictions over its sale and use.

Français:

- L'importation et la vente de *Salvia divinorum* pourraient être contrôlées en vertu de la *Loi sur les aliments et drogues* ou de la *Loi réglementant certaines drogues et autres substances*. Santé Canada étudie actuellement ce dossier et prendra les mesures qui s'imposent.
- Santé Canada recueille actuellement de l'information de source canadienne et étrangère sur cette plante et son ingrédient actif, la salvinorine A. Il évalue également les risques, notamment le potentiel d'abus et de dépendance, que la vente non contrôlée de la plante présente pour les Canadiens.
- S'il juge qu'il doit intervenir d'après l'information qu'il a obtenue, SC prendra toutes les mesures qui s'imposent pour protéger la santé des Canadiens contre les risques potentiels de *Salvia divinorum*. Il pourrait notamment communiquer au public de l'information sur les risques associés à cette plante ou en contrôler la vente et l'utilisation.

## SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

English:

Français:

---

### BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious  $\kappa$ -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

#### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*. In addition, although *Salvia divinorum* meets the definition of a natural health product, Health Canada has not yet elected to take compliance actions under the *Food and Drugs Act* or its Regulations.

Similarly, in the United States, *Salvia Divinorum* is not regulated under the *Controlled Substances Act*, although it is included on the Drug Enforcement Administration list of Chemicals and Substances of Concern. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few other jurisdictions. In Australia, it is illegal to possess *Salvia divinorum* as both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. Other jurisdictions that have placed controls on *Salvia* are Finland, Denmark and Norway.

#### Current Situation in Canada

As of December, 2007, the Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16

year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

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- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

ATTACHMENTS / PIÈCE(S)-JOINTE(S)

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13

\* HECS-OCS was consulted on this QP - Feb. 6, 2008

Contact Information / Personnes-Ressource
---

Primary/Primaire: Joan Kennedy	Telephone/Téléphone: xxx-xxxx-xxxx Mobile/Cellulaire:	Approved by/Approuvé par: A/Director General	Telephone/Téléphone: 613-957-6660 Mobile/Cellulaire: [REDACTED]
Secondary/Secondaire:	Telephone/Téléphone:  Mobile/Cellulaire:		

**Director/Contact:**  
**Directeur/Personne Ressource:** Chris Turner  
**Phone Number/ Numéro de tél.:** 613-954-6522  
**Author/ Auteur:** Joan Kennedy  
**Phone Number/ Numéro de tél.:** xxx-xxxx-xxxx

**Directorate-Bureau/ Direction-Bureau:** Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits biologiques, biotechnologiques et de santé naturels commercialisés

**Contact Signed/ Signature de la personne ressource:**  Contact Signed/Signature de la personne ressource

**Date Signed /Date Signé:** 2008-02-06

**DG Approved/ Approbation par le DG:**  D.G. Approved/Approbation par le D.G.

**DG Approved by/ Approuvé par le DG:**

**Date DG Approved/ Date de l'approbation par le DG:** 2008-02-06

**Directorate/ Direction:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/ Approbation par le SMA:**  ADM Approved/Approbation par le SMA

**ADM Approved by/ Approuvé par le SMA:** Meena Ballantyne - HPFB/DGPSA (613-957-1804)

**Date ADM Approved/ Date de l'approbation par le SMA:** 2008-02-06

**Branch/ Direction générale:** HPFB/ DGPSA

**Department/ Ministère:** Health Canada / Santé Canada

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Joan Kennedy Feb 6, 2008 - 01:43:14 PM Added French translation  
Joan Kennedy Feb 6, 2008 - 11:39:19 AM Moved from Working and marked "ADM Approved"  
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Georgette Franklin Feb 6, 2008 - 11:02:30 AM Made changes  
Scott Jordan Feb 6, 2008 - 10:31:16 AM updates  
Scott Jordan Feb 6, 2008 - 08:10:09 AM Updating

**Created By:** Joan Kennedy/HC-SC/GC/CA  
**Modified By:** Joan Kennedy/HC-SC/GC/CA  
**Date Created:** February 5, 2008  
**Date Modified:** February 6, 2008

Laura Cooney/HC-SC/GC/CA  
2008-03-13 03:26 PM

To Lyane Diotte/HC-SC/GC/CA@HWC  
cc  
bcc  
Subject ATI A-2007-01054/kc1

----- Forwarded by Laura Cooney/HC-SC/GC/CA on 2008-03-13 03:25 PM -----



Robin Marles/HC-SC/GC/CA  
2008-02-29 08:48 AM

To Jenifer Collette/HC-SC/GC/CA  
cc  
Subject Salvia QP Note

----- Forwarded by Robin Marles/HC-SC/GC/CA on 2008-02-29 08:44 AM -----

QUESTION PERIOD NOTE  
NOTE POUR LA PÉRIODE DE QUESTIONS

Date: February 6, 2008  
Classification: HPFB PROTECTED/ PROTÉGÉ DGPSA

English:

## **DRUGS - SALVIA DIVINORUM**

Français:

## **DROGUES - SALVIA DIVINORUM**

### **MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Media interest in Salvia divinorum is recurrent. To date questions around this substance have always been about its legality and what, if any, regulatory actions Health Canada is taking. There have been several reports from scientific and media sources, that indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de Salvia divinorum?

### **KEY MESSAGES - MESSAGES CLÉS**

English:

- The importation and sale of *Salvia divinorum* could either be restricted under the *Food and Drugs Act* or the *Controlled Drugs and Substances Act*. Health Canada is currently discussing the issue of *Salvia divinorum* and will take appropriate action.
- Health Canada is currently collecting information about the plant and its active ingredient, Salvinorin A from national and international sources, and assessing the risk that the unrestricted sale of the plant poses to Canadians, including its abuse and dependence potential.
- If the information collected warrants further action, Health Canada will take all necessary actions to safeguard Canadians from potential risks from *Salvia*. These actions may include public risk communications or imposing restrictions over its sale and use.

Français:

- L'importation et la vente de *Salvia divinorum* pourraient être contrôlées en vertu de la *Loi sur les aliments et drogues* ou de la *Loi réglementant certaines drogues et autres substances*. Santé Canada étudie actuellement ce dossier et prendra les mesures qui s'imposent.
- Santé Canada recueille actuellement de l'information de source canadienne et étrangère sur cette plante et son ingrédient actif, la salvinorine A. Il évalue également les risques, notamment le potentiel d'abus et de dépendance, que la vente non contrôlée de la plante présente pour les Canadiens.
- S'il juge qu'il doit intervenir d'après l'information qu'il a obtenue, SC prendra toutes les mesures qui s'imposent pour protéger la santé des Canadiens contre les risques potentiels de *Salvia divinorum*. Il pourrait notamment communiquer au public de l'

information sur les risques associés à cette plante ou en  
contrôler la vente et l'utilisation.

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**SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES**

English:

Français:

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**BACKGROUND / CONTEXTE**

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious *kappa* -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* . In addition, although *Salvia divinorum* meets the definition of a natural health product, Health Canada has not yet elected to take compliance actions under the *Food and Drugs Act* or its Regulations.

Similarly, in the United States, *Salvia Divinorum* is not regulated under the *Controlled Substances Act* , although it is included on the Drug Enforcement Administration list of Chemicals and Substances of Concern. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few other jurisdictions. In Australia, it is illegal to possess *Salvia divinorum* as both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. Other jurisdictions that have placed controls on *Salvia* are Finland, Denmark and Norway.

Current Situation in Canada

As of December, 2007, the Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions



(ARs) associated with *Salvia divinorum* , used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum* . All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

While *Salvia divinorum* meets the definition of a Natural Health Product (NHP), no products have been authorized by Health Canada, and *Salvia divinorum* does not appear to be sold as a "health product." *Salvia divinorum* could also be scheduled under the Controlled Drugs and Substances Act; however, more information and analysis is required. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on its list of substances of concern.--If the information collected warrants further action, the OCS may assess *Salvia divinorum* against for scheduling under the *Controlled Drugs and Substances Act* (CDSA) these criteria used for adding substances to the appropriate schedules of the CDSA.

These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13

**\* HECS-OCS was consulted on this QP - Feb. 6, 2008**

<b>Contact Information / Personnes-Ressource</b>
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Joan Kennedy	xxx-xxxx-xxxx <b>Mobile/Cellulaire:</b>	<b>Title/Titre:</b> A/Director General	613-957-6660 <b>Mobile/Cellulaire:</b>
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	<b>Mobile/Cellulaire:</b>		

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**Directeur/Personne**  
**Ressource:** Chris Turner  
**Phone Number/**  
**Numéro de tél.:** 613-954-6522

**Author/ Auteur:** Joan Kennedy  
**Phone Number/**  
**Numéro de tél.:** xxx-xxxx-xxxx

**Directorate-Bureau/**  
**Direction-Bureau:** Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits biologiques, biotechnologiques et de santé naturels commercialisés

**Contact Signed/**  
**Signature de la personne**  
**ressource:**  Contact Signed/Signature de la personne ressource

**Date Signed /Date Signé:** 2008-02-06

**DG Approved/**  
**Approbation par le DG:**  D.G. Approved/Approbation par le D.G.

**DG Approved by/**  
**Approuvé par le DG:**

**Date DG Approved/**  
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**Approbation par le SMA:**  ADM Approved/Approbation par le SMA

**ADM Approved by/**  
**Approuvé par le SMA:** Meena Ballantyne - HPFB/DGPSA (613-957-1804)

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**par le SMA:** 2008-02-06

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**Created By:** Joan Kennedy/HC-SC/GC/CA  
**Date Created:** February 5, 2008

**Modified By:** Joan Kennedy/HC-SC/GC/CA  
**Date Modified:** February 6, 2008

s.20(1)(c)



Theresa Schopf  
2005-05-09 12:08 PM

To: Jenny McLaughlin/HC-SC/GC/CA@HWC  
cc: Barbara Bartlett/HC-SC/GC/CA@HWC, Jenna Griffiths/HC-SC/GC/CA@HWC, Julie Robert/HC-SC/GC/CA@HWC, Karen Pilon/HC-SC/GC/CA@HWC, Lynn  
Subject: Re: Salvia Divinorum

Hi Jenny,

As you mentioned in your email, salvia divinorum is not a controlled substance. OCS is tracking its use in Canada; therefore, we welcome any valid data regarding its use in Canada. To date, most of the information we have concerning its use in Canada is anecdotal and not specific.

Regards,  
Theresa

Theresa Schopf, BScPharm., MBA  
Policy and Regulatory Affairs Division  
Office of Controlled Substances  
HECS/Health Canada

Tel:(613)946-6435  
Fax:(613) 946-4224  
Jenny McLaughlin



Jenny McLaughlin  
2005-05-06 05:46 PM

To: Theresa Schopf/HC-SC/GC/CA@HWC, Robin Marles/HC-SC/GC/CA@HWC, Raymond W Tsang/HC-SC/GC/CA@HWC, Barbara Bartlett/HC-SC/GC/CA@HWC, Karen Pilon/HC-SC/GC/CA@HWC, Lynn Macdonald/HC-SC/GC/CA@HWC, Simon Carvalho/HC-SC/GC/CA@HWC, Scott Jordan/HC-SC/GC/CA@HWC, Jenna Griffiths/HC-SC/GC/CA@HWC  
cc: Patricia Maynard/HC-SC/GC/CA@HWC, Nada El-Defrawy/HC-SC/GC/CA@HWC, Julie Robert/HC-SC/GC/CA@HWC, Marie Morrisey/HC-SC/GC/CA@HWC, Stéphane Gélinas/HC-SC/GC/CA@HWC, Sandra Cashin/HC-SC/GC/CA@HWC  
Subject: Salvia Divinorum

Hi all,

I would like to bring your attention to 3 complaints regarding the sale of Salvia Divinorum and reported adverse reactions.

2 complaints were received in our Quebec Operational Centre. The complainants had experienced an adverse reaction associated to the use of Salvia. The product is represented for sale as "Encens Special One Puff" and the product is sold in different concentration ; mild, medium and strong. Complainant mentioned that product is available OTC.

1 complaint was received in our Manitoba/Saskatchewan Operational Centre. The complaint was from a mother whose 16-year-old son had ingested some alcohol, then took a tablet of Salvia Divinorium (also known as Maria Pestora). She said her son went into a drug-induced psychosis - had no sense of reality, he was hallucinating, was suicidal, and the police came and put him in restraints. The complainant has been advised to report this adverse reaction to MHPD Adverse Reaction Centre 1-866-234-2345. [REDACTED] is allegedly selling Salvia singularly "by the tablet" for \$30 to \$40 per tablet. Absence of labelling indicates a risk to the public. There are 4 retail locations of [REDACTED] and they are wholesaling and selling this product on the Internet [REDACTED]. They appear to be importing the herb in bulk, and packaging the product with their own labelling [REDACTED]. It is standardized

20x Salvia with 72 mg of Salvinorin-A.

I understand that Salvia is not a controlled substance. Since Salvia is a natural substance, it would meet the "substance" part of the NHP definition but not the "function" part of the definition, as "hallucinogen" is not an acceptable claim for an NHP. Although Salvia poses a risk of abuse, I don't believe an HHE has ever been conducted, and therefore there is no identified risk for the substance itself.

I know that an IAS was prepared by NHPD and MHPD last summer but I'm not sure what the outcome of the discussions were at that time. **Can someone please advise as to which regulatory authority this substance would fall under? (NHP Regs v.s. CDSA v.s. Food and Drug Regs)**

Thanks,  
Jenny

Robin Marles

2005-07-21 06:24 PM

To: Julia Hill/HC-SC/GC/CA@HWC, Ouassim  
Meguellati/HC-SC/GC/CA@HWC, Patrice  
Lemyre/HC-SC/GC/CA@HWC, Isabelle Caron/HC-SC/GC/CA@HWC  
cc: bbowen@inspection.gc.ca  
Subject: Fwd: CBC article on Salvia divinorum...

Just wanted to let you know that NHPD and MHPD collaborated to prepare a health risk assessment on Salvia divinorum (Diviner's Sage). It does not pose a significant intrinsic risk to health (i.e. very low toxicity) due to a unique mechanism of action that does not involve the receptors in the brain responsible for addiction, but in fact acts at receptors that have anti-addiction activity (hence the street reports that it is not very much fun). The main risk to health would be from activities (such as driving) undertaken while under the influence of the drug.

Since it is being sold and used as a recreational drug (hallucinogen), it has not been interpreted as meeting the function portion of the definition of a natural health product. The Office of Controlled Substances is monitoring the situation, but so far has not decided to schedule Salvia divinorum as a controlled substance due to the low toxicity and lack of addiction potential.



Salvia divinorum IAS 2004-07-15.r

Robin.

----- Forwarded by Robin Marles/HC-SC/GC/CA on 2005-07-21 06:11 PM -----



"Bruce Bowen"  
<bbowen@inspection.gc.ca>  
c.ca>

2005-07-21 05:00 PM

To: <Robin\_Marles@hc-sc.gc.ca>  
cc: <Jenny\_Mclaughlin@hc-sc.gc.ca>, <Lance\_Hill@hc-sc.gc.ca>,  
<Marie\_Morrissey@hc-sc.gc.ca>, <Micheline\_Ho@hc-sc.gc.ca>,  
<Peter\_Chan@hc-sc.gc.ca>, <raymond\_w\_tsang@hc-sc.gc.ca>  
Subject: Fwd: CBC article on Salvia divinorum...

050721.Thursday

Heads up ... media interest in Salvia divinorum and its hallucinogenic properties ...see attached

Best Regards ... Bruce Bowen  
Content-Transfer-Encoding: quoted-printable  
Date: Thu, 21 Jul 2005 16:38:31 -0400  
From: "Mary Rutherford" <rutherfordm@inspection.gc.ca>  
To: "Bruce Bowen" <bbowen@inspection.gc.ca>  
Cc: "Robin Atkinson" <atkinsonr@inspection.gc.ca>, "Alan Monfette"  
<monfettea@inspection.gc.ca>, "Terry Desrochers"  
<tdesrochers@inspection.gc.ca>  
Subject: CBC article on Salvia divinorum...  
Mime-Version: 1.0  
Content-Type: text/plain; charset=ISO-8859-1  
Content-Disposition: inline

This might be one we want to add to the SOS document. Likely should not be added to food.

Mary

C B C . C A N e w s - F u l l S t o r y :

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Teens buying legal psychedelic herb, police warn  
Last Updated Thu, 21 Jul 2005 15:12:31 EDT  
CBC News

Teenagers across Canada are buying an herb that packs a powerful psychedelic punch. Health Canada and the RCMP say they're keeping a close eye on the legal sales.

Salvia divinorum, a sage-like plant, can produce intense hallucinations when smoked or chewed.

"When I first did it, within 30 seconds it was already doing its thing," said Blair Anderson, who co-owns a drug paraphernalia shop a few blocks from a high school in Edmonton. "I was thinking 'Man, this is just like LSD but it's happening really fast.'"

The store's co-owner, Colin Rogucki, said they decided not to sell the cheap drug to anyone under 18 because he thinks the drug's intensity makes it potentially dangerous to young teens.

The pair said they turn down many young people trying to get salvia to smoke.

"The drug is very common, easy to get and it's not illegal," said Constable Jason Lefebvre, a high school resource officer with Edmonton police. "So it seems natural that a lot of younger people are interested and curious about it and want to try it."

Students have reported the drug was disorienting, Lefebvre said. "They didn't say it was very much fun."

Edmonton police plan to provide more information about salvia to students and parents in September.

Police in Thunder Bay also noted the drug surfaced in their city this spring.

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**Robin Marles**  
2005-01-10 03:00 PM

To: Nathalie Lalonde/HC-SC/GC/CA@HWC  
CC:  
Subject: **Salvia divinorum**

Here is the review by MHPD, whose conclusions are included in the attached IAS.



Potential: Dependence Effect of **Salvia divinorum** **Salvia divinorum** IAS 2004-07-15.c

## **Report: Potential Dependence Effect of *Salvia divinorum***

Dr. Shahid Perwaiz  
Marketed Natural Health Products Division,  
MHPD

Dated: July 7, 2004.

### **Purpose/Objective:**

*Salvia divinorum* is one of several psychoactive plants, used by the Mazatec Indians, Mexico. *Salvia* is smoked to induce visual hallucinations, the diversity of which are described by its user to be similar to those induced by other hallucinogens such as mescaline, or psilocybin. Since *Salvia divinorum*, or any of its active ingredients are not specifically listed in the controlled Drugs and Substances Act, nor any Schedule of the Food and Drugs Act or its Regulations in Canada, some on-line botanical companies and drug promotional sites have advertised *Salvia* as a legal alternative to other plant hallucinogens like mescaline.

Salvinorin A is the active component of *Salvia divinorum*, and is most effective when vaporized and inhaled. Its actions in the brain are not well elucidated. However, recently it has been reported through *in vitro* assays, that "Salvinorin A" is the first known naturally occurring non-nitrogenous full agonist at kappa-opioid receptors, but functional assays are still lacking to determine the exact pharmacological mechanism of its action in the body. Most of the drugs which result in habit forming/dependence effects exert their activity through opioid receptor activation. The objective of this report is to provide background on whether *Salvia divinorum* has the potential to induce dependence effects.

### **Background:**

*Salvia divinorum* is a psychoactive plant, a member of the mint family, that has been used by Mazatec indigenous people of the Oaxaca for centuries for traditional spiritual practices. The primary active ingredient of *Salvia divinorum* is "salvinorin A" (there are B and C forms) is most effective when vaporized and inhaled. Chemically, Salvinorin A is a neoclerodane diterpene, a psychotropic terpenoid. Other plants with similar properties include *Cannabis sativa*, which contains tetrahydrocannabinol (THC), and *Artemisia absinthium*, also known as wormwood and used to make asbinthium. A dose of 200 to 500 micrograms of salvinorin A produces profound hallucinations when smoked. Its effects in the open field test in mice and locomotor activity tests in rats are similar to those of mescaline. A large body of evidence links the action of hallucinogenic agents (LSD, mescaline) to effects at serotonin (5-HT) receptor sites in the central nervous system (Aghajanian and Marek, 1999). Salvinorin A's actions in the brain are not well elucidated. However, recent tissue testing (*in vitro* assays) have suggested that "Salvinorin A" acts at the kappa opiate receptor site, but functional assays are lacking to determine the exact mechanism of action of this drug substance (Chavkin et al., 2004; Leander and Valdes, 1994; Roth et al., 2002).

Drug dependence is a physiologic state where continued administration of the drug is necessary to



prevent withdrawal; it can be of two types, physical and/or psychological dependence. The existence of three major groups of opioid receptors (mu, delta and kappa) in the central nervous system is well documented (Suzuki and Misawa, 1997). There are complicated interactions among opioid receptor types. The activation of kappa opioid receptor suppresses physical and psychological dependence on mu and delta opioid receptor agonists, but the activation of the delta opioid receptor potentiates the dependence on mu opioid receptor agonists. Various studies provide arguments to support substantial roles for mu-opioid receptors and the possible involvement of delta-opioid receptors in the development of physical and psychological dependence on morphine (Narita et al., 2001; Suzuki and Misawa, 1997). Most of the drugs used clinically are mu-opioid analgesics and are habit-forming. While both receptor types (delta and mu) provide analgesia, only the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dexamethorpan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor. (Gaveriaux-Ruff and Kieffer, 2002; Narita et al., 2001; Pasternak, 2003; Suzuki and Misawa, 1997). From behavioural, biochemical and molecular biological studies, it is suggested so far that development of physical dependence on morphine results predominantly from an activation of mu 1 and mu 2 opioid receptors which cause functional changes in Gi/o, adenylate cyclase, protein kinases A and C, beta-adrenoceptor and NMDA receptor in the locus coeruleus. However, activation of the mesolimbic dopamine system may lead to psychological dependence on opioids. (Narita et al., 2001; Suzuki and Misawa, 1997).

It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect. Recently, there have been significant advances in studies on the role of kappa-opioid receptor agonist in producing an aversive effect of other stimulants such as Morphine, cocaine, THC, alcohol, and other non-opioid addictions (Cui et al., 2000; Hahn et al., 2000; Mori et al., 2002; Raffa et al., 2003; Rosin et al., 1999; Rothman et al., 2000; Schenk et al., 1999; Tao et al., 1994). The activation of kappa-receptors also leads to the suppression of unpleasant mu/delta-mediated side effects such as dependence and respiratory depression. Considering the functional interaction between opioid receptor types, the co-administration of morphine-like compounds with kappa-receptor agonists may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

Salvinorin A is unique in that it is a potent, non-nitrogenous kappa-opioid selective agonist largely ignored by other known opioid agonists. Therefore, it would be devoid of the, mainly mu receptor mediated, side effects such as dependence and respiratory depression associated with morphine and its other analogues. It may thus be possible to use Salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, depression, and even excessive marijuana use. Being defined by their selectivity for the kappa-class of opioid receptor, Salvinorin A has the potential to offer a non-habit forming alternative. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

## **CONCLUSION:**

On the basis of available scientific literature, the potential dependence effects of *Salvia divinorum* are expected to remain very low because of the following:

1. Most of the drugs which cause dependence and addiction are mu-opioid agonists, while salvinorin A acts as a full agonist at kappa-opioid receptors and appears to possess no mu-activity.
2. Kappa-opioid receptor agonists are characterized as being able to modulate dependence-related behavioural effects of drugs like morphine and cocaine rather than causing dependence.
3. There have been no cases of dependence on *Salvia divinorum* or salvinorin A reported in the scientific literature.
4. The precise mechanism of interaction between salvinorin A and the brain to produce its hallucinogenic effects remains unclear.
5. The toxicity of Salvinorin A is relatively low, even at doses many times greater than what human are exposed to (Mowry et al., 2003).
6. Many individuals have reported experiencing negative effects (bitter taste, unpredictable and occasionally disturbing short-term mental effects) during their first experience with *Salvia divinorum* and indicate that they would not use it a second time.
7. One internet distributor indicated that only 1 in 10 customers places a repeat order for the drug.

#### **References:**

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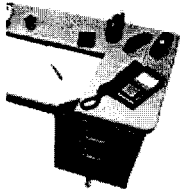
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Robin Marles/HC-SC/GC/CA  
2008-02-06 08:25 AM

To Kyra Paterson/HC-SC/GC/CA@HWC, Scott  
Jordan/HC-SC/GC/CA@HWC  
cc  
bcc  
Subject Fw: Salvia Divinorum

----- Forwarded by Robin Marles/HC-SC/GC/CA on 2008-02-06 08:25 AM -----

CCIM/HC-SC/GC/CA  
Sent by: Maggie Graham  
2007-09-05 06:12 PM

To Stephanie Lessard/HC-SC/GC/CA@HWC, Robin  
Marles/HC-SC/GC/CA@HWC, Valerie  
Assinewe/HC-SC/GC/CA@HWC  
cc CCIM/HC-SC/GC/CA@HWC  
Subject Re: Fw: Salvia Divinorum 

Christine Zaczynski

Christine Zaczynski  
2007-09-05 02:43 PM

To: Maggie Graham/HC-SC/GC/CA@HWC, CCIM/HC-SC/GC/CA@HWC  
cc: Jenny McLaughlin/HC-SC/GC/CA@HWC, Julie  
Thorpe/HC-SC/GC/CA@HWC  
Subject: Fw: Salvia Divinorum

Hey Maggie,

Please see below. We plan on moving forward with taking action on bulk Salvia products under the Natural Health Products Regulations.

We hope to use the HRA identifying the risk as a Type II in addition to the legal statement below (representation for use extended to off label).

Please provide us with any comments you may have on this.  
(Note that Simon's email has been cc'd to Phil and Nancy)

Christine

----- Forwarded by Christine Zaczynski/HC-SC/GC/CA on 2007-09-05 02:36 PM -----



Jenny  
McLaughlin/HC-SC/GC/CA  
2007-09-05 02:29 PM

To Christine Zaczynski/HC-SC/GC/CA@HWC  
cc Jason Andrus/HC-SC/GC/CA@HWC, Niyi  
Lawuyi/HC-SC/GC/CA@HWC, Julie  
Thorpe/HC-SC/GC/CA@HWC, Diane Wai Chung  
Lai/HC-SC/GC/CA@HWC, Jean Saint  
Pierre/HC-SC/GC/CA@HWC, Christiane  
Brown/HC-SC/GC/CA@HWC, Sarah  
Wiles/HC-SC/GC/CA@HWC, Christine  
Zaczynski/HC-SC/GC/CA@HWC, Michelle  
Gillespie/HC-SC/GC/CA@HWC, James



Bellis/HC-SC/GC/CA@HWC, Melissa  
Beauchamp/HC-SC/GC/CA@HWC, Sharon  
Mullin/HC-SC/GC/CA@HWC, Diana  
Dowthwaite/HC-SC/GC/CA@HWC

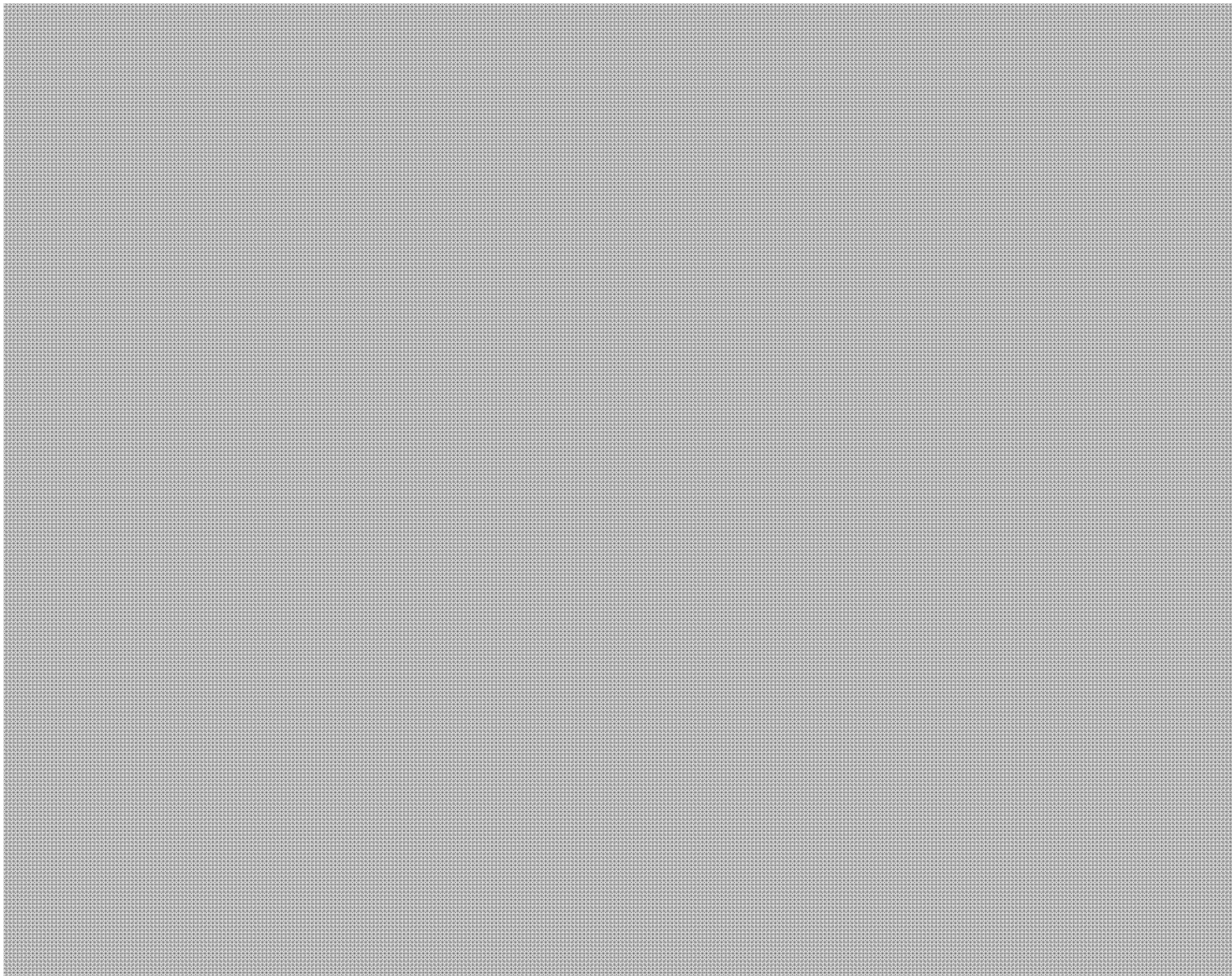
Subject Fw: Salvia Divinorum

Hi Christine,

See response from Simon below regarding the classification of salvia divinorum. Based on this and the fact that NHPD has determined that salvia products pose a Type II health hazard, I think the Inspectorate should start taking action (i.e. stop sale, recall, refusal at customs) consistently against salvia products, regardless of whether there are health claims being made.

Jenny

----- Forwarded by Jenny McLaughlin/HC-SC/GC/CA on 2007-09-05 02:25 PM -----



**Page(s) 000199 to\à 000199**

**Is(Are) exempted pursuant to section(s)  
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

**21(1)(b)**

**of the Access to Information Act  
de la Loi sur l'accès à l'information**



NHPD-MHPD Salvia IAS Nov 2006.doc



Salvia divinorum HRA June.07.wpd



Signal Assessment- Salvia divinorum June5.07wpd.wpd

Thanks,  
Jenny

----- Forwarded by Jenny McLaughlin/HC-SC/GC/CA on 2007-09-05 09:06 AM -----

CCIM/HC-SC/GC/CA

2007-08-08 05:59 PM

To Jenny McLaughlin/HC-SC/GC/CA@HWC

cc CCIM/HC-SC/GC/CA@HWC, Erica

Daley/HC-SC/GC/CA@HWC

Subject Re: Salvia Divinorum

Salut Jenny,

As per our discussion, given the Branch discussions on this product, at this time we are not able to process this request.

Please do not hesitate to call me to discuss.

Merci,  
Maggie

Jenny McLaughlin



Jenny McLaughlin

2007-08-07 04:38 PM

To: Ruby Yang/HC-SC/GC/CA@HWC

cc: Christine Zaczynski/HC-SC/GC/CA@HWC, Maggie

Graham/HC-SC/GC/CA@HWC, CCIM/HC-SC/GC/CA@HWC

Subject: Re: Salvia Divinorum

Hi Ruby,

Based on the label instructions for use, it appears that this product is to be used for a therapeutic effect. I would consider this product to be an NHP but will confirm with NHPD and get back to you ASAP.

Maggie - FYI. I will submit a PC request in the database now but as this product is being held at customs, please process asap.

Thanks,  
Jenny

Ruby Yang/HC-SC/GC/CA

Ruby Yang/HC-SC/GC/CA

2007-08-07 04:13 PM

To Christine Zaczynski/HC-SC/GC/CA@HWC

cc Jenny McLaughlin/HC-SC/GC/CA@HWC

Subject Salvia Divinorum

Hello



A shipment of Salvia Divinorum is being held by CBSA, the shipment contains 66 pkgs of Salvia Divinorum 10X and 69 pkgs of Salvia Divinorum 5X , label of the product attached for your reference.

I believe this is a repeated shipment, previous shipment contains same product addressed to the same individual with different address in the same city in January 2007.



Salvia\_Divinorum.pdf

I checked NHP Work Book and noticed that you have put a request similar to my situation, however, this one

- contains Oaxacan Salvia Divinorum Extract, and declared " For incense use only "
- The product is a consumer package not in bulk
- Please check the label, Directions,.....could we still consider the product a "NOT-NHP" ?

Would you please let me know if NHPD would support refusals of the shipment under the NHPR?

Thank you.

Ruby Yang  
Western Operational Centre

## **NHPD AND MHPD ISSUE ANALYSIS SUMMARY**

### ***Salvia divinorum* Regulatory Authority and Health Risks**

**Prepared by:** Jacinta Roberts and Robin Marles, NHPD, and Shahid Perwaiz, MHPD

**Draft Date:** June 24, 2004

**Draft Revised:** July 15, 2004

**Finalized:** July 15, 2004

**Updated:** November 3, 2006

#### **ISSUES**

1. Which regulatory authority is most appropriate for *Salvia divinorum* under various conditions of use?
2. What are the risks to consumers of this substance?

#### **BACKGROUND AND ISSUE ANALYSIS**

##### ***Salvia divinorum* as a Health Product**

*Salvia divinorum* Epling & Játiva is an herb in the mint family (Lamiaceae), native to Mexico, that is smoked as a hallucinogen. As a substance it falls under Item 1 of Schedule 1 (inclusion list) to the *Natural Health Products Regulations*, which includes: “a plant or plant material, an alga, a bacterium, a fungus or a non-human animal material.”

The main active ingredient of *Salvia divinorum* is a neoclerodane diterpene compound called salvinorin A, which currently falls under Schedule 1, item 2: “an extract or isolate of a substance described in item 1, the primary molecular structure of which is identical to that which it had prior to its extraction or isolation.”

In Canada neither the herb, *Salvia divinorum*, nor its active ingredients, such as salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* (CDSA), nor any Schedule of the *Food and Drugs Act* or its Regulations that would remove it from the purview of the *Natural Health Products Regulations*.

*Salvia divinorum* and its active constituents therefore meet the substance aspect of the regulatory definition of a natural health product.

Whether or not *Salvia divinorum* products meet the function aspect of the regulatory definition of a natural health product depends on the purpose for which the product is being manufactured, sold, or represented for use. According to Section 1(1) of the *Natural Health Products Regulations*, a natural health product means a substance that is manufactured, sold, or represented for use in:

- (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- (b) restoring or correcting organic functions in humans; or
- (c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

*Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/ constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1982).

With respect to potential modern uses, there is one human case study from Australia suggesting a possible antidepressant effect (Hanes 2001).

Since *Salvia divinorum* and salvininorin A under some conditions of use meet both the functional and substance portions of the definition of a natural health product and are not currently subject to any regulatory exclusions, if associated with a health claim finished products containing these substances could be considered to be natural health products (NHPs).

Until such time as the herb and its active constituent are scheduled under the CDSA or Schedule F to the *Food and Drug Regulations*, the NHPD has jurisdiction to receive a Product Licence Application for a therapeutic use. However, the safety assessment will be sufficiently rigorous to protect consumers' health, particularly with respect to the following safety factors:

- “Does the medicinal ingredient or product have a demonstrated potential for addiction, abuse or severe dependency that is likely to lead to harmful non-medicinal use?”
- “Does the medicinal ingredient or product have known adverse effects at the recommended or therapeutic dosage level?”
- “Does the medicinal ingredient or product have a therapeutic effect based on recently established pharmacological concepts, the consequences of which have not yet been fully established?”
- “Does the medicinal ingredient or product possess a high level of risk relative to expected benefits?”

The answers to these questions are as follows:

- Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in way that is quite different from other hallucinogens such as heroin or LSD.
- Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions.
- It is subject to abuse as a street drug.
- It acts on the brain in a way that is quite novel and for which the consequences have not yet been fully established.

For all those reasons, the risks of *Salvia divinorum* use compared to any expected benefits suggest that if it were to be regulated as a health product, it should require a prescription under the *Food and Drug Regulations*, rather than being regulated as an over-the-counter natural health product.

### ***Salvia divinorum as a Hallucinogen***

As with many other NHP substances, there are other uses for the herb that may in future be more appropriately regulated under a different framework.

*Salvia divinorum* is used as a hallucinogen in traditional divination rituals (Valdés et al. 1982) and is being widely touted on internet sites aimed at young adults and adolescents as a “legal” alternative street drug.

The current use and advertising of *Salvia divinorum* as a recreational hallucinogen does not meet the intent of the function component of the *Natural Health Products Regulations*’ definition of a natural health product. Nevertheless, even if it is being sold without labelled claims as leaf material in a plastic baggy, it is being represented for use in “modifying organic functions in humans” so from a compliance perspective *Salvia divinorum* falls under the jurisdiction of the *Food and Drugs Act*.

As a hallucinogen and drug of abuse, Health Canada’s Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances will collect relevant information specific to this herb and its active constituents.

### ***Salvia divinorum in Other Regulatory Jurisdictions***

In the U.S. Congress, *Salvia divinorum* was the subject of a bill (H.R.5607) entitled “To amend the Controlled Substances Act to place Salvinorin A in Schedule I” introduced on October 10, 2002, seeking to place the herb and its active constituent salvinorin A onto U.S. Controlled Substances Act Schedule 1 (drugs or other substances with a high potential for abuse, with no currently accepted medical use in treatment in the United States, and with respect to which there is a lack of accepted safety for use under medical supervision). Since November 11, 2002, the bill has been referred to the Subcommittee on Crime, Terrorism, and Homeland Security (<http://thomas.loc.gov/cgi-bin/bdquery/z?d107:HR05607:@@L&summ2=m&>, accessed June 24, 2004).

Currently, the FDA considers street drug alternatives such as *Salvia divinorum* to be unapproved new drugs and misbranded drugs under sections 505 and 502 of the Act (<http://www.fda.gov/cder/guidance/3602fnl.pdf>, accessed May 26, 2004) and has issued warning letters to a number of firms. Thus it appears that the U.S. has sufficient regulatory authority already to achieve the necessary level of control.

Both the herb and the active ingredient are listed on Schedule 9 of Australia’s Standard for the Uniform Scheduling of Drugs and Poisons on the basis of “high potential for abuse and risk to public health and safety,” but no substantiation of this risk was provided (<http://www.tga.health.gov.au/ndpsc/record/rr200111upd8.pdf>, accessed May 26, 2004). They are both also in Category B of the Danish list of controlled substances (<http://www.retsinfo.dk/delfin/html/b2003/0071405.htm>, accessed May 26, 2004).

### ***Scientific Details of the Potential of Salvia divinorum for Abuse***

*Salvia divinorum* is smoked to induce visual hallucinations, the diversity of which are described by its users to be similar to those induced by other hallucinogens such as

mescaline or psilocybin. Since neither *Salvia divinorum* nor any of its active ingredients are specifically listed in the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act* or its Regulations in Canada, some on-line botanical companies and drug promotional sites have advertised the herb as a legal alternative to other plant hallucinogens like mescaline. The objective of this section is to provide background on whether or not *Salvia divinorum* has the potential to induce dependence effects.

Salvinorin A (there are B and C forms) is a hallucinogen when vaporized and inhaled. Salvinorin A is a highly efficacious *kappa*-opioid receptor agonist of clinical interest for treatment and etiological studies of depression, dementia, bipolar disorder, and schizophrenia (Chavkin et al. 2004, Roth et al. 2002). Chemically, salvinorin A is a psychotropic diterpenoid.

Other plants with similar properties include *Cannabis sativa*, which contains the phenolic active principle, tetrahydrocannabinol (THC), and *Artemisia absinthium*, also known as wormwood and used to make the liqueur asbinthe, which contains the monoterpene active principle, thujone.

A dose of 200 to 500 micrograms of salvinorin A produces profound hallucinations when smoked. Its effects in the open field test in mice and locomotor activity tests in rats are similar to those of mescaline. A large body of evidence links the action of hallucinogenic agents (LSD, mescaline) to effects at serotonin (5-HT) receptor sites in the central nervous system (Aghajanian and Marek 1999). Salvinorin A's actions in the brain are not well elucidated. However, recent tissue testing (in vitro assays) have suggested that salvinorin A acts at the *kappa* opiate receptor site (Chavkin et al. 2004; Valdes 1994; Roth et al. 2002). Effects associated with *kappa* opioid receptor activation include analgesia, sedation, and dysphoria (Barker et al. 2002). Using in vitro methods, Margolis et al. (2003) have found evidence that the mechanism of action of *kappa* opiate receptor agonists may involve direct inhibition of midbrain (ventral tegmental area) dopaminergic neurons that play a critical role in motivation and reinforcement of goal-directed behaviours, and have also been implicated in the addictive process initiated by drugs such as morphine.

Drug dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal; it can be of two types, physical and/or psychological dependence. The existence of three major groups of opioid receptors (*mu*, *delta* and *kappa*) in the central nervous system is well documented (Suzuki and Misawa 1997). There are complicated interactions among opioid receptor types. The activation of the *kappa* opioid receptor suppresses physical and psychological dependence on *mu* and *delta* opioid receptor agonists, but the activation of the *delta* opioid receptor potentiates the dependence on *mu* opioid receptor agonists. Various studies provide arguments to support substantial roles for *mu*-opioid receptors and the possible involvement of *delta*-opioid receptors in the development of physical and psychological dependence on morphine (Narita et al. 2001; Suzuki and Misawa 1997).

Most of the drugs used clinically that are mu-opioid analgesics are habit-forming. While both receptor types (delta and mu) provide analgesia, only the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dextramethorpan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor (Gaveriaux-Ruff and Kieffer 2002; Narita et al. 2001; Pasternak 2003; Suzuki and Misawa 1997). From behavioural, biochemical and molecular biological studies, it is suggested so far that development of physical dependence on morphine results predominantly from an activation of mu 1 and mu 2 opioid receptors which cause functional changes in Gi/o, adenylate cyclase, protein kinases A and C, beta-adrenoceptor and NMDA receptor in the locus coeruleus. However, activation of the mesolimbic dopamine system may lead to psychological dependence on opioids (Narita et al. 2001; Suzuki and Misawa 1997).

It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect, i.e. dysphoria rather than euphoria (Kumor et al. 1986; Rothman et al. 2000). Recently, there have been significant advances in studies on the role of kappa opioid receptor agonists in producing an aversive effect of other stimulants such as morphine, cocaine, THC, alcohol, and in other non-opioid addictions (Cui et al. 2000; Hahn et al. 2000; Collins et al. 2001; Mori et al. 2002; Raffa et al. 2003; Rosin et al. 1999; Rothman et al. 2000; Schenk et al. 1999; Tao et al. 1994). The activation of kappa-receptors also leads to the suppression of unpleasant mu/delta-mediated side effects such as dependence and respiratory depression. Considering the functional interaction between opioid receptor types, the co-administration of morphine-like compounds with kappa-receptor agonists may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

Salvinorin A is unique in that it is a potent, non-nitrogenous, selective kappa opioid agonist distinct in its actions from other known opioid agonists. Therefore, it appears to be devoid of the mainly mu receptor-mediated side effects such as dependence and respiratory depression associated with morphine and its other analogues. It may thus be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, depression, and even excessive marijuana use. Being defined by its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

In conclusion, on the basis of available scientific literature, the potential addiction or dependence effects of *Salvia divinorum* are expected to remain very low because of the following:

- Most of the drugs which cause dependence and addiction are mu-opioid agonists, while salvinorin A acts as a full agonist at kappa opioid receptors and appears to possess no mu opioid receptor activity.

- Kappa opioid receptor agonists are characterized as being able to modulate dependence-related behavioural effects of drugs like morphine and cocaine rather than causing dependence.
- There have been no cases of dependence on *Salvia divinorum* or salvinorin A reported in the scientific literature.
- The precise mechanism of interaction between salvinorin A and the brain to produce its hallucinogenic effects remains unclear.
- The toxicity of salvinorin A is relatively low, even at doses many times greater than what humans are exposed to (Mowry et al., 2003).
- Many individuals have reported experiencing negative effects (bitter taste, unpredictable and occasionally disturbing short-term mental effects) during their first experience with *Salvia divinorum* and indicate that they would not use it a second time.

#### ***Canadian Reports of Adverse Reactions to Salvia divinorum Products***

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with products said to contain *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum* products. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of tablets said to contain *Salvia divinorum* and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

#### **PRESENT HEALTH CANADA ACTIONS:**

1. Adverse reactions to *Salvia divinorum* or salvinorin A reported through the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) and those reported in the United States and other jurisdictions are being monitored continuously, recognizing that it is unlikely that adverse reaction reports for these substances will be adequately documented due to *Salvia divinorum*'s use primarily as an hallucinogen. Some information might also be available from Poison Control Centres but there is apparently no uniform means for communication between Poison Control Centres at this time.
2. Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances is collecting relevant information specific to this herb and its active constituents.
3. A Customs Lookout is already in place and should be continued to restrict importation.

4. *Salvia divinorum* and its active principles are being represented for use in modifying organic functions in humans and are therefore classified as health products that fall under the jurisdiction of the *Food and Drugs Act*. To protect the health of Canadians, they are subject to compliance actions by the Health Products and Food Branch Inspectorate in accordance with their Policy 0001.

**NEXT STEPS:**

1. If the information collected warrants further action, the Office of Controlled Substances will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedule of the *Controlled Drugs and Substances Act*. These criteria include:
  - international requirements and trends in control/scheduling;
  - chemical and pharmacological similarity to other drugs listed in the CDSA;
  - dependence potential;
  - likelihood of abuse/misuse;
  - extent of abuse/misuse in Canada;
  - danger to public health and safety, and
  - legitimate use in Canada.
2. If *Salvia divinorum* is added to one of the Schedules to the *Controlled Drugs and Substances Act* it will become subject to compliance actions by the federal, provincial, and municipal police forces instead of the HPFB Inspectorate.



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Health Canada Santé  
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Health Products and Food Branch  
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## Health Risk Assessment of *Salvia divinorum* as a Health Product

Marketed Biologicals, Biotechnology and Natural Health Products Bureau  
Marketed Health Products Directorate  
and  
Bureau of Product Review and Assessment,  
Natural Health Products Directorate

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### **Issue:**

In the last several years, Health Canada has become aware of the use of the plant *Salvia divinorum* as a recreational hallucinogen, and as a “legal alternative” to illicit drugs. In certain parts of North America, this plant has been traditionally used for religious, as well as for health purposes. *Salvia divinorum* meets the criteria for regulation under the *Natural Health Products Regulations*; however, as a hallucinogen, it may also meet the criteria of a substance regulated under the *Controlled Drugs and Substances Act*, or the *Food and Drug Regulations*.

This risk assessment was undertaken to determine the potential risks from the use of *Salvia divinorum* as a health product, and will help determine potential compliance actions to be taken on products available on the Canadian market, containing *Salvia divinorum* or its active constituents.

### **Background:**

*Salvia divinorum* is a plant from the mint family. It is also known by a number of common names such as Diviners Sage, Magic Sage, Mexican Sage, Sage of the Seers, and Herba Maria (Natural Medicines Comprehensive Database, 2007). The plant has been used in traditional and spiritual practices by the Mazatec Indians of Oaxaca, Mexico, to produce “mystical” or hallucinogenic experiences (Diaz, 1976).

Health Canada has received four reports of adverse reactions involving psychotropic effects, associated with the use of *Salvia divinorum*. There have been several reports (scientific articles, case reports, media enquiries/articles) which indicate that *Salvia divinorum* has the potential for abuse, and is being used by adolescents and young adults for its hallucinogenic properties. In addition, *Salvia* is being widely touted on internet sites aimed at these population groups, as a “legal” alternative to street drugs.

In Canada, neither the herb *Salvia divinorum*, nor its active constituents such as salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* (CDSA), nor any Schedule of the *Food and Drugs Act and Regulations*. *Salvia divinorum* meets the definition of a natural health product (NHP) if marketed in Canada with health claims. However, the current use and advertising of *Salvia divinorum* as a recreational hallucinogen does not meet the intent of the functional component of the definition of a natural health product. In addition, as a hallucinogen and potential drug of abuse, Health Canada's Office of Controlled Substances (OCS) has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the OCS will collect relevant information specific to this herb and its active constituents, in relation to its psychotropic use.

Since *Salvia divinorum* in some circumstances meets the definition of a NHP and is not listed in any Schedule to the CDSA, nor any Schedule of the *Food and Drugs Act* or its Regulations, it is appropriate to assess the health risk associated with the use of *Salvia divinorum*, when used as a health product.

#### **Traditional Use:**

##### Non-Psychoactive Use:

When consumed orally, *Salvia divinorum* has been used traditionally to treat diarrhoea, constipation, anaemia, headache, rheumatism and alcohol addiction, as well as for regulation of urination. It is also used topically in traditional settings for treating ulcers of the skin (Natural Medicines Comprehensive Database, 2007; Valdes et al., 1982).

##### Psychoactive Use:

*Salvia divinorum* has been used traditionally by the Mazatec people of Oaxaca, Mexico, for religious ceremonies, in order to produce "mystical" and hallucinogenic experiences. The psychoactive effects can be produced by chewing the leaves, or by inhalation of the smoke from the leaves.

#### **Non-Traditional Use:**

##### Non-Psychoactive Use:

No information is available on *Salvia divinorum*-containing products currently marketed for health-related purposes. Some research, however, suggests therapeutic potential for salvinorin A (see Therapeutic Potential section, below).

##### Psychoactive Use:

The main non-traditional use of *Salvia divinorum* relates to its psychoactive properties and use as a street drug. The hallucinogenic properties can be achieved by a variety of means, and

products available commercially for such purposes include dried leaves, extracts, plant cuttings, tinctures, tablets, essence and leaf juice. Products can be taken orally (tablets, leaves extract), sublingually (tincture) and by inhalation (smoking of dried leaves, extract), to experience hallucinogenic effects.

### **Hazard Assessment and Characterisation:**

#### Pharmacokinetics:

The main active constituent of *Salvia divinorum*, both from the perspective of psychoactive and potential therapeutic use, appears to be the diterpene salvinorin A.

The pharmacokinetics of salvinorin A have not been studied extensively; however, it is apparent that when taken orally, the hallucinogenic effects depend on absorption by the oral mucosa, as salvinorin A is largely inactivated in the gastrointestinal tract (Siebert, 1994). Although some psychotropic activity has been noted after drinking the leaf juice, the effects are much more mild compared to the chewing of the leaves (Siebert, 1994). Siebert (1994) administered 2 mg of encapsulated salvinorin A to human subjects. Swallowing the capsules produced no detectable psychotropic activity. Thus, the most effective way (orally) to use the plant or its purified constituents to achieve hallucinogenic effects is to ensure the salvinorin A remains in the mouth for a period of time, allowing buccal absorption. Other studies on the pharmacokinetics and potential therapeutic effects of salvinorin A have relied on non-oral routes of exposure (Schmidt et al., 2005; McCurdy et al., 2006).

It should be noted that since salvinorin A is postulated as the phytochemical in *Salvia divinorum* that has potential therapeutic effect, the plant and its extracts may only be effective when administered non-orally. More research is required to clarify the potential therapeutic uses of *Salvia divinorum*. More detail is provided below.

#### Toxicology studies on *Salvia divinorum* and salvinorin A:

No studies appear to have been performed to determine the adverse effects of *Salvia divinorum*, or its chemical constituents, in humans.

With regard to animal toxicity studies, only one published report is available. Mowry et al. (2003) examined the short term effects of salvinorin A in rats. Swiss-Webster rats of both sexes, 4-6 months of age, were administered salvinorin A by intraperitoneal injection at doses of 0 (vehicle control), 400, 800, 1600, 3200 and 6400 ug/kg/day for 14 days. A total of 114 animals were used, specific numbers in each group were not reported. The authors did not observe any effects on cardiac conduction (PR or QT intervals), heart rate, body temperature or galvanic skin response. In a separate study, a nonsignificant rise in pulse pressure was observed after 20 and 40 minutes of salvinorin A exposure in anesthetized rats administered a single dose of 1600 ug/kg. In the repeat-dose study, no histologic differences were noted at any salvinorin A doses for either sex in the liver, spleen, kidney, bone marrow or brain tissue. The authors concluded that while salvinorin A is a potent hallucinogen, it has relatively low toxicity.

Mowry et al. (2003) also noted a literature report of a single dose of 1g/kg bw of an extract of *Salvia divinorum*, injected in mice (specific route unknown), where no toxic effects were noted. The actual reference provided by Mowry et al. for this study (Valdes et al., 1984), does not make mention of the actual dose, route of administration, or animal species employed, but notes that this administration produced behavioural patterns resembling the intoxication in humans.

Longer terms studies on the potential toxic effects of salvinorin A, or the whole plant, are not available, and no specialized studies (eg. teratology studies) appear to have been published in the scientific literature to date.

#### Psychotropic effects and mechanism of action:

The psychotropic effects induced by salvinorin A include altered perception, hallucinations, ataxia, depersonalization, hysterical laughter, incoherent speech and unconsciousness (Siebert DJ, 1994). Onset and intensity of the effects of salvinorin A depend on the dose and route of administration. A route that avoids the hepatic first-pass effect (sublingual, inhalation) produces rapid and intense effects.

The effects of *Salvia divinorum* can last up to two hours after absorption through the oral mucosa, while effects of inhaled salvia can last up to 30 minutes. A minimum dose of 200-500 µg of purified salvinorin A, or 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled (Bucheler et al., 2005).

Various studies have claimed that the psychotropic effects of *Salvia divinorum* closely resemble the symptoms of schizophrenia induced by other drugs such as LSD, phencyclidine or ketamine (Hansen et al., 1988; Javitt and Zukin, 1991; Valdes, 1994).

Salvinorin A has been shown to be a potent agonist of the kappa-opioid receptor (Chavkin et al., 2004). Research has shown that the hallucinogenic effects of salvinorin A are mediated through its kappa-opioid receptor agonist activity (Zhang et al, 2005).

Salvinorin A is structurally different from other naturally occurring classical hallucinogens such as mescaline, psilocybin and lysergic acid diethylamide. Typical doses of other hallucinogens (LSD, mescaline and psilocybin) required to produce hallucinogenic effects are 50-250 ug, 100 mg and 5 mg, respectively (Wolowich et al., 2006), while a minimum dose of 200-500 µg of purified salvinorin A can produce intense psychoactive affects, when vapourised and inhaled (Natural Medicines Comprehensive Database, 2007). Therefore, salvinorin A has more potency compared to mescaline and psilocybin, both of which are controlled substances in Canada. The Natural Medicines Comprehensive Database (2007) notes that “salvinorin A is the most potent hallucinogen known.”

#### Adverse reactions associated with the use of *Salvia divinorum*:

Domestic reports: See the appendix for detailed causality assessments of the adverse reaction reports submitted to Health Canada. Health Canada has received four reports of adverse reactions (ARs) associated with the use of *Salvia divinorum*. All of these ARs involved psychotropic effects. Out of the four AR reports, three cases involving inhalation were

associated with hallucinogenic effects and were considered to be non-serious reactions. The fourth case, however, was considered serious and was associated with the oral use of the chemical constituent salvinorin A. As well, it should be noted that, in this case report, salvinorin A was consumed in a therapeutic drug form (one tablet containing 57 mg of salvinorin A), although this commercially available product was meant to provide psychotropic, rather than therapeutic, effects. In this particular case, the product produced the effects when combined with alcohol.

Summary of Canadian domestic AR cases associated with *Salvia divinorum* or salvinorin A

Total number of cases	4
Route of exposure	Oral (1) & Inhalation (3)
Age range	16 yrs - 56 yrs
Gender	2 male, 2 female
Causality	oral - 1 possible; inhalation - 2 possible, 1 probable

International reports: Two case reports of salvia abuse have been published in the scientific literature.

- (1) An international case report involving *Salvia divinorum* was published in which a young man (19 years of age) described his perceptions after inhaling the smoke from *Salvia divinorum*. The peak psychotropic effects, including prickling of the skin, fever-like hot flashes, muscular tremor, and depersonalization, were reached in less than five minutes after inhalation of an unknown amount of dried leaves (Bucheler et al., 2005).
- (2) Most recently, another published case of *Salvia divinorum* abuse involved a 15-year-old male who presented to psychiatric emergency services with acute onset of paranoia, déjà vu, blunted affect, thought blocking and slowed speech, after smoking *Salvia divinorum* over an unknown period of time. During his hospitalization all symptoms improved significantly except the feeling of déjà vu. Based on this case presentation, the author suggested that the feelings of déjà vu may be considered long-term effects of Salvia use (Singh, 2007). However, given that this is the only case report in which déjà vu was associated with the use of *Salvia divinorum*, more reports are needed to substantiate this finding.

In addition to the above-mentioned case reports, in 2006, a case report was reported in the US in which a 17-year-old boy committed suicide after smoking *Salvia divinorum* for unknown period of time (<http://www.kvbc.com/Global/story.asp?S=4893692>). Alcohol and general depression



were the main confounders in this case. As a result of this case, however, the state of Delaware passed a law outlawing *Salvia divinorum*, and classifying it as a Schedule I controlled substance with other hallucinogenic substances

(<http://www.jointogether.org/news/headlines/inthenews/2006/youths-death-inspires.html>). It should be noted that suicidal symptoms were also observed in one of the four domestic cases of *Salvia divinorum* abuse reported to Health Canada.

#### Dose-response assessment

The dose-response for non-psychoactive adverse effects of *Salvia divinorum* or salvinorin A, by any route of administration, either in animals or humans, is unknown. No statistically significant findings were noted in the only available study (Mowry et al., 2003), in which NOELs of 1600 ug/kg bw and 6400 ug/kg bw/day were noted for acute physiologic effects, and short-term histological effects, respectively, using intraperitoneal injection. No longer term studies are available.

The intensity of the psychotropic effects in humans, induced by *Salvia divinorum*, has been noted as dose-dependent; however, a quantitative dose-response assessment has not been carried out. It is known, however, that the minimum dose required to produce hallucinogenic effects by inhalation is about 200 ug salvinorin A (Bucheler et al., 2005).

#### Potential for Dependence, Addiction, and Abuse

It is well known that *Salvia divinorum* or purified salvinorin A can produce various psychotropic effects (altered perception, hallucinations, ataxia, hysterical laughter, and incoherent speech) in humans. As noted above, the intensity of the psychological effects induced by salvinorin A is dose-dependent: high doses can produce extreme effects, such as depersonalisation with loss of reality, and intense psychosis which could be enough for users to harm themselves or others unintentionally (Siebert, 1994). In addition, the symptoms associated with *Salvia divinorum* are expected to be similar to those seen with other hallucinogens, although the duration of effects can be much shorter, depending on the route of exposure (inhalation vs. buccal absorption).

Drug dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal; it can be of two types, physical and/or psychological. Dependence can be influenced by certain receptor types, such as opioid receptors. The existence of three major groups of opioid receptors (mu, delta and kappa) in the central nervous system is well documented (Suzuki and Misawa 1997). There exist complicated interactions among opioid receptor types. The activation of the kappa opioid receptor suppresses physical and psychological dependence produced by mu and delta opioid receptor agonists, but the activation of the delta opioid receptor potentiates the dependence of mu opioid receptor agonists. Various studies provide arguments to support substantial roles for mu-opioid receptors and the possible involvement of delta-opioid receptors in the development of physical and psychological dependence produced by morphine (Narita et al. 2001; Suzuki and Misawa 1997).

Most of the drugs used clinically that are mu-opioid analgesics are habit-forming. While both receptor types (delta and mu) provide analgesia, only stimulation of the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dexamethorpan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor (Gaveriaux-Ruff and Kieffer 2002; Narita et al. 2001; Pasternak 2003; Suzuki and Misawa 1997). Using in vitro methods, Margolis et al. (2003) demonstrated that the mechanism of action of kappa opioid receptor agonists may involve direct inhibition of midbrain (ventral tegmental area) dopaminergic neurons, that play a critical role in motivation and reinforcement of goal-directed behaviours, and are excited by addictive substances such as morphine. It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect, i.e. dysphoria rather than euphoria (Kumor et al. 1986; Rothman et al. 2000). The activation of kappa-receptors also leads to the suppression of mu/delta-mediated side effects such as dependence and respiratory depression.

Salvinorin A is unique in that it is a potent, non-nitrogenous, selective kappa opioid agonist, distinct in its actions from other known opioid receptor agonists. It appears to be devoid of the mainly mu receptor-mediated side effects such as dependence and respiratory depression associated with morphine and its analogues. It may, thus, be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, depressive illness, and even excessive marijuana use. Being defined by its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative to addictive drugs. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

Although *Salvia divinorum* does not appear to cause dependency, it has the potential for abuse/misuse, especially by young adults. Health Canada has received four domestic case reports of adverse reactions (ARs) associated with the use of *Salvia divinorum* (three inhaled and one oral). In addition, Health Canada is aware of several media reports published on the issue of *Salvia divinorum*, specifically its presence on the market as a legal alternative to illicit drugs. This has prompted the concern of police (eg. Saskatoon Star-Phoenix, December 21, 2006). Furthermore, there are two international cases of salvia abuse published in scientific journals. However, it is important to note that accumulated case reports cannot be used to determine the incidence of a reaction, nor the risk associated with use of a product, because of the unknown number of individuals exposed to the product and because of the significant under-reporting of ARs. In any case, it should be noted that the Canadian Adverse Drug Reaction Monitoring Program is not an appropriate tool to obtain information concerning adverse reactions associated with the use of *Salvia divinorum* as a street drug.

It has been suggested that *Salvia divinorum* is the most marketed herbal substances available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Siemann et al., 2006; Dennehy et al., 2005). In 2000, a large number of *Salvia divinorum* plants were seized at a large scale plantation in Switzerland, which suggest that its use is increasing as a recreational drug in Europe (Giroud et al, 2000). Several countries (Australia, Denmark, Finland, Italy, Norway, Sweden and some states of the US) have either banned or included *Salvia divinorum* in their list of *controlled substances*.

The above evidence would suggest that any therapeutic products containing *Salvia divinorum* and/or salvinorin A could be misused or abused for their potential psychotropic activities.

### **Therapeutic potential of *Salvia divinorum* and salvinorin A**

Recent studies have suggested that salvinorin A acts at kappa opioid receptor sites (Chavkin et al. 2004; Valdes 1994; Roth et al. 2002). Selective kappa receptor agonists have been shown to produce analgesic effects with potential for reduced tolerance and dependence (Tidgewell et al., 2004). Animal studies have shown that salvinorin A has short-acting anti-nociceptive effects which operate via kappa opioid receptors (McCurdy et al., 2006). Considering the functional interaction between opioid receptor types noted above, the co-administration of morphine-like compounds with kappa-receptor agonists, such as salvinorin A, may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

There have been significant advances in studies on the role of kappa opioid receptor agonists in producing aversive effects and in the potential modulation of withdrawal from other substances such as morphine, cocaine, THC, alcohol, and in other non-opioid addictions (Cui et al. 2000; Hahn et al. 2000; Mori et al. 2002; Raffa et al. 2003; Rosin et al. 1999; Rothman et al. 2000; Schenk et al. 1999; Tao et al. 1994). As noted above, it may, thus, be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, clinical depression, and even excessive marijuana use. Because of its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative to these drugs, and may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001). Nevertheless, salvinorin A is a well recognised hallucinogen in its own right.

One study suggests that the salvinorin A may be used as a novel molecular candidate for the development of antipsychotic drugs and could be used to treat psychiatric (schizophrenia, bipolar depression) and neuropsychiatric disorders (Alzheimer's disease, dementia) (Sheffler and Roth, 2003).

It should be noted that the above-mentioned therapeutic potentials of *Salvia divinorum* are extrapolated from the results of preliminary investigations, and therefore, much more evidence is needed to substantiate the therapeutic use of *Salvia divinorum* or salvinorin A.

### **Exposure Assessment:**

It is not feasible to assess the exposure to *Salvia divinorum* or salvinorin A from the use of health products, as such products do not appear to exist in Canada, currently. Based on currently available information, however, it is possible that any therapeutic doses of this plant or its active constituents may produce adverse psychoactive effects (see below).

### **Risk Characterization:**

Although little scientific information exists regarding dose-response for *Salvia divinorum* or salvinorin A, risks associated with their use can be assessed in a qualitative manner.

The single toxicological study in animals alludes to the low toxicity of salvinorin A, at least with respect to certain physiological and histological effects. No information, however, is available on the potential long-term effects of exposure to *Salvia divinorum* or salvinorin A, and no studies have looked at the potential for other effects such as teratogenicity.

The psychotropic, and potentially therapeutic effects, elicited by salvinorin A are dependant on the route of exposure. Inhalation and buccal absorption are the most efficient; however, the bioavailability is greatly reduced when ingested without prolonged contact with the oral mucosa.

It is unknown if any potentially therapeutic effects of *Salvia divinorum* /salvinorin A would be achieved via inhalation or ingestion. Although the psychotropic effects appear to be dose-dependent, without more information on the dose-response of the hallucinogenic or therapeutic effects of *Salvia divinorum* or salvinorin A, the risk cannot be fully characterized. However, since the hallucinogenic and potentially therapeutic effects are both dependant on salvinorin A's affinity for the kappa opioid receptor, it is possible that any exposure to the plant or its active constituents, at a dose required for therapeutic use, may result in some degree of psychoactivity. Although selective kappa receptor agonists have been shown to produce analgesic effects, adverse effects such as psychotomimesis, dysphoria and diuresis have been observed in studies investigating their therapeutic use (Barker et al. 2002; Tidgewell et al., 2004). Thus, the potential for psychoactivity, and therefore abuse, with any future therapeutic use of *Salvia divinorum* or salvinorin A, cannot be discounted at the present time.

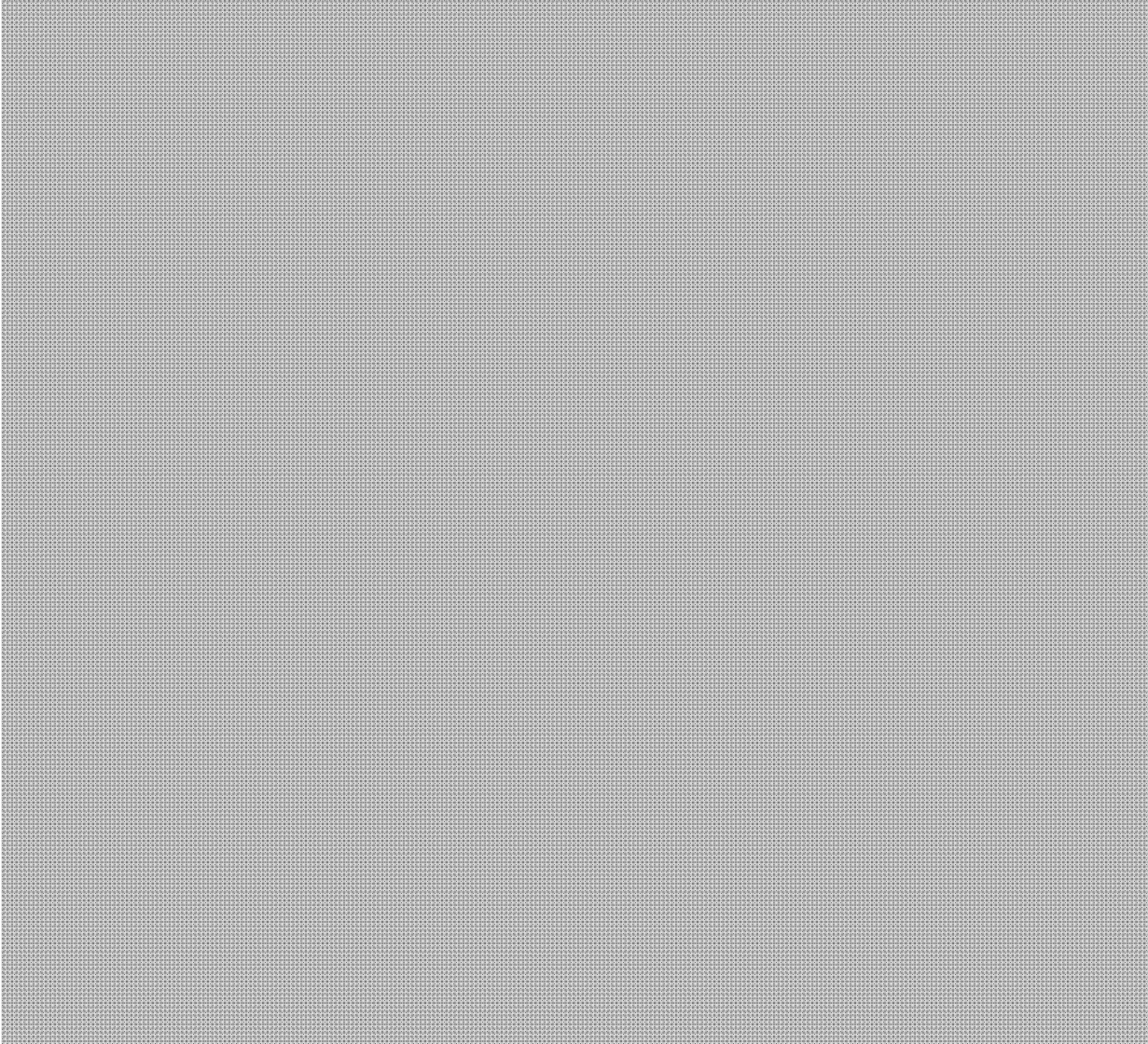
### **Summary and Conclusions:**

Salvinorin A appears to have low acute and short-term toxicity, although only one limited toxicological study in animals was identified in the scientific literature. No long-term studies have been published, and the long-term safety of this compound has not yet been established. The scientific literature does not support the possibility of developing dependency with *Salvia divinorum* use; however, its use has the potential for misuse or abuse. *Salvia divinorum* and salvinorin A have the ability to induce dose-dependent, moderate to severe hallucinogenic effects in humans, depending on the route of administration.

The fact that a clear dose-response has not been established for the potential therapeutic benefits of salvinorin A, and that the psychotropic and potentially therapeutic actions rely on the same mechanism of action, suggest that any therapeutic activity established in the future may also produce unwanted psychotropic effects. Therefore, the psychotropic activity of *Salvia divinorum* and salvinorin A may lead to the abuse of any health products proposed in the future.

In addition to the above, one of the potential therapeutic uses of salvinorin A is in the treatment of addiction to illicit drugs such as cocaine and heroin. Such potential use should be carried out under the supervision of a qualified physician.

Recommendations:

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Authors:

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## APPENDIX

### CAUSALITY ASSESSMENTS OF ADVERSE REACTIONS

Updated May 22, 2007

FINAL

Natural Health Product: *Salvia divinorum*

Purpose of the assessment:

To review the adverse reactions<sup>1</sup> associated with the use of *Salvia divinorum*. (Domestic case reports are reviewed with respect to causality<sup>2</sup> and seriousness<sup>3</sup>)

Date of review commenced:

May 2005 - ongoing monitoring

Medical evaluator(s):

[REDACTED]

Approved:

Dr. M. Murty (Sept. 9/05; revised May 22, 2007)

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<sup>1</sup>Natural Health Product Regulations: <http://canadagazette.gc.ca/partII/2003/20030618/html/sor196-e.html>

An **adverse reaction** is defined as a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function. (*réaction indésirable*)

<sup>2</sup> Based on the WHO causality algorithm unless otherwise specified. (*See appendix for WHO algorithm*)

<sup>3</sup>Natural Health Product Regulations: <http://canadagazette.gc.ca/partII/2003/20030618/html/sor196-e.html>

A **serious adverse reaction** means a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death. (*réaction indésirable grave*):

Search Strategy:

Adverse reactions suspected to be associated with *Salvia divinorum* were searched, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to May 3, 2005)]

Executive summary:

There are 4 domestic Canadian case reports of neuropsychiatric adverse effects associated with the use of *Salvia divinorum* (3 "non-serious" cases associated with inhalation route of administration and 1 "serious" case associated with oral ingestion).

The 'serious' case of psychosis associated with oral use was confounded by concomitant alcohol and therefore, the causality assignment is "Possible".

One of the inhaled cases was assessed as 'probable' but the reaction was not 'serious'.

Conclusion: In the serious case, Salvia was sold in a drug form, a tablet containing 57 or 72 mg of Salvinorin-A. In this case concomitant use of Salvia and alcohol most likely contributed to the adverse reaction of psychosis.

In the 3 non serious cases, there was disorientation and hallucination after taking one "puff" of *Salvia divinorum*.

From a clinical perspective, the main concern is the easy access, availability in retail outlets to adolescents without controls and the potential for misuse, as suggested by the AR case report of prolonged psychoses in an adolescent. Additionally, the hallucinogenic effects of Salvia may put individuals in life-threatening situations for themselves and others (driving while under the influence of Salvia). Although the case was confounded by alcohol and details of "intervention" were not specified in the report, it is likely that the Salvia component had contributed significantly to the psychoses, requiring restraint, observation/monitoring prior to the incarceration. Psychoses is a medically significant event and causality remains "Possible" and "Serious".

It is important to note that CADRMP is not the proper tool for monitoring the risk associated with Salvia in this context, because CADRMP is not designed or promoted for the collection of street drug effects. Rather, CADRMP is designed and promoted for the collection of adverse reactions associated with health products, and Salvia used in the current context would not be considered a health product.

Further monitoring and public education are necessary to regulate and possibly restrict *Salvia divinorum*.

Total domestic AR case reports associated with the use of *Salvia divinorum* up to May 31, 2005

Source of ADRs	# of cases report	route		psychosis	hallucination disorientation	Causality certain	Causality probable	Causality possible	Serious	Fatal outcome
		oral								
CADRMP	4	oral	1	1				1	1	0
		inhalation	3		3		1	2	0	0

Summary of Causality Assessment of reaction associated with the use of *Salvia divinorum*

Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177866 consumer Jan 12, 2005	27yr/F	-Unknown - Disorientation, hallucination, not recognizing people around her.	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No	Recovered (Effect lasted 5 minutes)	Probable	No

Case summary no 0177866

A 27 year old woman experienced disorientation, not recognizing people in the room, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. Patient reported prior use of mescaline and LSD and that the effect of those were not as bad ("moins pires"). The patient was on no other medications. This is not an unexpected reaction to *Salvia divinorum*.

There is no evidence from the case report that she had recently taken other hallucinogenic substances.

The causality was assigned as probable.  
The adverse reaction judged as not serious.

Case ID reporter  date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177865  consumer  Jan 12, 2005	28yr/M	-Unknown -Disorientation, hallucination, - foaming at the mouth	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No -no other medications -past med history - unknown	Recovered (Effect lasted 5 minutes)	Possible	No

Case summary no 0177865

A 28 year old man experienced disorientation, foaming at the mouth, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. There was no concomitant medication. Past medical history is unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.  
The adverse reaction judged as not serious.

Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
179969 consumer Feb. 17, 2005	56yr/F	-Unknown -Disorientation, hallucination, does not recognize husband	<i>Salvia divinorum</i> Al sasia encens special	Inhalation	1 puff taken	Unknown	Recovered (total effect 30 minutes)	Possible	No

Case summary no 0179969

A 56 year old woman experienced 30 minutes of disorientation and vivid hallucination after taking 1 puff of *Salvia divinorum*. The reaction was very intense for 10 minutes and then decreased in intensity. The past medical history, concomitant medication and NHP usage are unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.

The adverse reaction judged as not serious.

Case ID reporter date received	Age/ gender/ weight	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
0185128  Consumer (parent)  May 31, 2005	16yr/M  150lbs	March 29, 2005/ -drug induced psychosis -incoherent -suicidal - restrained -threatened to kill police officers -amnesia (does not remember any of these events) -jailed	Salvia/ aka Maria Pastora	oral/ 1 tablet "the 30\$ pill" 57mg*	single dose	Yes  <u>Concomitant intake of:</u> Alcohol ("few drinks")  <u>Concomitant condition:</u> ADD	Recovered	Possible	Yes

Case summary no 0185128:

On March 23, 2005, a 16 year old male experienced drug induced psychosis: was incoherent, was suicidal, needed to be restrained, threatened to kill police officers, was jailed and had amnesia of these events after taking a single tablet of *Salvia* ( aka Maria Pastra). He had also consumed a few drinks of alcohol. He had an underlying Attention Deficit Disorder (ADD) but was not receiving medication for this. He had previously taken *Salvia* "on its own" (route of administration unknown) with no adverse reaction.

Additional information obtained through the ADR specialist:

\* Follow up request for more information obtained July 28 2005, confirmed that the tablet was oral "30 \$ pill" purchased "behind the counter" at [REDACTED]

This outlet sells a *Salvia* 10x containing 57 mg of Salvinorin-A for 29.98\$ and a *Salvia* 20x containing 72 mg of Salvinorin-A for 39.98\$.

Further information received August 18 2005: When *Salvia* was taken previously, it was the same dose (30\$ pill orally). The only thing different was that on previous occasions, the patient did not have alcohol with it.

This is a case where there was no adverse reaction with previous use of *Salvia* (same dosage, same distributor, same route of administration) but when associated with alcohol, it had a severe adverse reaction.

[REDACTED]

The causality was assigned as possible with alcohol as a confounder.  
The adverse reaction was judged as serious because it required intervention.

#### Appendix

##### WHO algorithm of Causality Categories:

1	Probably/Likely:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
2	Possible:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
3	Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
4	Conditional/Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.
5	Unassessible/Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Marketed Health Products Directorate  
Marketed Biologicals, Biotechnology  
and Natural Health Products Bureau  
Signal Assessment  
**[*Salvia divinorum* - a potential drug for abuse]**

Date of Version 1: 2005-12-16

Updated: 2007-06-05

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**BUREAU:**

- |  |  |
|--|--|
| <input type="checkbox"/> Director General's Office (DGO)   | <input type="checkbox"/> Office of Pediatric Initiatives (OPI)                       |
| <input type="checkbox"/> Marketed Health Products Safety & Effectiveness Information Bureau (MHPSEIB)                | <input type="checkbox"/> Marketed Pharmaceuticals and Medical Devices Bureau (MPMDB) |
| <input checked="" type="checkbox"/> Marketed Biologicals, Biotechnology and Natural Health Products Bureau (MBBNHPB) | <input type="checkbox"/> Therapeutic Effectiveness and Policy Bureau (TEPB)          |
|  | <input type="checkbox"/> Business Transformation Program Services Bureau             |
- 

- Date of presentation at BEC-RM:
- Proposed date to present at BEC-RM:

**Subject matter:**

- Product's trade/generic names: *Salvia divinorum*
- Product class: Natural Health Product; Recreational drug
- Main indication(s): used as a hallucinogenic agent
- Therapeutic class: Natural Health Product
- Status:  marketed  
 not marketed-authorized

**Early Warning statement:**

- *Salvia divinorum* is a plant from the mint family that has been used in traditional and spiritual practices by the Mazatec Indians of Oaxaca, Mexico to produce "mystical" or hallucinogenic experiences. Health Canada has received four reports of adverse reactions associated with the use of *Salvia divinorum*. In addition, there have been several reports (scientific articles, case reports, media enquiries/articles) which indicate that *Salvia divinorum* has a potential for abuse, and is being used by adolescents and young adults for its hallucinogenic properties. MHPD will share the signal assessment document summarizing all information concerning the health risks associated with *Salvia divinorum* in Canada, as well as recommendations for mitigating the risk with other HPFB directorates (NHPD, HPFBI) and OCS (HECS), and will develop appropriate risk mitigation strategies, as deemed necessary.

**Background provided by which Officer/Directorate:**

- Shahid Perwaiz, MBBNHPB, MHPD

**What is the issue?**



- A search of the Canadian Adverse Reaction Information System (CADRIS) (March 31, 2007) revealed four reports of adverse reactions (ARs) associated with the use of *Salvia divinorum* or its active constituents. All of these ARs involved psychotropic effects.
- Some recently published articles (Siemann et al., 2006; Dennehy et al., 2005) have reported *Salvia divinorum* to be one of the most marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse among adolescents and young adults.
- Recently, the media (Calgary Herald on April 8, 2007; the Saskatoon StarPhoenix on December 21, 2006; Le Journal de Montreal on November 16, 20/06 and Radio-Canada on November 22, 2005) have shown interest in the issue of *Salvia divinorum*, specifically its presence on the market as a legal alternative to illicit drugs (<http://server09.densan.ca/health/newlook/showfile.asp?URL=/health/clips/070408/f00329AF.htm>, <http://www.radio-canada.ca/radio/sansfrontieres/66659.shtml>, ).
- This information (case reports, media interest and publications) triggered MBBNHPB to review the safety of *Salvia divinorum* and to provide recommendations to mitigate the potential risk of abuse associated with *Salvia divinorum* use.

### Why is this an issue?

- Health Canada has received four reports of adverse reactions (ARs) associated with the use of *Salvia divinorum*. Out of the four ARs reports, three cases involving inhalation were associated with hallucinogenic effects and were considered to be non-serious reactions. The fourth case, however, was considered serious and was associated with the oral use of the chemical constituent salvinorin A. As well, it should be noted that in this case report, salvinorin A was consumed in a therapeutic drug form (tablets containing 57 or 72 mg of salvinorin A) which makes it an unapproved health product being sold on the Canadian market.

Total number of cases	4
Route of exposure	Oral (1) & Inhalation (3)
Age range	16 yrs - 56 yrs
Gender	2 male, 2 female
Causality	oral - 1 possible; inhalation - 2 possible, 1 probable

*Please see Appendix B for the detailed causality assessment report.*

- An international case report of *Salvia divinorum* poisoning was published in which a young man (19 years of age) described his perceptions after inhaling *Salvia divinorum*. The peak psychotropic effects, including prickling of the skin, fever-like hot flashes, muscular tremor, and depersonalization, were reached in less than five minutes after inhalation of dried leaves of *Salvia divinorum* (Bucheler et al., 2005).
- Recently, another published case of *Salvia divinorum* abuse involving a 15-year-old male who presented to a hospital emergency ward with acute onset of psychotropic effects

including paranoia, déjà vu, blunted affect and “thought blocking and slow speech” following the smoking of *Salvia divinorum* over an unknown period of time. Over the course of hospitalization (duration of hospitalization was not mentioned), all symptoms improved significantly, except the feeling of déjà vu. Based on this case presentation, the author believed that the feelings of déjà vu may be considered a long-term effect of salvia use (Singh, 2007). However, it should be noted that this is the only case report of déjà vu reported to be associated with the use of *Salvia divinorum*, and therefore, more reports/studies are needed to substantiate this finding.

- In 2006, a U.S. case report of suicide was reported, in which a 17-year-old male died after he had started to smoke *Salvia divinorum* over an unknown period of time (<http://www.kvbc.com/Global/story.asp?S=4893692>). Alcohol and general depression were the main confounders in this case. As a result of this case, the state of Delaware passed a law which outlawed *Salvia divinorum* and included it as a Schedule I controlled substance, with other hallucinogenic substances (<http://www.jointogether.org/news/headlines/inthenews/2006/youths-death-inspires.html>). It should be noted that suicidal symptoms were also observed in one of the four domestic cases of *Salvia divinorum* abuse reported to Health Canada. (Appendix B).
- Various studies have claimed that the psychotropic effects of *Salvia divinorum* closely resemble the symptoms of schizophrenia induced by other drugs such as LSD, phencyclidine or ketamine. Open field testing has also indicated that salvinorin A has a potency equivalent to that of mescaline (Hansen et al., 1988; Javitt and Zukin, 1991; Valdes, 1994).
- Salvia is sold in the form of dried leaves, extracts, plant cuttings, tinctures, tablets, and essences. The active ingredient isolated from the leaves of *Salvia divinorum* is salvinorin A which is a powerful naturally-occurring non-nitrogenous hallucinogen that stimulates kappa-opioid receptors (KOR) (Chavkin et al., 2004). The effects induced by salvinorin A include altered perception, hallucinations, ataxia, depersonalization, hysterical laughter, incoherent speech and unconsciousness (Siebert DJ, 1994). Onset and intensity of the effects of salvinorin A depend upon the dose and route of administration. A route that avoids the hepatic first-pass effect (sublingual, inhalation) will likely produce fast and intense effects. The effects of Salvia can last up to two hours after absorption through the oral mucosa, while effects of inhaled Salvia can last up to 30 minutes. A minimum dose of 200-500 µg of purified salvinorin A, or 0.1 - 0.5 g of dried leaves of *Salvia divinorum* produced intense psychoactive effects when inhaled (Bucheler et al., 2005). It should be noted that typical doses of other hallucinogens (LSD, mescaline and psilocybin) required to produce hallucinogenic effects are 50-250 µg, 100 mg and 5 mg, respectively (Wolowich et al., 2006). Therefore, salvinorin A has more potency as compared to mescaline and psilocybin, both of which are controlled substances in Canada.
- There has been a growing trend of cultivation of *Salvia divinorum* observed in South and North America as well as in Europe. Several authors warned that *Salvia divinorum* might become a new recreational drug (Pravin RM, 2006 ;Bucheler et al., 2005; Giroud et al., 2000; Halpern, 2004), and recent media reports suggest that this warning was accurate.

- On December 21, 2006, the Saskatoon StarPhoenix (in addition to the Ottawa Citizen, the Edmonton Journal and the Regina Leader-Post) reported that police in Saskatoon were concerned that "it may only be a matter of time" for problems to arise from persons using *Salvia divinorum*. One Saskatoon police officer was quoted as saying: "Stores shouldn't be selling it to anybody period. It's legal and that's a problem." Furthermore, on November 16, 2006, Le Journal de Montréal published a report entitled "Un hallucinogène légal Santé Canada a cependant la Salvia divinorum à l'oeil" which indicated that Health Canada was evaluating the possibility of imposing restrictions over the sale and use of *Salvia divinorum*, similar to actions of certain countries. Given that *Salvia* does not have long-term adverse effects or the risk of dependence, the article suggested that Health Canada did not consider the short-term hallucinogenic effects to be sufficiently significant health risks to impose restrictions over its sale. In fact, according to the article, *Salvia divinorum* had been sold in certain Quebec retail outlets since 2000, as a hallucinogen. The article quoted an RCMP officer as saying that prevention of *Salvia divinorum*'s use was necessary, and that Quebec's law enforcers' hands were tied because Health Canada had not categorized *Salvia divinorum* as a controlled substance, despite its effects being comparable to the illicit drugs cannabis and LSD. Additionally, the law enforcement officer indicated that if an individual were stopped for erratic driving under *Salvia divinorum*'s influence, they would be charged for driving while impaired. These media and police reports further emphasized *Salvia divinorum*'s potential for abuse by young Canadians, for its hallucinogenic properties. It is clear that media interest in this issue has increased recently, and that the abuse problem is becoming increasingly known to Canadians.
- On October 6, 2006, the HPFBI Ontario Region received an enquiry from MP Joe Preston's office (Elgin-Middlesex, London, Ontario riding). A constituent inquired as to why the hallucinogenic product, *Salvia divinorum*, was available as an over-the-counter product. This enquiry suggested that *Salvia divinorum* was being sold to Canadians at the retail level, as a recreational drug. However, there were no details obtained concerning the retail location or product format/claims characterizing the enquiry.
- In Canada, *Salvia divinorum* and its active constituents are not listed in any schedule of the *Controlled Drugs and Substances Act*, nor any schedule of the *Food and Drugs Act and Regulations*. As such, *Salvia divinorum*, if marketed without health claims, can be sold on the Canadian market without any restriction. In addition, based on the above discussion, it appears that *Salvia divinorum* is widely available, and has the potential for misuse/abuse by young adults, as suggested by one of the four domestic AR case reports and two international case reports. Additionally, the hallucinogenic effects of *Salvia* may put individuals in life-threatening situations (e.g., driving while under the influence of *Salvia*).

#### **International Regulatory Situation on *Salvia divinorum*:**

- **United States:** *Salvia divinorum* and salvinorin A are not currently controlled in the United States. However, a number of states have imposed restrictions and/or controls on *Salvia divinorum* and/or salvinorin A. Louisiana passed a bill (Louisiana, 2005) in 2005, which made 40 plants, including *Salvia divinorum*, illegal if sold for human consumption. Both

Delaware (2006) and Missouri (2005) have added *Salvia divinorum* and salvinorin A onto Schedule I, making them controlled substances. Tennessee (2006) and Oklahoma (2006) passed legislation on *Salvia divinorum* in 2006 making it illegal to possess, produce, manufacture, or distribute. In addition, The American Federal Drug Enforcement Agency (DEA) has also placed *Salvia divinorum* on a list of drugs and chemicals “of concern,” without legal implications (US DEA, 2002).

- **Australia:** In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long-term effects, and both the herb and its active constituent are listed on schedule 9 of Australia’s Standard for the Uniform Schedule of Drugs & Poisons (TGA, 2002).
- **Denmark:** *Salvia divinorum* and salvinorin A are classed as 'category B' drugs in Denmark. Category B includes psilocybin mushrooms, cocaine, amphetamine, and several others substances that are only legal for medicinal and scientific purposes. Possession carries a penalty of up to two years in prison (<http://www.retsinfo.dk/delfin/html/b2003/0071405.htm>)
- **Finland:** In Finland, it is illegal to import *Salvia divinorum*, without a prescription from a doctor (<http://www.hs.fi/sivuaeiloytynyt/?kaikkiSanat=juttu.asp?id=20021003KO2>).
- **Italy:** On June 25, 2004 the Italian Ministry of Health issued an ordinance prohibiting the sale of *Salvia divinorum* and its active constituent, salvinorin A. On January 11, 2005, the Ministry of Health made possession of *Salvia divinorum* and salvinorin A illegal by placing them in “*Tabella I*” of the *Tabella Sostanze Stupefacenti o Psicotrope* (<http://gazzette.comune.jesi.an.it/2005/54/2.htm>).
- **Norway:** In Norway, *Salvia divinorum* is not controlled, but has the status of a psychoactive drug (Bucheler et al., 2005)
- **Sweden:** On April 1<sup>st</sup> 2006, *Salvia divinorum* and salvinorin A were added to Sweden's list of controlled substances (<http://62.95.69.15/>).

#### **Benefits associated with the use of *Salvia divinorum*:**

Salvinorin A (a chemical constituent of *Salvia divinorum*) is a potent kappa opioid receptor agonist. Selective kappa receptor agonists have been shown to produce analgesic effects with potential for reduced tolerance and dependence. However, psychotomimesis (hallucinogenic and/or psychotic effects), dysphoria and diuresis have been observed with their therapeutic use (Tidgewell et al., 2004). In addition, various publications indicate that kappa opioid receptors may be involved in addictive behaviours associated with CNS stimulants such as cocaine. In fact, given its kappa opioid receptor agonist properties, it has been proposed that salvinorin A could be used in the treatment of certain types of drug abuse (Mello et al., 2000; Shippenberg et al., 2001; Schenk et al., 1999; 2000). Also, there is one human case study from Australia suggesting a possible antidepressant effect of *Salvia divinorum* (Hanes 2001). Additionally, a study suggested that salvinorin A could be used as a novel molecular candidate for the development of antipsychotic drugs, or could be used to treat certain psychiatric (schizophrenia, bipolar disorder) and neuropsychiatric (Alzheimer’s disease, dementia) diseases (Sheffler and Roth, 2003). It should be noted, however, that these potential therapeutic uses of *Salvia divinorum* are extrapolated from the results of preliminary investigations, and therefore, more studies are needed to substantiate these putative benefits.

With respect to its traditional therapeutic uses, *Salvia divinorum* has been used to treat diarrhoea, constipation, anaemia, headache, rheumatism, ulcers of the skin and alcohol addiction, as well as for regulation of urine flow (Natural Medicines Comprehensive Database, 2007; Valdes et al., 1982). However, there is no scientific evidence available in the published literature about the safety and

effectiveness of these traditional therapeutic uses.

While its benefits remain to be established, salvinorin A's hallucinogenic effects have been well documented, and these could easily result in risk to individuals. As noted above, these effects include: altered perception, hallucinations, ataxia, depersonalization, incoherent speech and unconsciousness in humans (Siebert DJ, 1994). Additionally, given that its pharmacological action (kappa-opioid receptor agonist) is quite unique compared to other hallucinogens (some of which act via the serotonin 5-HT receptor), salvinorin A's long-term effects remain to be established. Therefore, the risks of *Salvia divinorum* use, relative to speculated benefits, suggest that if it were to be regulated as a health product, it should be available by prescription only, and used under medical supervision (ie. added to Schedule F of the *Food and Drug Regulations*). A more detailed assessment would be required in order to make a final determination on the scheduling of *Salvia divinorum*.

### **Who is involved?**

- MBBNHPB, NHPD, HPFBI and the Office of Controlled Substances (OCS, HECS Branch)

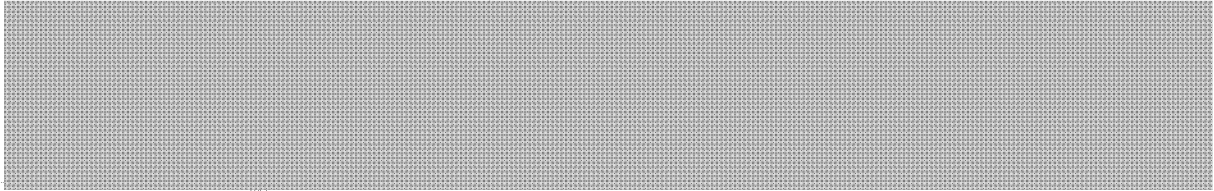
### **What action has been taken?**

- Neither *Salvia divinorum* nor its active constituent (Salvinorin A) have been authorised for sale, as health products in Canada, as confirmed by the Natural Health Products Directorate (NHPD) and the Therapeutic Products Directorate's (TPD) Submission & Information Policy Division (SIPD).
- CADRMP has confirmed four case reports of psychotropic effects associated with *Salvia divinorum* in Canada. These comprise psychological adverse reactions associated with the use of *Salvia divinorum* (three via inhalation and one taken orally). In the one 'serious' case, oral usage was associated with psychosis but alcohol was a significant confounder and the causality was assessed as 'possible'. The three cases involving inhalation were judged to be 'non serious'. One of these three cases was assessed as 'probable' (see Appendix B).
- NHPD, in collaboration with MHPD, had drafted an Issue Analysis Summary (IAS) in 2004 on the issue of health risks associated with the use of *Salvia divinorum* and its regulation in Canada. This IAS was updated in October 2006 (see Appendix A).  
The Office of Controlled Substances (OCS) of the HECS Branch, has placed *Salvia divinorum* on its list of substances to monitor. OCS confirmed that as part of this action, Health Canada would work with its partners, including law enforcement agencies and international counterparts, to collect relevant information on this herb.
- A Customs Lookout is already in place to restrict the importation of *Salvia divinorum*.
- Jocelyn Kula of the Office of Controlled Substances, HECS Branch, convened a multi-directorate meeting with HPFB (NHPD, TPD, HPFBI, PACRB) on May 16, 2007 to

discuss the *Salvia divinorum* issue. It was decided at the meeting that *Salvia divinorum* meets the definition of a NHP, if marketed in Canada with health claims, and therefore, compliance action could be taken according to the Compliance Policy for Natural Health Products and the HPFBI's compliance and Enforcement Policy (POL-001), if it were deemed a risk to health. It was also decided in the meeting that MHPD in collaboration with NHPD would develop a Health Risk Assessment (HRA) document on potential health risks associated with the use of *Salvia divinorum*. This HRA document would help HPFBI to determine the appropriate compliance action to be taken on *Salvia divinorum* products available on the Canadian market. In the meantime, the OCS would work with its partners within the department, other government departments, law enforcement agencies and its international counterparts to collect relevant information specific to this herb and its active constituents. The OCS would assess *Salvia divinorum* against the following criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA).

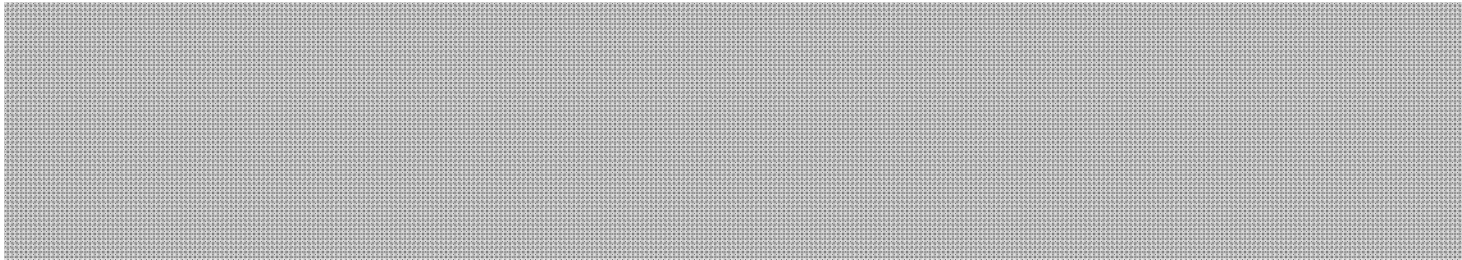
- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

•



**What are the key activities and time line?**

- An anticipatory QP note on this issue was finalized on November 22, 2006.
- MHPD, in collaboration with NHPD, will conduct a health risk assessment (HRA) on *Salvia divinorum*'s use as a health product .
- MHPD will share this ISR document with NHPD, HECSB, HPFBI and TPD in order to obtain their opinion on our recommendation as well as their sign-off.





**Attachments:**

Appendix A: IAS prepared by NHPD and MHPD.

Appendix B: Causality Assessments of Adverse Reactions associated with use of Salvia divinorum, conducted by MHPD.

**Approved By:** Dr. Scott Jordan, A/Manager Scientific section, MBBNHPB, MHPD

**Date:** June 5, 2007

**Approved By:** Dr. Jenna Griffiths, A/Director, NHP section of MBBNHPB

**Date:** June 5, 2007

**Approved By:** Dr. Chris Turner, DG, MHPD

**Date:**

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## APPENDIX A:

### NHPD AND MHPD ISSUE ANALYSIS SUMMARY

#### *Salvia divinorum* Regulatory Authority and Health Risks

**Prepared by:** Jacinta Roberts and Robin Marles, NHPD, and Shahid Perwaiz, MHPD

**Draft Date:** June 24, 2004

**Draft Revised:** July 15, 2004

**Finalized:** July 15, 2004

**Updated:** October 17, 2006

### ISSUES

1. Which regulatory authority is most appropriate for *Salvia divinorum* under various conditions of use?
2. What are the risks to consumers of this substance?

### BACKGROUND AND ISSUE ANALYSIS

#### *Salvia divinorum* as a Health Product

*Salvia divinorum* Epling & Játiva is an herb in the mint family (Lamiaceae), native to Mexico, that is smoked as a hallucinogen. As a substance it falls under Item 1 of Schedule 1 (inclusion list) to the *Natural Health Products Regulations*, which includes: "a plant or plant material, an alga, a bacterium, a fungus or a non-human animal material."

The main active ingredient of *Salvia divinorum* is a neoclerodane diterpene compound called salvinorin A, which currently falls under Schedule 1, item 2: "an extract or isolate of a substance described in item 1, the primary molecular structure of which is identical to that which it had prior to its extraction or isolation."

In Canada neither the herb, *Salvia divinorum*, nor its active ingredients, such as salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* (CDSA), nor any Schedule of the *Food and Drugs Act* or its Regulations that would remove it from the purview of the *Natural Health Products Regulations*.

*Salvia divinorum* and its active constituents therefore meet the substance aspect of the regulatory definition of a natural health product.

Whether or not *Salvia divinorum* products meet the function aspect of the regulatory definition of a natural health product depends on the purpose for which the product is being manufactured, sold, or

represented for use. According to Section 1(1) of the *Natural Health Products Regulations*, a natural health product means a substance that is manufactured, sold, or represented for use in:

- (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- (b) restoring or correcting organic functions in humans; or
- (c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

*Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/ constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1982).

With respect to potential modern uses, there is one human case study from Australia suggesting a possible antidepressant effect (Hanes 2001).

Since *Salvia divinorum* and salvinorin A under some conditions of use meet both the functional and substance portions of the definition of a natural health product and are not currently subject to any regulatory exclusions, if associated with a health claim finished products containing these substances could be considered to be natural health products (NHPs).

Until such time as the herb and its active constituent are scheduled under the CDSA or Schedule F to the *Food and Drug Regulations*, the NHPD has jurisdiction to receive a Product Licence Application for a therapeutic use. However, the safety assessment will be sufficiently rigorous to protect consumers' health, particularly with respect to the following safety factors:

- “Does the medicinal ingredient or product have a demonstrated potential for addiction, abuse or severe dependency that is likely to lead to harmful non-medicinal use?”
- “Does the medicinal ingredient or product have known adverse effects at the recommended or therapeutic dosage level?”
- “Does the medicinal ingredient or product have a therapeutic effect based on recently established pharmacological concepts, the consequences of which have not yet been fully established?”
- “Does the medicinal ingredient or product possess a high level of risk relative to expected benefits?”

The answers to these questions are as follows:

- Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in a way that is quite different from other hallucinogens such as heroin or LSD.
- Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions.
- It is subject to abuse as a street drug.

- It acts on the brain in a way that is quite novel and for which the consequences have not yet been fully established.

For all these reasons, the risks of *Salvia divinorum* use compared to any expected benefits suggest that if it were to be regulated as a health product, it should require a prescription under the *Food and Drug Regulations*, rather than being regulated as an over-the-counter natural health product. As such, TPD should be consulted on this issue.

### ***Salvia divinorum as a Hallucinogen***

As with many other NHP substances, there are other uses for the herb that may in future be more appropriately regulated under a different framework.

*Salvia divinorum* is used as a hallucinogen in traditional divination rituals (Valdés et al. 1982) and is being widely touted on internet sites aimed at young adults and adolescents as a “legal” alternative street drug.

The current use and advertising of *Salvia divinorum* as a recreational hallucinogen does not meet the intent of the function component of the *Natural Health Products Regulations*' definition of a natural health product. Nevertheless, even if it is being sold without labelled claims as leaf material in a plastic baggy, it is being represented for use in “modifying organic functions in humans” so from a compliance perspective *Salvia divinorum* falls under the jurisdiction of the *Food and Drugs Act*.

As a hallucinogen and drug of abuse, Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances will collect relevant information specific to this herb and its active constituents.

### ***Salvia divinorum in Other Regulatory Jurisdictions***

In the U.S. Congress, *Salvia divinorum* was the subject of a bill (H.R.5607) entitled “To amend the Controlled Substances Act to place Salvinorin A in Schedule I” introduced on October 10, 2002, seeking to place the herb and its active constituent salvinorin A onto U.S. Controlled Substances Act Schedule 1 (drugs or other substances with a high potential for abuse, with no currently accepted medical use in treatment in the United States, and with respect to which there is a lack of accepted safety for use under medical supervision). Since November 11, 2002, the bill has been referred to the Subcommittee on Crime, Terrorism, and Homeland Security

(<http://thomas.loc.gov/cgi-bin/bdquery/z?d107:HR05607:@@L&summ2=m&>, accessed June 24, 2004). Currently, the FDA considers street drug alternatives such as *Salvia divinorum* to be unapproved new drugs and misbranded drugs under sections 505 and 502 of the Act

(<http://www.fda.gov/cder/guidance/3602fml.pdf>, accessed May 26, 2004) and has issued warning letters to a number of firms. Thus it appears that the U.S. has sufficient regulatory authority already to achieve the necessary level of control.

Both the herb and the active ingredient are listed on Schedule 9 of Australia's Standard for the Uniform Scheduling of Drugs and Poisons on the basis of "high potential for abuse and risk to public health and safety," but no substantiation of this risk was provided (<http://www.tga.health.gov.au/ndpsc/record/rr200111upd8.pdf>, accessed May 26, 2004). They are both also in Category B of the Danish list of controlled substances (<http://www.retsinfo.dk/delfin/html/b2003/0071405.htm>, accessed May 26, 2004).

### ***Scientific Details of the Potential of *Salvia divinorum* for Abuse***

*Salvia divinorum* is smoked to induce visual hallucinations, the diversity of which are described by its users to be similar to those induced by other hallucinogens such as mescaline or psilocybin. Since neither *Salvia divinorum* nor any of its active ingredients are specifically listed in the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act* or its Regulations in Canada, some on-line botanical companies and drug promotional sites have advertised the herb as a legal alternative to other plant hallucinogens like mescaline. The objective of this section is to provide background on whether or not *Salvia divinorum* has the potential to induce dependence effects.

Salvinorin A (there are B and C forms) is a hallucinogen when vaporized and inhaled. Salvinorin A is a highly efficacious *kappa*-opioid receptor agonist of clinical interest for treatment and etiological studies of depression, dementia, bipolar disorder, and schizophrenia (Chavkin et al. 2004, Roth et al. 2002). Chemically, salvinorin A is a psychotropic diterpenoid.

Other plants with similar properties include *Cannabis sativa*, which contains the phenolic active principle, tetrahydrocannabinol (THC), and *Artemisia absinthium*, also known as wormwood and used to make the liqueur asbinthe, which contains the monoterpenoid active principle, thujone.

A dose of 200 to 500 micrograms of salvinorin A produces profound hallucinations when smoked. Its effects in the open field test in mice and locomotor activity tests in rats are similar to those of mescaline. A large body of evidence links the action of hallucinogenic agents (LSD, mescaline) to effects at serotonin (5-HT) receptor sites in the central nervous system (Aghajanian and Marek 1999). Salvinorin A's actions in the brain are not well elucidated. However, recent tissue testing (in vitro assays) have suggested that salvinorin A acts at the *kappa* opiate receptor site (Chavkin et al. 2004; Valdes 1994; Roth et al. 2002). Effects associated with *kappa* opioid receptor activation include analgesia, sedation, and dysphoria (Barker et al. 2002). Using in vitro methods, Margolis et al. (2003) have found evidence that the mechanism of action of *kappa* opiate receptor agonists may involve direct inhibition of midbrain (ventral tegmental area) dopaminergic neurons that play a critical role in motivation and reinforcement of

goal-directed behaviours, and are excited by addictive substances such as morphine.

Drug dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal; it can be of two types, physical and/or psychological dependence. The existence of three major groups of opioid receptors (mu, delta and kappa) in the central nervous system is well documented (Suzuki and Misawa 1997). There are complicated interactions among opioid receptor types. The activation of the kappa opioid receptor suppresses physical and psychological dependence on mu and delta opioid receptor agonists, but the activation of the delta opioid receptor potentiates the dependence on mu opioid receptor agonists. Various studies provide arguments to support substantial roles for mu-opioid receptors and the possible involvement of delta-opioid receptors in the development of physical and psychological dependence on morphine (Narita et al. 2001; Suzuki and Misawa 1997).

Most of the drugs used clinically that are mu-opioid analgesics are habit-forming. While both receptor types (delta and mu) provide analgesia, only the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dexamethorpan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor (Gaveriaux-Ruff and Kieffer 2002; Narita et al. 2001; Pasternak 2003; Suzuki and Misawa 1997). From behavioural, biochemical and molecular biological studies, it is suggested so far that development of physical dependence on morphine results predominantly from an activation of mu 1 and mu 2 opioid receptors which cause functional changes in Gi/o, adenylate cyclase, protein kinases A and C, beta-adrenoceptor and NMDA receptor in the locus coeruleus. However, activation of the mesolimbic dopamine system may lead to psychological dependence on opioids (Narita et al. 2001; Suzuki and Misawa 1997).

It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect, i.e. dysphoria rather than euphoria (Kumor et al. 1986; Rothman et al. 2000). Recently, there have been significant advances in studies on the role of kappa opioid receptor agonists in modulating addictive and dependence effects of other stimulants such as morphine, cocaine, THC, alcohol, and in other non-opioid addictions (Cui et al. 2000; Hahn et al. 2000; Mori et al. 2002; Raffa et al. 2003; Rosin et al. 1999; Rothman et al. 2000; Schenk et al. 1999; Tao et al. 1994). The activation of kappa-receptors also leads to the suppression of unpleasant mu/delta-mediated side effects such as dependence and respiratory depression. Considering the functional interaction between opioid receptor types, the co-administration of morphine-like compounds with kappa-receptor agonists may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

Salvinorin A is unique in that it is a potent, non-nitrogenous, selective kappa opioid agonist distinct in its actions from other known opioid agonists. Therefore, it appears to be devoid of the mainly mu receptor-mediated side effects such as dependence and respiratory depression associated with morphine and its other analogues. It may thus be possible to use salvinorin A to treat heroin, cocaine, alcohol and

amphetamine dependency, depression, and even excessive marijuana use. Being defined by its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

In conclusion, on the basis of available scientific literature, the potential addiction or dependence effects of *Salvia divinorum* are expected to remain very low because of the following:

- Most of the drugs which cause dependence and addiction are mu-opioid agonists, while salvinorin A acts as a full agonist at kappa opioid receptors and appears to possess no mu opioid receptor activity.
- Kappa opioid receptor agonists are characterized as being able to modulate dependence-related behavioural effects of drugs like morphine and cocaine rather than causing dependence.
- There have been no cases of dependence on *Salvia divinorum* or salvinorin A reported in the scientific literature.
- The precise mechanism of interaction between salvinorin A and the brain to produce its hallucinogenic effects remains unclear.
- The toxicity of salvinorin A is relatively low, even at doses many times greater than what humans are exposed to (Mowry et al., 2003).
- Many individuals have reported experiencing negative effects (bitter taste, unpredictable and occasionally disturbing short-term mental effects) during their first experience with *Salvia divinorum* and indicate that they would not use it a second time.

#### ***Canadian Reports of Adverse Reactions to Salvia divinorum Products***

Adverse reactions suspected to be associated with *Salvia divinorum* were sought, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to March 31, 2007). The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with products said to contain *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum* products. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of tablets said to contain *Salvia divinorum* and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

#### **PRESENT HEALTH CANADA ACTIONS:**



1. Adverse reactions to *Salvia divinorum* or salvinorin A reported through the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) and those reported in the United States and other jurisdictions are being monitored continuously, recognizing that it is unlikely that adverse reaction reports for these substances will be adequately documented due to *Salvia divinorum*'s use primarily as an hallucinogen. Some information might also be available from Poison Control Centres but there is apparently no uniform means for communication between Poison Control Centres at this time.
2. Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the Office of Controlled Substances is collecting relevant information specific to this herb and its active constituents.
3. A Customs Lookout is already in place and should be continued to restrict importation.
4. *Salvia divinorum* and its active principles are being represented for use in modifying organic functions in humans and are therefore classified as health products that fall under the jurisdiction of the *Food and Drugs Act*. To protect the health of Canadians, they are subject to compliance actions by the Health Products and Food Branch Inspectorate in accordance with their Policy 0001.

#### **NEXT STEPS:**

1. If the information collected warrants further action, the Office of Controlled Substances will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedule of the *Controlled Drugs and Substances Act*. These criteria include:
  - international requirements and trends in control/scheduling;
  - chemical and pharmacological similarity to other drugs listed in the CDSA;
  - dependence potential;
  - likelihood of abuse/misuse;
  - extent of abuse/misuse in Canada;
  - danger to public health and safety, and
  - legitimate use in Canada.
2. If *Salvia divinorum* is added to one of the Schedules to the *Controlled Drugs and Substances Act* it will become subject to compliance actions by the federal, provincial, and municipal police forces instead of the HPFB Inspectorate.

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## Appendix B

### CAUSALITY ASSESSMENTS OF ADVERSE REACTIONS

Updated May  
22, 2007

FINAL

#### Natural Health Product: *Salvia divinorum*

##### Purpose of the assessment:

To review the adverse reactions<sup>1</sup> associated with the use of *Salvia divinorum*. (Domestic case reports are reviewed with respect to causality<sup>2</sup> and seriousness<sup>3</sup>)

---

<sup>1</sup>Natural Health Product Regulations: <http://canadagazette.gc.ca/partII/2003/20030618/html/sor196-e.html>

An **adverse reaction** is defined as a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function. (*réaction indésirable*)

<sup>2</sup> Based on the WHO causality algorithm unless otherwise specified. (*See appendix for WHO algorithm*)

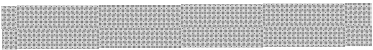
<sup>3</sup>Natural Health Product Regulations: <http://canadagazette.gc.ca/partII/2003/20030618/html/sor196-e.html>

A **serious adverse reaction** means a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death. (*réaction indésirable grave*):

**Date of review commenced:**

May 2005 - ongoing monitoring

**Medical evaluator(s):**



**Approved:**

Dr. M. Murty (Sept. 9/05; revised May 22, 2007)

**Search Strategy:**

Adverse reactions suspected to be associated with *Salvia divinorum* were searched, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to May 3, 2005)]

**Executive summary:**

There are 4 domestic Canadian case reports of neuropsychiatric adverse effects associated with the use of *Salvia divinorum* (3 “non-serious” cases associated with inhalation route of administration and 1 “serious” case associated with oral ingestion).

The ‘serious’ case of psychosis associated with oral use was confounded by concomitant alcohol and therefore, the causality assignment is “Possible”.

One of the inhaled cases was assessed as ‘probable’ but the reaction was not ‘serious’.

**Conclusion:** In the serious case, Salvia was sold in a drug form, a tablet containing 57 or 72 mg of Salvinorin-A. In this case concomitant use of Salvia and alcohol most likely contributed to the adverse reaction of psychosis.

In the 3 non serious cases, there was disorientation and hallucination after taking one “puff” of *Salvia divinorum*.

From a clinical perspective, the main concern is the easy access, availability in retail outlets to adolescents without controls and the potential for misuse, as suggested by the AR case report of prolonged psychosis in an adolescent. Additionally, the hallucinogenic effects of Salvia may put individuals in life-threatening situations for themselves and others (driving while under the influence of Salvia). Although the case was confounded by alcohol and details of "intervention" were not specified in the report, it is likely that the Salvia component had contributed significantly to the psychosis, requiring restraint, observation/monitoring prior to the incarceration. Psychosis is a medically significant event and causality remains "Possible" and "Serious".

It is important to note that CADRMP is not the proper tool for monitoring the risk associated with Salvia in this context, because CADRMP is not designed or promoted for the collection of street drug effects. Rather, CADRMP is designed and promoted for the collection of adverse reactions associated with health products, and Salvia used in the current context would not be considered a health product.

Further monitoring and public education are necessary to regulate and possibly restrict Salvia divinorum.

**Total domestic AR case reports associated with the use of Salvia divinorum up to May 31, 2005**

Source of ADRs	# of cases report	route		psychosis	hallucination disorientation	Causality certain	Causality probable	Causality possible	Serious	Fatal outcome
CADRMP	4	oral	1	1				1	1	0
		inhalation	3		3		1	2	0	0

Summary of Causality Assessment of reaction associated with the use of *Salvia divinorum*

Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177866 consumer Jan 12, 2005	27yr/F	-Unknown - Disorientation, hallucination, not recognizing people around her.	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No	Recovered (Effect lasted 5 minutes)	Probabl e	No

Case summary no 0177866

A 27 year old woman experienced disorientation, not recognizing people in the room, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. Patient reported prior use of mescaline and LSD and that the effect of those were not as bad ("moins pires"). The patient was on no other medications. This is not an unexpected reaction to *Salvia divinorum*.

There is no evidence from the case report that she had recently taken other hallucinogenic substances.

The causality was assigned as probable.

The adverse reaction judged as not serious.



Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177865 consumer Jan 12, 2005	28yr/M	-Unknown -Disorientation, hallucination, - foaming at the mouth	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No -no other medications -past med history - unknown	Recovered (Effect lasted 5 minutes)	Possible	No

Case summary no 0177865

A 28 year old man experienced disorientation, foaming at the mouth, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. There was no concomitant medication. Past medical history is unknown. These are not unexpected reactions to *Salvia divinorum*, except foaming at the mouth.

The causality was assigned as possible.

The adverse reaction judged as not serious.

Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
179969 consumer Feb. 17, 2005	56yr/F	-Unknown -Disorientation, hallucination, does not recognize husband	<i>Salvia divinorum</i> Al sasia encens special	Inhalation	1 puff taken	Unknown	Recovered (total effect 30 minutes)	Possible	No

Case summary no 0179969

A 56 year old woman experienced 30 minutes of disorientation and vivid hallucination after taking 1 puff of *Salvia divinorum*. The reaction was very intense for 10 minutes and then decreased in intensity. The past medical history, concomitant medication and NHP usage are unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.

The adverse reaction judged as not serious.

Case ID	Age/ gender/ weight	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
0185128  Consumer (parent)  May 31, 2005	16yr/M  150lbs	March 29, 2005/ -drug induced psychosis -incoherent -suicidal - restrained -threatened to kill police officers -amnesia (does not remember any of these events) -jailed	Salvia/ aka Maria Pastora	oral/ 1 tablet “the 30\$ pill” 57mg*	single dose	Yes  <u>Concomitant intake of:</u> Alcohol (“few drinks”)  <u>Concomitant condition:</u> ADD	Recovered	Possible	Yes

Case summary no 0185128:

On March 23, 2005, a 16 year old male experienced drug induced psychosis: was incoherent, was suicidal, needed to be restrained, threatened to kill police officers, was jailed and had amnesia of these events after taking a single tablet of *Salvia* ( aka Maria Pastra). He had also consumed a few drinks of alcohol. He had an underlying Attention Deficit Disorder (ADD) but was not receiving medication for this. He had previously taken *Salvia* “on its own” (route of administration unknown) with no adverse reaction.

Additional information obtained through the ADR specialist:

\* Follow up request for more information obtained July 28 2005, confirmed that the tablet was oral "30 \$ pill" purchased "behind the counter" [redacted]  
 This outlet sells a Salvia 10x containing 57 mg of Salvinorin-A for 29.98\$ and a Salvia 20x containing 72 mg of Salvinorin-A for 39.98\$.

Further information received August 18 2005: When Salvia was taken previously, it was the same dose (30\$ pill orally). The only thing different was that on previous occasions, the patient did not have alcohol with it.

This is a case where there was no adverse reaction with previous use of *Salvia* (same dosage, same distributor, same route of administration) but when associated with alcohol, it had a severe adverse reaction.

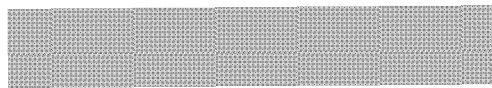
The causality was assigned as possible with alcohol as a confounder.

The adverse reaction was judged as serious because it required intervention.

Appendix

WHO algorithm of Causality Categories:

1	Probably/Likely:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
2	Possible:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
3	Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.



4	Conditional/Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.
5	Unassessible/Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

**Page(s) 000262 to\à 000264**

**Is(Are) exempted pursuant to section(s)  
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

**20(1)(b), 20(1)(c)**

**of the Access to Information Act  
de la Loi sur l'accès à l'information**

## **Report: Potential Dependence Effect of *Salvia divinorum***

Dr. Shahid Perwaiz  
Marketed Natural Health Products Division,  
MHPD

Dated: July 7, 2004.

### **Purpose/Objective:**

*Salvia divinorum* is one of several psychoactive plants, used by the Mazatec Indians, Mexico. *Salvia* is smoked to induce visual hallucinations, the diversity of which are described by its user to be similar to those induced by other hallucinogens such as mescaline, or psilocybin. Since *Salvia divinorum*, or any of its active ingredients are not specifically listed in the controlled Drugs and Substances Act, nor any Schedule of the Food and Drugs Act or its Regulations in Canada, some on-line botanical companies and drug promotional sites have advertised *Salvia* as a legal alternative to other plant hallucinogens like mescaline.

Salvinorin A is the active component of *Salvia divinorum*, and is most effective when vaporized and inhaled. It's actions in the brain are not well elucidated. However, recently it has been reported through *in vitro* assays, that "Salvinorin A" is the first known naturally occurring non-nitrogenous full agonist at kappa-opioid receptors, but functional assays are still lacking to determine the exact pharmacological mechanism of its action in the body. Most of the drugs which result in habit forming/dependence effects exert their activity through opioid receptor activation. The objective of this report is to provide background on whether *Salvia divinorum* has the potential to induce dependence effects.

### **Background:**

*Salvia divinorum* is a psychoactive plant, a member of the mint family, that has been used by Mazatec indigenous people of the Oaxaca for centuries for traditional spiritual practices. The primary active ingredient of *Salvia divinorum* is "salvinorin A" (there are B and C forms) is most effective when vaporized and inhaled. Chemically, Salvinorin A is a neoclerodane diterpene, a psychotropic terpenoid. Other plants with similar properties include *Cannabis sativa*, which contains tetrahydrocannabinol (THC), and *Artemisia absinthium*, also known as wormwood and used to make asbinthium. A dose of 200 to 500 micrograms of salvinorin A produces profound hallucinations when smoked. It's effects in the open field test in mice and locomotor activity tests in rats are similar to those of mescaline. A large body of evidence links the action of hallucinogenic agents (LSD, mescaline) to effects at serotonin (5-HT) receptor sites in the central nervous system (Aghajanian and Marek, 1999). Salvinorin A's actions in the brain are not well elucidated. However, recent tissue testing (*in vitro* assays) have suggested that "Salvinorin A" acts at the kappa opiate receptor site, but functional assays are lacking to determine the exact mechanism of action of this drug substance (Chavkin et al., 2004; Leander and Valdes, 1994; Roth et al., 2002).

Drug dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal; it can be of two types, physical and/or psychological dependence. The existence of three major groups of opioid receptors (mu, delta and kappa) in the central nervous system is well documented (Suzuki and Misawa, 1997). There are complicated interactions among opioid receptor types. The activation of kappa opioid receptor suppresses physical and psychological dependence on mu and delta opioid receptor agonists, but the activation of the delta opioid receptor potentiates the dependence on mu opioid receptor agonists. Various studies provide arguments to support substantial roles for mu-opioid receptors and the possible involvement of delta-opioid receptors in the development of physical and psychological dependence on morphine (Narita et al., 2001; Suzuki and Misawa, 1997). Most of the drugs used clinically are mu-opioid analgesics and are habit-forming. While both receptor types (delta and mu) provide analgesia, only the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dexamethorpan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor. (Cravenaux-Ruff and Krieller, 2002; Namba et al., 2001; Pasternak, 2003; Suzuki and Misawa, 1997). From behavioural, biochemical and molecular biological studies, it is suggested so far that development of physical dependence on morphine results predominantly from an activation of mu 1 and mu 2 opioid receptors which cause functional changes in Gi/o, adenylate cyclase, protein kinases A and C, beta-adrenoceptor and NMDA receptor in the locus coeruleus. However, activation of the mesolimbic dopamine system may lead to psychological dependence on opioids. (Narita et al., 2001; Suzuki and Misawa, 1997).

It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect. Recently, there have been significant advances in studies on the role of kappa-opioid receptor agonist in producing an aversive effect of other stimulants such as Morphine, cocaine, THC, alcohol, and other non-opioid addictions (Cui et al., 2000; Hahn et al., 2000; Mori et al., 2002; Raffa et al., 2003; Rosin et al., 1999; Rothman et al., 2000; Schenk et al., 1999; Tao et al., 1994). The activation of kappa-receptors also leads to the suppression of unpleasant mu/delta-mediated side effects such as dependence and respiratory depression. Considering the functional interaction between opioid receptor types, the co-administration of morphine-like compounds with kappa-receptor agonists may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

Salvinorin A is unique in that it is a potent, non-nitrogenous kappa-opioid selective agonist largely ignored by other known opioid agonists. Therefore, it would be devoid of the, mainly mu receptor mediated, side effects such as dependence and respiratory depression associated with morphine and its other analogues. It may thus be possible to use Salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, depression, and even excessive marijuana use. Being defined by their selectivity for the kappa-class of opioid receptor, Salvinorin A has the potential to offer a non-habit forming alternative. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

## **CONCLUSION:**

On the basis of available scientific literature, the potential dependence effects of *Salvia divinorum*



are expected to remain very low because of the following:

1. Most of the drugs which cause dependence and addiction are mu-opioid agonists, while salvinorin A acts as a full agonist at kappa-opioid receptors and appears to possess no mu-activity.
2. Kappa-opioid receptor agonists are characterized as being able to modulate dependence-related behavioural effects of drugs like morphine and cocaine rather than causing dependence.
3. There have been no cases of dependence on *Salvia divinorum* or salvinorin A reported in the scientific literature.
4. The precise mechanism of interaction between salvinorin A and the brain to produce its hallucinogenic effects remains unclear.
5. The toxicity of Salvinorin A is relatively low, even at doses many times greater than what human are exposed to (Mowry et al., 2003).
6. Many individuals have reported experiencing negative effects (bitter taste, unpredictable and occasionally disturbing short-term mental effects) during their first experience with *Salvia divinorum* and indicate that they would not use it a second time.
7. One internet distributor indicated that only 1 in 10 customers places a repeat order for the drug.

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## Pattern of use and subjective effects of *Salvia divinorum* among recreational users

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### Abstract

**Background:** *Salvia divinorum* is a member of the Lamiaceae family and contains the psychotropic diterpene and kappa-opioid receptor agonist salvinorin-A. Originally a shamanic inebriant used by the Mexican Mazatec Indians, the plant and its preparations are becoming increasingly popular among non-traditional users.

**Methods:** Demographic data and information on pattern of use and subjective effects were obtained by means of self-report questionnaires from a sample of 32 recreational users of salvia and other psychedelics.

**Results:** Involvement with salvia appeared to be a recent phenomenon. Smoking the extract was the preferred form of administration. Subjective effects were described as intense but short-lived, appearing in less than 1 min and lasting 15 min or less. They included psychedelic-like changes in visual perception, mood and somatic sensations, and importantly, a highly modified perception of external reality and the self, leading to a decreased ability to interact with oneself or with one's surroundings.

**Conclusions:** Although some aspects of the subjective effects reported were similar to high doses of classical psychedelics with serotonin-2A receptor agonist activity, the intense derealization and impairment reported appear to be a characteristic of salvia. The observed simultaneous high scores on the LSD and PCAG subscales of the Addiction Research Center Inventory (ARCI) have been previously reported for other kappa-opioid agonists, and support kappa receptor activation as the probable pharmacologic mechanism underlying the modified state of awareness induced by salvia.

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**Keywords:** *Salvia divinorum*; Pattern of use; Subjective effects; Retrospective assessment

### 1. Introduction

*Salvia divinorum* (Lamiaceae) is a psychotropic mint whose leaves are used for medicinal and religious purposes by Mazatec shamans in the Mexican state of Oaxaca (Wasson, 1962; Valdes et al., 1983). The Mazatecs, who call the plant “ska pastora” or “ska Maria pastora”, meaning “leaves of the shepherdess” or “leaves of Mary the shepherdess”, traditionally ingest the plant as a water infusion or by eating the fresh leaves (Wasson, 1962; Valdes et al., 1983). Early ethnological research found

that the Mazatecs regard the psychotropic effects elicited by the plant as weak and use it only in substitution of the psilocybin-containing mushrooms when these are scarce (Wasson, 1962). However, the plant's apparently weak potency could be due to limited absorption of the active principle when ingested orally (Ott, 1995).

Despite its initial reputation as a lesser drug, interest for salvia has greatly increased in recent years among recreational users for the modified state of awareness it can elicit. The use of salvia has spread to Europe and North America in a similar fashion to other natural drugs, as the DMT-containing ayahuasca did a decade ago (Riba and Barbanoj, 2005). However, unlike many ayahuasca users, current non-traditional users of salvia have accessed the plant and its preparations outside a religious context, mainly through “smart shops” and internet websites selling

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psychotropic plants and extracts, paraphernalia and dietary supplements (Dennehy et al., 2005). The term “smart shop” originated in The Netherlands and describes stores where natural psychoactive drugs such as ephedra, mescaline-containing cacti, psilocybian mushrooms and salvia extracts are sold. Such stores can also be found in Spain but their activities have been restricted since a decree was issued prohibiting the sale of a large number of plants, including salvia (see <http://www.boe.es>, number 32, 6 February 2004).

*S. divinorum* owes its psychoactive properties to salvininorin-A, its main active principle. This compound is a neoclerodane diterpene which was first isolated and identified by Ortega et al. (1982), and shortly after by Valdes et al. (1984). Recent pharmacological research has found it to be a highly selective full agonist of the kappa-opioid receptor (Roth et al., 2002; Butelman et al., 2004; Chavkin et al., 2004). Salvininorin-A is the only non-nitrogenous natural compound known to date to exert agonistic activity at these sites. Furthermore, in contrast with the classical psychedelics, salvininorin-A does not interact with the serotonin-2A receptor, but presumably induces its psychotropic effects through activation of the kappa-opioid receptor.

Contrary to what was initially assumed, salvininorin-A can be quite powerful. Inhalation of the vaporized active principle has been found to be active in doses as low as 200 µg (Siebert, 1994), in the same range as LSD. Recreational users have developed methods of administration that appear to lead to intense psychoactivity. These include chewing the leaves and retaining the juices in the mouth to allow absorption through the mucosa and obtaining concentrated extracts that can be administered either sublingually, applied to the buccal mucosa, or smoked (Siebert, 1994; Ott, 1995). The subjective effects described in self-experiments and case reports range widely, from increased relaxation, to laughter, colored visions, out-of-body experiences and loss of consciousness (Siebert, 1994; Bücheler et al., 2005; Dennehy et al., 2005).

In the present study we aimed to obtain systematic information on the pattern of use and the nature of the subjective effects elicited by salvia in recreational users. Self-report questionnaires were administered to the participants to obtain demographic and subjective effect data.

## 2. Methods

### 2.1. Sample

The sample was recruited by direct approach by the first author, who also conducted the interviews. Potential participants had to have used salvia at least once in their lifetime. Given the infrequent nature of the behavior under study, adaptive sampling was used with participants referring to acquaintances who had also had experience with the drug (Thompson and Collins, 2002). Several leads were followed, so participants did not belong to a single social network. After initial contact with the first author, participants were given the forms, which they took away, filled out and later returned to the investigator. Anonymity of the information was guaranteed and all the participants gave their written consent to participate. The study was approved by the ethics committee at the Hospital de Sant Pau in Barcelona. Participants had not taken part in any clinical study conducted by our group and did not receive any payment for their participation in the present survey.

Demographic information was collected from the participants, together with information on drug use history and salvia use history, route of administration,

pleasant and unpleasant after-effects, and any potential problems they might have experienced derived from salvia use. Information on salvia-induced subjective effects was obtained by means of the retrospective assessment of drug effects when they last took salvia.

### 2.2. Subjective effect measures

Retrospective assessment of the subjective effects induced by salvia was conducted by means of self-assessment questionnaires. The following questionnaires were administered:

The Hallucinogen Rating Scale or HRS (Strassman et al., 1994) measures psychedelic-induced subjective effects and includes 71 items distributed into six scales: *Somaesthesia*, reflecting somatic effects including interoceptive, visceral and tactile effects; *affect*, sensitive to emotional and affective responses; *volition*, indicating the volunteer's capacity to willfully interact with his/her “self” and/or the environment; *cognition*, describing modifications in thought processes or content; *perception*, measuring visual, auditory, gustatory and olfactory experiences; finally *intensity*, which reflects the strength of the overall experience. The range of scores for all scales is 0–4. In the present study, a Spanish version of the questionnaire was administered (Riba et al., 2001a). The HRS has proven sensitive to various psychedelics such as intravenous DMT (Strassman et al., 1994), oral psilocybin (Gouzoulis-Mayfrank et al., 1999) and ayahuasca (Riba et al., 2001b, 2003).

The ARCI (Martin et al., 1971) consists of five scales or groups: MBG, morphine-benzedrine group, measuring euphoria and positive mood; PCAG, pentobarbital-chlorpromazine-alcohol group, measuring sedation; LSD, lysergic acid diethylamide scale, measuring somatic-dysphoric effects; BG, the benzedrine group, measuring intellectual energy and efficiency, and the A scale, an empirically derived scale measuring amphetamine-like effects. The range of scores is 0–16 for MBG, –4 to 11 for PCAG, –4 to 10 for LSD, –4 to 9 for BG, and 0–11 for A. A validated Spanish version was administered (Lamas et al., 1994).

The State-Trait Anxiety Inventory-S (STAI-S) is a brief 20-item self-rating scale for the assessment of state anxiety (Spielberger et al., 1970). A validated Spanish version was administered (Seisdedos, 2002). The normative data for the Spanish adaptation differs from the original data for the American version. The reported mean (S.D.) values reported for State anxiety in the normal population are 20.54 (10.56) for male adults and 23.30 (11.93) for female adults (Seisdedos, 2002).

The Altered States of Consciousness Questionnaire (“Aussergewöhnliche Psychische Zustände”, APZ) developed by Dittrich (1998). It includes 72 items distributed in three subscales: *Oceanic Boundlessness* (“Ozeanische Selbststengrenzung”, OSE), measuring changes in the sense of time, derealization and depersonalization; *Dread of Ego-Dissolution* (“Angstvolle Ichauflösung”, AIA) measuring thought disorder and decreased body and thought control associated with arousal and anxiety and *Visionary Restructuring* (“Visionäre Umstrukturierung”, VUS) referring to visual phenomena, such as illusions, hallucinations and synesthesia and to changes in the significance of objects. The range of scores is 0–13 for OSE, 0–22 for AIA, and 0–14 for VUS. A Spanish version of the questionnaire previously used in clinical studies involving psychedelic drugs was administered (Riba et al., 2002).

### 2.3. Statistical analysis

The data presented in the present paper are descriptive in nature and accordingly, descriptive statistics are provided in Section 3. Percentages are reported for categorical variables and means and standard deviations for continuous variables obtained from subjective effect questionnaires.

Given the small sample size, no inferential statistics were used to find differences associated with gender or route of administration.

## 3. Results

### 3.1. Demographic characteristics of the sample

A total of 32 salvia users were recruited, 18 (56%) of whom were male and 14 (44%) were female. The mean age of the sam-

ple was 25 years (S.D.: 4.32; range: 18–40 years). Education level was high with 23 (72%) of the sample having completed high school and 7 (22%) having obtained a university degree. At the time of the survey, 22 (69%) were attending university. Seventeen participants (53%) were full-time students, 6 (19%) combined studies with part-time jobs, 7 (22%) worked exclusively, and 2 (6%) were unemployed.

### 3.2. History of drug use (other than salvia)

Except for two participants, all those in the study (93.7%) had a drink containing alcohol weekly. The average number of alcoholic drinks per week among the drinkers was 3.13 (S.D.: 2.69, range: 1–14). More than four-fifths of the participants (84.4%) were smokers, with a mean number of 14 cigarettes per day (S.D.: 6.74, range: 1–25). Except for one participant, all participants (96.9%) consumed cannabis at least once a week. The average number of cannabis joints was 21.32 per week (S.D.: 15.68, range: 2–70). They also had wide experience with other drugs; ecstasy had been used by 88%, cocaine by 84%, amphetamines 69%, opiates 56%, benzodiazepines 36%, and GHB 9%.

Ninety-four percent of the volunteers had at some time used a psychedelic/hallucinogen, the most frequent being psilocybian mushrooms (78% of all participants), followed by LSD (63%), ketamine (34%), ayahuasca (28%), *Amanita muscaria* (13%), peyote (6.3%) mescaline (3%) and *Datura stramonium* (3%). Ten volunteers (31%) reported having consumed “other psychedelics” not listed in the questionnaire. Specified were: 2C-B (four volunteers), San Pedro (one volunteer) and *Argyrea nervosa* (one volunteer).

### 3.3. History and pattern of use of salvia

Participants appeared to have first experienced salvia only recently, with 88% having used it for the first time in the last year. The average number of times the drug was consumed was 2 (range: 1–5). The source of the salvia was a “smart shop” in 88% of the cases and in the remaining 12% it had been obtained from a friend, without further specifying the source.

All participants had consumed salvia as an extract and three (9%) had also used the leaves. Commercially available extracts usually consist of ground salvia leaves impregnated with salvia tincture, so that the final product may contain 5, 10 or 20 times the original salvinin-A concentration.

Regarding the preferred route of administration, 75% reported having smoked the extract, 22% reported combining sublingual and smoked administration and 3% (one subject) reporting smoking the leaves and the extract combined. As to the smoking technique, all volunteers reported using a bong or a pipe. No participant reported smoking it in the form of cigarettes or mixing salvia with tobacco or marijuana. When asked about the psychotropic potency of salvia, 75% of the participants described the experience elicited by salvia from “intense” to “very intense” or “extremely intense”, with only 19% as “moderate” and 6% describing it as “slight”.

Participants were asked to state the best and the worst aspects of their salvia experiences. These are listed in Table 1.

The most commonly cited positive effects were the “trip” the drug elicits (41%), followed by its euphoric (28%) and dissociative effects (19%). Among the worst aspects, its short duration (38%) was the most frequently cited. Sixteen percent of the volunteers mentioned the lack of control over the experience and 13% the unpleasant after-effects as the worst aspect of salvia. Thirteen percent of the volunteers could find no negative aspect related to the experience.

Fourteen volunteers (44%) reported having experienced some degree of malaise, hang-over or “comedown” immediately after the acute effects of salvia. These effects are also listed in Table 1 and essentially describe physical and mental tiredness. All volunteers unanimously agreed that these unpleasant effects were no longer present 1 day after salvia use, and that they had never experienced any mid-term unpleasant sensations they could attribute to salvia. Only one volunteer commented on having had problems with studies, work or relatives due to the use of salvia. He complained that friends who do not habitually use psychotropic substances were worried about his experimenting with drugs.

Twenty participants (63%) commented that the effects of salvia were similar to those of other drugs. Subjects in this subgroup cited the following drugs, from most to least frequent: psilocybian mushrooms (55%), ayahuasca (20%), ketamine (20%), LSD (20%), marijuana (20%), MDMA (15%), opium (15%), poppers (15%), 2C-B (15%), *Amanita muscaria* (10%) and DMT (5%).

Finally, when asked if they would like to take salvia regularly, only 44% of the subjects responded affirmatively.

### 3.4. Retrospective assessment of the most recent salvia consumption

Participants responded to the subjective effect questionnaires recalling the effects they had experienced when they last took salvia. Fifty-six percent of the participants had used salvia for the last time within the preceding month, and 38% had last used salvia between the preceding month and the preceding year. Only 6% of the participants had used salvia more than a year ago.

The preparation or part of the plant they had used on this last occasion was the extract in 91% of the cases and the leaves in 6% of the cases, while 3% declared having used a combination of smoked leaves plus smoked extract. Regarding the route of administration, 72% had smoked the extract, whereas 19% had combined smoking the extract and placing the extract sublingually. Two volunteers (6%) had smoked the leaves and one volunteer (3%) had combined smoking both the leaves and the extract.

As to the intensity of the experience, all participants declared having experienced psychotropic effects; these were “slight” for 6% of volunteers, “moderate” for 22% of the sample, “intense” for 12%, “very intense” for 41% and “extremely intense” for 19%.

The onset of effects was found to be “instantaneous” by 31% of the volunteers, “less than a minute” by 57% of the volunteers,

Table 1  
Volunteers' written descriptions of the best and worst aspects of salvia and any unpleasant after-effect

Best things about using salvia	n	Worst things about using salvia	n	Unpleasant after-effects	n
The "trip", entering another reality	13	Short duration	12	Tiredness	4
Laughter, happiness, well-being	9	Lack of control over the experience	5	Heaviness of head, like after smoking many marihuana joints	4
Separation from body, dissociation	6	Unpleasant after-effects	4	Dizziness	3
Visual effects	5	None	4	Physically exhausted	3
Rapid onset of effects	3	Unpleasant physical effects	3	Grogginess	1
Its great potency	3	Excessively intense	2	Mental slowness	1
Relaxation	2	Effects are unreliable	1		
Perceptual modifications	2	Onset too rapid	1		
The "high"	2				
Loss of consciousness	2				
Novelty	2				
Pleasant after-effects	1				
Mental clarity	1				
Escape	1				
Auditory effects	1				
Dizziness	1				

n: number of subjects reporting a specific effect.

"from 1 to 5 min" by 6% of the volunteers. Only one volunteer (3%) declared that "from 5 to 15 min" had elapsed and another (3%) declared that "half an hour had elapsed". Separating by route of administration, the onset of effects after smoking the extract was found to be "instantaneous" or "less than a minute" according to 91% of participants who chose this route. Only 67% of those participants who combined sublingual extract plus smoked extract described the onset with one of these two categories.

Table 2  
Mean (S.D.) scores obtained for the HRS, ARCI and APZ questionnaire subscales

HRS	Scores
Somaesthesia	1.42 (0.62)
Affect	1.66 (0.53)
Perception	1.53 (0.88)
Cognition	1.32 (0.70)
Volition	1.98 (0.55)
Intensity	2.50 (0.53)
ARCI	Scores
A	4.41 (1.81)
BG	-0.34 (1.64)
MBG	5.75 (3.06)
PCAG	2.75 (3.38)
LSD	4.25 (2.43)
APZ	Scores
OSE	6.09 (3.44)
AIA	6.28 (4.30)
VUS	4.78 (3.99)

A: amphetamine scale; BG: benzedrine group; MBG: morphine-benzedrine group; PCAG: pentobarbital-chlorpromazine-alcohol group; LSD: lysergic acid diethylamide scale. OSE: Oceanic Boundlessness; AIA: Dread of Ego-Dissolution VUS: Visionary Restructuralization.

The duration of effects was described as "less than a minute" by 6% of participants, "between 1 and 5 min" by 60% of participants, "between 5 and 15 min" by 19%, "between 15 and 30 min" by 9% of participants. Only one volunteer (3%) described the duration to be "between 30 min and 1 h" and another (3%) described duration "between 1 and 2 h". Separating by route of administration, 70% of those who had smoked the extract chose the options "less than a minute" or "between 1 and 5 min", compared to 50% who combined sublingual plus smoked administration. Effects lasting longer than 5 min were described by 13% of participants who smoked the extract, and by 33% of participants who combined sublingual plus smoked.

3.4.1. *HRS, ARCI and APZ questionnaires.* Table 2 shows mean scores and standard deviations for the different subscales of these three questionnaires.

3.4.2. *STAI-S.* A mean (S.D.) score of 27.3 (8.5) was obtained for the STAI-S questionnaire. Separated by gender, scores of 26.9 (1.6) were obtained for male participants and 27.8 (2.8) for female participants.

#### 4. Discussion

Results from the present study show that awareness and involvement with salvia appears to be a recent phenomenon. Most participants had had their first contact with salvia during the last year, and had consumed it on average only on two occasions, mainly smoking the extract, which almost all participants had acquired in "smart shops". It is worth mentioning here that the survey was conducted during the second half of 2003 and the first-half of 2004. In February 2004 a decree from the Spanish government prohibited the sale of salvia in the country ([www.boe.es](http://www.boe.es), number 32, 6 February 2004), but the product was still available for some months after that date. It is likely that Spanish users will now turn to internet sites or to "smart shops"

in other countries, such as The Netherlands, in order to purchase the product.

Although the effects of salvia were compared by the participants to those of other psychedelics, they differed in various aspects, particularly their extremely short duration. The effects seem to be by far the shortest amongst perception-modifying drugs, surpassing intravenous DMT (Strassman et al., 1994). Other important qualitative differences found are discussed below.

Scores on the HRS subscales confirm the psychedelic-like effects of salvia. Mean scores on all but one subscale (cognition) were higher than the values our group had obtained in two clinical trials in which we evaluated the effects of fully psychotropic doses of ayahuasca equivalent to 0.50–1.0 mg DMT/kg body weight (Riba et al., 2001b, 2003) and fell between the scores obtained for intravenous doses of 0.2 and 0.4 mg DMT/kg body weight (Strassman et al., 1994). Interestingly, the score in the volition subscale, which reflects the subject's degree of incapacitation, is the highest ever observed by our group in clinical (Riba et al., 2001b, 2003) and in survey studies (Riba et al., 2001a) and is even larger than that recorded by Strassman and colleagues after the highest intravenous DMT dose they administered (Strassman et al., 1994).

The pattern of scores on the ARCI shows high values for the MBG and LSD subscales. We have also observed high scores on these subscales following ayahuasca (Riba et al., 2001b, 2003) and they highlight the coexistence of somatic and dysphoric effects with positive mood. A high score in the A scale and a low score in the BG are also typical of the psychedelics. Although these drugs display stimulant-like properties, they do not lead to high scores in the BG scale, which measures subjectively-perceived intellectual efficiency. However, what is remarkable about salvia is the score obtained in the PCAG subscale. The score is unusually high for a psychedelic. High scores on the PCAG subscale have usually been reported in individuals experiencing "fatigue, weakness and sluggishness" after sedatives, such as alcohol, benzodiazepines and the opiate pentazocine (Arasteh et al., 1999).

Scores on the APZ-OSE subscale provide insight into the high degree of derealization experienced by the participants, in line with the most frequently cited positive aspect of the drug, i.e. the sensation of entering another reality. The score obtained is higher than that observed by our group after the administration of an ayahuasca dose corresponding to 0.8 mg DMT/kg body weight (Riba et al., 2002). The APZ-AIA and APZ-VUS were also higher than in the mentioned study, pointing out the high intensity of the derealization and visionary phenomena induced by salvia.

Scores on the STAI indicated levels of state anxiety above the normative mean both for male and female subjects. The obtained values fall between percentiles 70 and 75 for the males and percentiles 65 and 70 for the females (Seisdedos, 2002). These results indicate that the experience induced by salvia causes a certain degree of anxiety. Taking into consideration these STAI scores, elevations in the PCAG can be interpreted as reflecting an incapacitating rather than an anxiolytic effect. This interpretation is in line with the decreased ability to interact with them-

selves or their surroundings reflected by the high HRS-Volition score and the marked degree of derealization and anxious depersonalization reflected by the APZ-OSE and APZ-AIA subscales, respectively. Thus, the pattern of responses obtained for salvia with the self-assessment instruments administered would reflect a psychedelic effect profile accompanied by a highly modified perception of external reality and a decreased ability of the individual to interact with themselves or their surroundings.

An interesting aspect of the subjective effect profile of salvia is the simultaneous high scores on the LSD and PCAG scales observed. This is not a characteristic feature of the classical psychedelics displaying serotonin-2A agonist activity. However, this unusual pattern combining modifications in somatic-dysphoric effects and sedation/impairment has been reported for agonists of the opioid kappa receptor. Thus, pentazocine (Arasteh et al., 1999; Zacny et al., 1998) and enadoline (Walsh et al., 2001) have been shown to elevate scores in the LSD and PCAG scales. At high doses, these drugs can cause modifications in visual perception and depersonalization (Walsh et al., 2001), which has led some authors to describe kappa receptor agonism as capable of inducing "psychotomimetic" effects (Pfeiffer et al., 1986; Walsh et al., 2001).

The present results constitute a preliminary approach to the subjective effects of salvia. The investigation has several limitations associated with its naturalistic and exploratory nature. Information was obtained from a small sample of experienced psychedelic/hallucinogen users. These volunteers were regular users of other psychoactive agents such as cannabis and had experimented with rarely used drugs like ayahuasca. The investigators had no control over the salvia doses consumed, and the possibility of an interaction with the participants' daily cannabis use cannot be ruled out. The pattern of subjective effects observed may therefore be difficult to extrapolate to the general population or to other drug users unfamiliar with psychedelics/hallucinogens. Also, the retrospective assessment performed does not substitute for the immediate assessment of the psychotropic effects of salvia, ideally in the context of clinical trials administering known doses of the drug and implementing optimal designs.

To sum up, smoking extracts of salvia appears to be the most common form of use of the drug among recreational users. In the sample studied, this form of administration led to a very fast onset of effects which were intense but short-lived. The psychotropic effects reported bear similarities to those induced by the classical psychedelics regarding changes in perception, mood and somatic sensations. However, the increased derealization observed and the consequent decrease in the ability to interact with themselves and their surroundings appears to be particularly high for salvia. Although the perception- and reality-modifying potency seems higher, the profile of subjective effects induced by salvia is compatible with that of other kappa agonists, thus supporting the activation of this receptor as the drug's mechanism of action in humans. However, considering the limitations associated with field investigations, the reported results should be considered as preliminary. Carefully planned clinical studies are warranted to further elucidate the pharmacology of salvia in humans.



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## Use of Nonprohibited Hallucinogenic Plants: Increasing Relevance for Public Health?

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A Case Report and Literature Review on the Consumption of *Salvia divinorum*  
(Diviner's Sage)

**Introduction:** We want to call attention to a mint plant, called diviner's sage (*Salvia divinorum*), originally used in shamanic ceremonies of the Mazatec Indians of Mexico. On numerous websites of the internet, this ancient herbal drug and its extracts are offered as a legal means of widening individual awareness. Regarding its dose-response relationship, the active ingredient, salvinorin A, is one of the most potent naturally occurring hallucinogens. Laws on controlled substances, except for Finland, Denmark and Australia, do not prohibit cultivating, consuming or dealing with *Salvia divinorum*. Ingestion by smoking, vaporis-

ing or chewing, induces a short-lived inebriant state with intense, bizarre feelings of depersonalization. This article wants to be a signal for physicians or psychotherapists to take *Salvia* into consideration, when exploring young people for drug use. **Methods:** We report the individual perceptions of a young man consuming *Salvia divinorum*. We review the scarce scientific literature and consider relevant internet websites. **Discussion:** We define open issues for further investigations and try to discuss why *Salvia divinorum* may be of interest for teenagers and young adults in Europe.

### Introduction

In 2002 the number of offences, especially among children and adolescents involving the possession and purchase of cannabis, rose by more than 6% to 139 082/year in Germany [3]. Similar observations are documented from abroad [7,9]. These figures may reflect a changing attitude of young people towards drug use in general. Intoxication by nonprohibited drugs of herbal origin like *Datura* (*Datura Stramonium*) or Angel's Trumpet (*Brugmansia suaveolens* or *sanguinea*) plays an increasing role in emergency medicine [10,18,28].

We want to point out a newcomer among drugs of herbal origin: A Mexican mint, a sage plant, called "*Salvia divinorum*". For many centuries, it has been used by shamans of the Mazatec Indians in

the state of Oaxaca, Mexico, in healing and divination ceremonies. In 1962, however, it was characterized botanically for the first time by Epling and Játiva [13]. For ritual purposes, five up to 80 pairs of fresh leaves are chewed or crushed and prepared as a bitter tasting, foamy infusion [43]. To date, six different ingredients (salvinorin A-F) have been isolated from its leaves [27]. In 1982 the main psychoactive compound, salvinorin A (Divinorin A), was identified by two independent research groups [29,45]. Salvinorin A, which is not water-soluble, is only absorbed by the respiratory and, to a lesser extent, by the oral mucosa. Dried leaves of *Salvia divinorum* are smoked as a joint, consumed in water pipes or vaporized and inhaled. About 1.5 g of pure salvinorin A can be extracted from one kilogram of air-dried leaves, gained from about 8 kg of fresh leaves [37,43]. According to biochemical reports, it is easier to obtain salvinorin A than to extract

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lysergic acid diethylamide (LSD) or than to produce phencyclidine derivatives [44]. In minimum doses above 200 to 500 µg, purified salvinorin A has shown intense psychoactive effects [37].

As the content of salvinorin A in one gram of dried leaves may vary from 0.9 to 3.8 mg [19], only 0.1–0.5 g of these leaves are required for a hallucinogenic trip, when inhaled. Fortified plant-extracts however, can also be ordered via the internet. They contain up to 25 mg salvinorin A per gram. On the internet, esoteric websites or ethnobotanical shops openly offer Salvia as a means of improving the air in rooms or as a legal hemp alternative at an affordable price [e.g. 2,16,25,31]. Five grams of dried Salvia leaves cost between 5 to 12.50 €, not including shipping charges.

The cultivation of *Salvia divinorum* has spread from South and North America to Canada and Europe. Recently, the plant was identified in the greenhouses of a Swiss horticulturist [17].

As clinical effects of *Salvia divinorum* in adolescents have not been described in medical literature, we would now like to recount the psychedelic experiences of a teenager. We have also reviewed available scientific articles as well as trip reports and accessible sites of the internet.

### Case report

In February 2003, the mother of a 19-year old high school student preparing for his A-levels consulted the Department of Clinical Pharmacology of the University Hospital Tuebingen for information concerning the potential health risks of *Salvia divinorum*. She had accidentally noticed a dreadful offensive odour coming from her son's room. While smoking the dried leaves, the young man hardly reacted to her approach and seemed to suffer from a reduced awareness. His face had a strange, transcendental and mask-like expression. The young man was a good student. Apart from habitual smoking, no other drug use was reported by the parents who thought him to be "normal" regarding his social and academic skills. His IQ was tested as above 140.

A standardized psychiatric interview revealed neither personal nor family histories of major psychiatric disorders. The young man reported that he had been chewing or inhaling dried leaves of *Salvia divinorum* twice a week for about six months, alone or in the company of friends. His most important motivation to consume Salvia is the unique sensation of being disconnected from his own body during the trip. This extracorporeal existence in a new "astral body" gives him a very "good" feeling of recreation. He also describes vestibular hallucinations that provide an illusion of hovering above the floor, or penetrating the natural limits of his own room. In these moments, he believes to gain a more mature insight not only into his own personality but also into philosophical or ethical problems. Almost immediately – he estimates in less than five minutes after inhaling – the peak of psychotropic effects seems to be reached. During the trip, he experiences somatic sensations like prickling of the skin, fever-like hot flashes, muscular tremor, and a sort of ringing in the ears. All these effects, including the desired feeling of changing his personality and an increased status of self-consciousness, complete-

ly disappear within 30 minutes. For some hours afterwards, he reports shivering and exhaustion that render him unable to learn or memorize school assignments. The young student attributes this lack of concentration not to a prolonged drug effect but to the need of reflecting the overwhelming perceptions during the trip.

He denies having optical or verbal hallucinations, "bad trips" nor fits of panic. During the last months, his trips seemed to follow similar patterns as described above. Nevertheless, he reports his impression that the amount of Salvia material, necessary for one trip, will have to be increased gradually in order to maintain the original effective strength. The young man says that he has a good feeling about the safety of *Salvia divinorum*. He is convinced to be well informed by numerous websites on the internet which do not describe severe short term nor long term health risks such as intoxication or an induction of psychoses.

### Discussion

#### Sources of information on *Salvia divinorum*

Reliable, systematic observations on the psychotropic activities of *Salvia divinorum* or its ingredients in human beings are scarce: Searching databases like MEDLINE or BIOSIS, we found a publication on psychotropic effects following the use of fresh Salvia leaves in six human volunteers, as well as after the application of purified salvinorin A in 20 volunteers [37]. In another paper, two ethnobotanical researchers report their own observations after drinking a Salvia infusion in two different concentrations [43].

On the internet however, "*Salvia divinorum*" is linked to numerous websites of ethnobotanical shops, consumers and "experienced specialists" that provide details on botanical cultivation, on dosing and sometimes even publish "guidelines" for a safe and satisfying use of "the magic mint" [e.g. 1,16,35,42]. In chat-rooms such as [33], users communicate and discuss their experiences during the trips. Amateur researchers even publish the results of their private "double-blind" and "placebo-controlled" tests in search of the optimal Salvia dose for meditation [40].

#### Clinical effects

The young boy, who lives about 100 km away from our clinic told us about his trip experiences in a clinically drug-free condition. As Salvia and its ingredients cannot be detected by usual drug-screening methods, we did not perform blood or urine analysis. We excluded the concomitant use of other hallucinogens by interview. The student reported Salvia effects like depersonalization, widening of consciousness, the subjective illusion of rapid movements, flying or hovering, as being comfortable feelings. They seem to outreach negative side effects of Salvia use such as impaired vigilance and coordination. Although horror-trips appear to be rare, on the internet, some consumers delineate frightening attacks of panic, mostly due to the loss of self-control and to the profound experience of losing contact with consensual reality. As this is "nothing for beginners", most of the websites recommend the presence of a sober "trip sitter" [14,35]. He should also protect the Salvia consumer against injury due to somnambulistic activities or to coordination disturbances [38].

Onset and duration of the young man's trips correspond to the data reported on websites and in a scientific publication: After inhaling a bolus of the active ingredient, hallucinogenic feelings are intense but very short-lived. They occur rapidly after 30 seconds and disappear within one hour [38]. Hallucinogenic effects after oral ingestion of salvinorin A begin within 3–5 minutes. These perceptual distortions may return for up to 4 hours, sometimes experienced as "flashbacks" [43]. Hysterical laughter is observed, but *Salvia divinorum* is said to have only a weak influence on the prevailing mood of the consumer and rarely changes it [37]. This is an important difference to LSD or hallucinogenic mushrooms.

Salvia provides the experience of voyages leading the individual to places of the past, especially from childhood. It may cause vivid illusions of a self-metamorphosis into things like water or animals, culminating in the individual conviction of having definitely abandoned human existence [37].

Doses of salvinorin A needed for hallucinogenic effects, vary from one individual to the other. Different Salvia websites report that about 10 to 15% of the consumers do not experience any psychotropic effects at all! In doses exceeding 1 mg salvinorin A, out-of-body experiences, i.e. advanced "trip levels", are frequent [37]. On awakening after very high trip levels, the consumer may completely have lost his recollection of having taken any drug [35].

These psychotomimetic effects of *Salvia divinorum* closely resemble schizophrenia symptoms induced by other distinct classes of drugs: Serotonergic agonists (e.g. LSD) and especially antagonists of the NMDA (*N*-methyl-*D*-aspartate) glutamate receptor like phencyclidine (PCP, Angel dust) or ketamine [21,22]. Indeed, web-reports describe similarities of Salvia associated perceptions with LSD or Ketamine [1,34], but it is often emphasized, that the depersonalization caused by Salvia has a unique and specific character [37]. In 2002, the active ingredient, salvinorin A, has been shown to be a potent and strong agonist of cerebral kappa-opioid receptors (KOR) [6,32,36]. This interaction may cause the reported vegetative reactions to Salvia like sweating, chill and increased diuresis, which may be related to the interaction with KOR. The same effects were shown by synthetic agents stimulating KOR like spiradoline in humans [46]. Salvia induced illusions are intensified by rest and darkness [43]. The afterglow of former Salvia trips as well as the concomitant intake of other psychoactive agents like ethanol, cannabis, LSD or hallucinogenic mushrooms have been mentioned to determine the individual feeling [35].

#### **Pharmacokinetics and pharmacodynamics of the active ingredient, Salvinorin A**

Salvinorin A, a neoclerodane diterpene, is the only known non-alkaloidal hallucinogen [6]. Beside the fact, that it is not easily absorbed by the gastrointestinal system [37], data on bioavailability, on metabolism or excretion and on interactions with food, drugs or narcotic agents are not published. In terms of its psychoactive effects doses of above 200 µg, salvinorin A rivals in potency with the synthetic hallucinogen LSD acting in doses of 50–250 µg [44].

Pharmacodynamic aspects of salvinorin A and its derivatives have been studied more exactly in the last decade [6,32,36]. In human and nonhuman cell cultures, salvinorin A has proven to be a selective, full and very efficacious agonist for KOR [6,32]. It does not interact with 5-hydroxytryptamine 2A-receptors, like classical hallucinogens such as LSD, psilocybin or mescaline do, and shows no affinity to  $\mu$ - or  $\delta$ -opioid receptors nor did it interact with binding-sites for norepinephrine, dopamine, glutamine and GABA-transporters [32]. Psychotropic effects of salvinorin A appear to be the result of KOR stimulation. This hypothesis is supported by the recently published behavioral effects of salvinorin A in primates [4]. Salvinorin A is the first naturally occurring non-nitrogenous agent and stimulates KOR to the same extent like dynorphin, the endogenous KOR-agonist [6].

Due to their reduced affinity to KOR, therapeutically used opioid-antagonists like naloxone or naltrexone are not regarded as a very potent antidote for salvinorin A [15,23,24].

#### **Pharmacotherapeutic potential**

KOR mediated neurotropic effects are analgesia, sedation, dysphoria and perceptual distortions [12,15,30]. Selective stimulation of KOR by salvinorin A may be a pharmacological model to study the promotion of schizophrenia, dementia or bipolar depression. KOR-antagonists like nor-binaltorphimine, have shown antidepressant effects by ameliorating psychomotoric functions in rats [26]. Paradoxically, a case-report of a 26-year old woman documents the complete resolution of a perennial depression since ingesting 0.5–0.75 g of Salvia leaves three times per week sublingually [20]. This is surprising, since the dysphoric side effects of KOR-agonists normally form an obstacle to their use as analgesics, for instance, see [46].

Stimulation or blockade of cerebral KOR may also modulate cardiovascular functions. Experimental investigations in animals show an influence on blood pressure, on the ischemic tolerance of the myocardium and on the induction of cardiac arrhythmias [8,47,48].

#### **User population and legal aspects**

To date, the vast majority of *Salvia divinorum* consumers are younger adults and adolescents. As "Diviner's mint" is not a party-drug [35,43], it appeals to individual experimentalists. On the internet, they define themselves as a kind of community, ingesting the plant or its extracts not to satisfy an addiction, but as a tool for meditative introspection [5,42]. In international conferences, psychotherapists, artists, ethnobotanists, anthropologists, pharmacologists and consumers discussed, how the plant could serve modern people in daily life to perform meditation or healing rituals [40].

Salvinorin A fails to meet the criteria of chemical similarity to other hallucinogens. Therefore, in most of the countries the plant and its compounds are not banned by national laws for controlled substances. In Australia however, the possession of *Salvia divinorum* is illicit [14]. This is officially justified by concerns about its unknown addictive potential and long-term effects. In Europe, only Finland and Denmark have added Salvia to the list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of a psychoactive drug. The American Drug Enforce-

ment Agency (DEA) has placed *Salvia divinorum* on a list of drugs or chemicals "of concern", without legal implications at present. Consumers have meanwhile founded a "*Salvia Divinorum* Defense Fund" in order to prevent more restrictions on *Salvia* use [5,33].

## Conclusion

*Salvia divinorum* might become increasingly attractive to adolescents and young adults for several reasons:

- It can be easily ordered at an affordable price.
- The use of *Salvia divinorum* promises philosophical insights or escapism for young people seeking their own personality. Furthermore, adherence to an international "*Salvia* community" may be socially attractive.
- Numerous internet sources offer a mixture of esoteric advice, practical warnings and instructions on the use of the plant. The consumer may take this subtle promotion of *Salvia* products as "evidence-based" in a scientific sense and underestimate known and unknown health risks.

## Open issues

As a consequence, the following questions deserve more attention in research:

1. Unidentified, salvinorin-induced intoxications by an unintentional intake of more than 500–1000 µg salvinorin A may be more frequent than presumed, because salvinorin A in blood or urine is not examined by the drug screenings, available at the moment.
2. The influence of *Salvia* use on social behavior and on daily activities like driving a car or handling technical devices should be observed.
3. Psychotomimetic effects of *Salvia divinorum*, especially in teenagers and young adults should be documented systematically, e.g. by using a standardized questionnaire to assess altered states of consciousness [11].
4. Long term effects of Salvinorin A especially in combination with conventional hallucinogens or psychoactive drugs must be watched carefully. They might promote the manifestation of endogenous psychoses in predisposed persons.
5. The addictive potential of *Salvia divinorum* is still a matter of debate. Stimulated cerebral KOR may develop mechanisms of tolerance that mediate withdrawal behavior [39,41].
6. Pharmacokinetics and molecular mechanisms of salvinorin A as well as interactions with ethanol or psychoactive drugs should be investigated. Finally the potential of this naturally occurring KOR-agonist for exploring and alleviating psychiatric conditions, has to be determined.

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## Health Risk Assessment of *Salvia divinorum* as a Health Product

Marketed Biologicals, Biotechnology and Natural Health Products Bureau  
Marketed Health Products Directorate  
and  
Bureau of Product Review and Assessment,  
Natural Health Products Directorate

June 5, 2007

### Issue:

In the last several years, Health Canada has become aware of the use of the plant *Salvia divinorum* as a recreational hallucinogen, and as a “legal alternative” to illicit drugs. In certain parts of North America, this plant has been traditionally used for religious, as well as for health purposes. *Salvia divinorum* meets the criteria for regulation under the *Natural Health Products Regulations*; however, as a hallucinogen, it may also meet the criteria of a substance regulated under the *Controlled Drugs and Substances Act*, or the *Food and Drug Regulations*.

This risk assessment was undertaken to determine the potential risks from the use of *Salvia divinorum* as a health product, and will help determine potential compliance actions to be taken on products available on the Canadian market, containing *Salvia divinorum* or its active constituents.

### Background:

*Salvia divinorum* is a plant from the mint family. It is also known by a number of common names such as Diviners Sage, Magic Sage, Mexican Sage, Sage of the Seers, and Herba Maria (Natural Medicines Comprehensive Database, 2007). The plant has been used in traditional and spiritual practices by the Mazatec Indians of Oaxaca, Mexico, to produce “mystical” or hallucinogenic experiences (Diaz, 1976).

Health Canada has received four reports of adverse reactions involving psychotropic effects, associated with the use of *Salvia divinorum*. There have been several reports (scientific articles, case reports, media enquiries/articles) which indicate that *Salvia divinorum* has the potential for abuse, and is being used by adolescents and young adults for its hallucinogenic properties. In

addition, Salvia is being widely touted on internet sites aimed at these population groups, as a “legal” alternative to street drugs.

In Canada, neither the herb *Salvia divinorum*, nor its active constituents such as salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* (CDSA), nor any Schedule of the *Food and Drugs Act and Regulations*. *Salvia divinorum* meets the definition of a natural health product (NHP) if marketed in Canada with health claims. However, the current use and advertising of *Salvia divinorum* as a recreational hallucinogen does not meet the intent of the functional component of the definition of a natural health product. In addition, as a hallucinogen and potential drug of abuse, Health Canada’s Office of Controlled Substances (OCS) has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the OCS will collect relevant information specific to this herb and its active constituents, in relation to its psychotropic use.

Since *Salvia divinorum* in some circumstances meets the definition of a NHP and is not listed in any Schedule to the CDSA, nor any Schedule of the *Food and Drugs Act* or its Regulations, it is appropriate to assess the health risk associated with the use of *Salvia divinorum*, when used as a health product.

### **Traditional Use:**

#### Non-Psychoactive Use:

When consumed orally, *Salvia divinorum* has been used traditionally to treat diarrhoea, constipation, anaemia, headache, rheumatism and alcohol addiction, as well as for regulation of urination. It is also used topically in traditional settings for treating ulcers of the skin (Natural Medicines Comprehensive Database, 2007; Valdes et al., 1982).

#### Psychoactive Use:

*Salvia divinorum* has been used traditionally by the Mazatec people of Oaxaca, Mexico, for religious ceremonies, in order to produce “mystical” and hallucinogenic experiences. The psychoactive effects can be produced by chewing the leaves, or by inhalation of the smoke from the leaves.

### **Non-Traditional Use:**

#### Non-Psychoactive Use:

No information is available on *Salvia divinorum*-containing products currently marketed for health-related purposes. Some research, however, suggests therapeutic potential for salvinorin A (see Therapeutic Potential section, below).



### Psychoactive Use:

The main non-traditional use of *Salvia divinorum* relates to its psychoactive properties and use as a street drug. The hallucinogenic properties can be achieved by a variety of means, and products available commercially for such purposes include dried leaves, extracts, plant cuttings, tinctures, tablets, essence and leaf juice. Products can be taken orally (tablets, leaves extract), sublingually (tincture) and by inhalation (smoking of dried leaves, extract), to experience hallucinogenic effects.

### **Hazard Assessment and Characterisation:**

#### Pharmacokinetics:

The main active constituent of *Salvia divinorum*, both from the perspective of psychoactive and potential therapeutic use, appears to be the diterpene salvinorin A.

The pharmacokinetics of salvinorin A have not been studied extensively; however, it is apparent that when taken orally, the hallucinogenic effects depend on absorption by the oral mucosa, as salvinorin A is largely inactivated in the gastrointestinal tract (Siebert, 1994). Although some psychotropic activity has been noted after drinking the leaf juice, the effects are much more mild compared to the chewing of the leaves (Siebert, 1994). Siebert (1994) administered 2 mg of encapsulated salvinorin A to human subjects. Swallowing the capsules produced no detectable psychotropic activity. Thus, the most effective way (orally) to use the plant or its purified constituents to achieve hallucinogenic effects is to ensure the salvinorin A remains in the mouth for a period of time, allowing buccal absorption. Other studies on the pharmacokinetics and potential therapeutic effects of salvinorin A have relied on non-oral routes of exposure (Schmidt et al., 2005; McCurdy et al., 2006).

It should be noted that since salvinorin A is postulated as the phytochemical in *Salvia divinorum* that has potential therapeutic effect, the plant and its extracts may only be effective when administered non-orally. More research is required to clarify the potential therapeutic uses of *Salvia divinorum*. More detail is provided below.

#### Toxicology studies on *Salvia divinorum* and salvinorin A:

No studies appear to have been performed to determine the adverse effects of *Salvia divinorum*, or its chemical constituents, in humans.

With regard to animal toxicity studies, only one published report is available. Mowry et al. (2003) examined the short term effects of salvinorin A in rats. Swiss-Webster rats of both sexes, 4-6 months of age, were administered salvinorin A by intraperitoneal injection at doses of 0 (vehicle control), 400, 800, 1600, 3200 and 6400 ug/kg/day for 14 days. A total of 114 animals were used, specific numbers in each group were not reported. The authors did not observe any effects on cardiac conduction (PR or QT intervals), heart rate, body temperature or galvanic skin response. In a separate study, a nonsignificant rise in pulse pressure was observed after 20 and 40 minutes of salvinorin A exposure in anesthetized rats administered a single dose of 1600

ug/kg. In the repeat-dose study, no histologic differences were noted at any salvinorin A doses for either sex in the liver, spleen, kidney, bone marrow or brain tissue. The authors concluded that while salvinorin A is a potent hallucinogen, it has relatively low toxicity.

Mowry et al. (2003) also noted a literature report of a single dose of 1g/kg bw of an extract of *Salvia divinorum*, injected in mice (specific route unknown), where no toxic effects were noted. The actual reference provided by Mowry et al. for this study (Valdes et al., 1984), does not make mention of the actual dose, route of administration, or animal species employed, but notes that this administration produced behavioural patterns resembling the intoxication in humans.

Longer terms studies on the potential toxic effects of salvinorin A, or the whole plant, are not available, and no specialized studies (eg. teratology studies) appear to have been published in the scientific literature to date.

#### Psychotropic effects and mechanism of action:

The psychotropic effects induced by salvinorin A include altered perception, hallucinations, ataxia, depersonalization, hysterical laughter, incoherent speech and unconsciousness (Siebert DJ, 1994). Onset and intensity of the effects of salvinorin A depend on the dose and route of administration. A route that avoids the hepatic first-pass effect (sublingual, inhalation) produces rapid and intense effects.

The effects of *Salvia divinorum* can last up to two hours after absorption through the oral mucosa, while effects of inhaled salvia can last up to 30 minutes. A minimum dose of 200-500 µg of purified salvinorin A, or 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled (Bucheler et al., 2005).

Various studies have claimed that the psychotropic effects of *Salvia divinorum* closely resemble the symptoms of schizophrenia induced by other drugs such as LSD, phencyclidine or ketamine (Hansen et al., 1988; Javitt and Zukin, 1991; Valdes, 1994).

Salvinorin A has been shown to be a potent agonist of the kappa-opioid receptor (Chavkin et al., 2004). Research has shown that the hallucinogenic effects of salvinorin A are mediated through its kappa-opioid receptor agonist activity (Zhang et al, 2005).

Salvinorin A is structurally different from other naturally occurring classical hallucinogens such as mescaline, psilocybin and lysergic acid diethylamide. Typical doses of other hallucinogens (LSD, mescaline and psilocybin) required to produce hallucinogenic effects are 50-250 ug, 100 mg and 5 mg, respectively (Wolowich et al., 2006), while a minimum dose of 200-500 µg of purified salvinorin A can produce intense psychoactive affects, when vapourised and inhaled (Natural Medicines Comprehensive Database, 2007). Therefore, salvinorin A has more potency compared to mescaline and psilocybin, both of which are controlled substances in Canada. The Natural Medicines Comprehensive Database (2007) notes that "salvinorin A is the most potent hallucinogen known."

Adverse reactions associated with the use of *Salvia divinorum*:

Domestic reports: See the appendix for detailed causality assessments of the adverse reaction reports submitted to Health Canada. Health Canada has received four reports of adverse reactions (ARs) associated with the use of *Salvia divinorum*. All of these ARs involved psychotropic effects. Out of the four AR reports, three cases involving inhalation were associated with hallucinogenic effects and were considered to be non-serious reactions. The fourth case, however, was considered serious and was associated with the oral use of the chemical constituent salvinorin A. As well, it should be noted that, in this case report, salvinorin A was consumed in a therapeutic drug form (one tablet containing 57 mg of salvinorin A), although this commercially available product was meant to provide psychotropic, rather than therapeutic, effects. In this particular case, the product produced the effects when combined with alcohol.

Summary of Canadian domestic AR cases associated with *Salvia divinorum* or salvinorin A

Total number of cases	4
Route of exposure	Oral (1) & Inhalation (3)
Age range	16 yrs - 56 yrs
Gender	2 male, 2 female
Causality	oral - 1 possible; inhalation - 2 possible, 1 probable

International reports: Two case reports of salvia abuse have been published in the scientific literature.

- (1) An international case report involving *Salvia divinorum* was published in which a young man (19 years of age) described his perceptions after inhaling the smoke from *Salvia divinorum*. The peak psychotropic effects, including prickling of the skin, fever-like hot flashes, muscular tremor, and depersonalization, were reached in less than five minutes after inhalation of an unknown amount of dried leaves (Bucheler et al., 2005).
- (2) Most recently, another published case of *Salvia divinorum* abuse involved a 15-year-old male who presented to psychiatric emergency services with acute onset of paranoia, déjà vu, blunted affect, thought blocking and slowed speech, after smoking *Salvia divinorum* over an unknown period of time. During his hospitalization all symptoms improved significantly except the feeling of déjà vu. Based on this case presentation, the author suggested that the feelings of déjà vu may be considered long-term effects of Salvia use (Singh, 2007). However, given that this is the only case report in which déjà vu was

associated with the use of *Salvia divinorum*, more reports are needed to substantiate this finding.

In addition to the above-mentioned case reports, in 2006, a case report was reported in the US in which a 17-year-old boy committed suicide after smoking *Salvia divinorum* for unknown period of time (<http://www.kvbc.com/Global/story.asp?S=4893692>). Alcohol and general depression were the main confounders in this case. As a result of this case, however, the state of Delaware passed a law outlawing *Salvia divinorum*, and classifying it as a Schedule I controlled substance with other hallucinogenic substances (<http://www.jointogether.org/news/headlines/inthenews/2006/youths-death-inspires.html>). It should be noted that suicidal symptoms were also observed in one of the four domestic cases of *Salvia divinorum* abuse reported to Health Canada.

#### Dose-response assessment

The dose-response for non-psychoactive adverse effects of *Salvia divinorum* or salvinorin A, by any route of administration, either in animals or humans, is unknown. No statistically significant findings were noted in the only available study (Mowry et al., 2003), in which NOELs of 1600 ug/kg bw and 6400 ug/kg bw/day were noted for acute physiologic effects, and short-term histological effects, respectively, using intraperitoneal injection. No longer term studies are available.

The intensity of the psychotropic effects in humans, induced by *Salvia divinorum*, has been noted as dose-dependent; however, a quantitative dose-response assessment has not been carried out. It is known, however, that the minimum dose required to produce hallucinogenic effects by inhalation is about 200 ug salvinorin A (Bucheler et al., 2005).

#### Potential for Dependence, Addiction, and Abuse

It is well known that *Salvia divinorum* or purified salvinorin A can produce various psychotropic effects (altered perception, hallucinations, ataxia, hysterical laughter, and incoherent speech) in humans. As noted above, the intensity of the psychological effects induced by salvinorin A is dose-dependent: high doses can produce extreme effects, such as depersonalisation with loss of reality, and intense psychosis which could be enough for users to harm themselves or others unintentionally (Siebert, 1994). In addition, the symptoms associated with *Salvia divinorum* are expected to be similar to those seen with other hallucinogens, although the duration of effects can be much shorter, depending on the route of exposure (inhalation vs. buccal absorption).

Drug dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal; it can be of two types, physical and/or psychological. Dependence can be influenced by certain receptor types, such as opioid receptors. The existence of three major groups of opioid receptors ( $\mu$ ,  $\delta$  and  $\kappa$ ) in the central nervous system is well

documented (Suzuki and Misawa 1997). There exist complicated interactions among opioid receptor types. The activation of the kappa opioid receptor suppresses physical and psychological dependence produced by mu and delta opioid receptor agonists, but the activation of the delta opioid receptor potentiates the dependence of mu opioid receptor agonists. Various studies provide arguments to support substantial roles for mu-opioid receptors and the possible involvement of delta-opioid receptors in the development of physical and psychological dependence produced by morphine (Narita et al. 2001; Suzuki and Misawa 1997).

Most of the drugs used clinically that are mu-opioid analgesics are habit-forming. While both receptor types (delta and mu) provide analgesia, only stimulation of the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dexamethorpan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor (Gaveriaux-Ruff and Kieffer 2002; Narita et al. 2001; Pasternak 2003; Suzuki and Misawa 1997). Using in vitro methods, Margolis et al. (2003) demonstrated that the mechanism of action of kappa opioid receptor agonists may involve direct inhibition of midbrain (ventral tegmental area) dopaminergic neurons, that play a critical role in motivation and reinforcement of goal-directed behaviours, and are excited by addictive substances such as morphine. It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect, i.e. dysphoria rather than euphoria (Kumor et al. 1986; Rothman et al. 2000). The activation of kappa-receptors also leads to the suppression of mu/delta-mediated side effects such as dependence and respiratory depression.

Salvinorin A is unique in that it is a potent, non-nitrogenous, selective kappa opioid agonist, distinct in its actions from other known opioid receptor agonists. It appears to be devoid of the mainly mu receptor-mediated side effects such as dependence and respiratory depression associated with morphine and its analogues. It may, thus, be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, depressive illness, and even excessive marijuana use. Being defined by its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative to addictive drugs. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

Although *Salvia divinorum* does not appear to cause dependency, it has the potential for abuse/misuse, especially by young adults. Health Canada has received four domestic case reports of adverse reactions (ARs) associated with the use of *Salvia divinorum* (three inhaled and one oral). In addition, Health Canada is aware of several media reports published on the issue of *Salvia divinorum*, specifically its presence on the market as a legal alternative to illicit drugs. This has prompted the concern of police (eg. Saskatoon Star-Phoenix, December 21, 2006). Furthermore, there are two international cases of salvia abuse published in scientific journals. However, it is important to note that accumulated case reports cannot be used to determine the incidence of a reaction, nor the risk associated with use of a product, because of the unknown number of individuals exposed to the product and because of the significant under-reporting of ARs. In any case, it should be noted that the Canadian Adverse Drug Reaction Monitoring

Program is not an appropriate tool to obtain information concerning adverse reactions associated with the use of *Salvia divinorum* as a street drug.

It has been suggested that *Salvia divinorum* is the most marketed herbal substances available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Siemann et al., 2006; Dennehy et al., 2005). In 2000, a large number of *Salvia divinorum* plants were seized at a large scale plantation in Switzerland, which suggest that its use is increasing as a recreational drug in Europe (Giroud et al, 2000). Several countries (Australia, Denmark, Finland, Italy, Norway, Sweden and some states of the US) have either banned or included *Salvia divinorum* in their list of *controlled substances*.

The above evidence would suggest that any therapeutic products containing *Salvia divinorum* and/or salvinorin A could be misused or abused for their potential psychotropic activities.

### **Therapeutic potential of *Salvia divinorum* and salvinorin A**

Recent studies have suggested that salvinorin A acts at kappa opioid receptor sites (Chavkin et al. 2004; Valdes 1994; Roth et al. 2002). Selective kappa receptor agonists have been shown to produce analgesic effects with potential for reduced tolerance and dependence (Tidgewell et al., 2004). Animal studies have shown that salvinorin A has short-acting anti-nociceptive effects which operate via kappa opioid receptors (McCurdy et al., 2006). Considering the functional interaction between opioid receptor types noted above, the co-administration of morphine-like compounds with kappa-receptor agonists, such as salvinorin A, may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

There have been significant advances in studies on the role of kappa opioid receptor agonists in producing aversive effects and in the potential modulation of withdrawal from other substances such as morphine, cocaine, THC, alcohol, and in other non-opioid addictions (Cui et al. 2000; Hahn et al. 2000; Mori et al. 2002; Raffa et al. 2003; Rosin et al. 1999; Rothman et al. 2000; Schenk et al. 1999; Tao et al. 1994). As noted above, it may, thus, be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, clinical depression, and even excessive marijuana use. Because of its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative to these drugs, and may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001). Nevertheless, salvinorin A is a well recognised hallucinogen in its own right.

One study suggests that the salvinorin A may be used as a novel molecular candidate for the development of antipsychotic drugs and could be used to treat psychiatric (schizophrenia, bipolar depression) and neuropsychiatric disorders (Alzheimer's disease, dementia) (Sheffler and Roth, 2003).

It should be noted that the above-mentioned therapeutic potentials of *Salvia divinorum* are extrapolated from the results of preliminary investigations, and therefore, much more evidence is needed to substantiate the therapeutic use of *Salvia divinorum* or salvinorin A.

### **Exposure Assessment:**

It is not feasible to assess the exposure to *Salvia divinorum* or salvinorin A from the use of health products, as such products do not appear to exist in Canada, currently. Based on currently available information, however, it is possible that any therapeutic doses of this plant or its active constituents may produce adverse psychoactive effects (see below).

### **Risk Characterization:**

Although little scientific information exists regarding dose-response for *Salvia divinorum* or salvinorin A, risks associated with their use can be assessed in a qualitative manner.

The single toxicological study in animals alludes to the low toxicity of salvinorin A, at least with respect to certain physiological and histological effects. No information, however, is available on the potential long-term effects of exposure to *Salvia divinorum* or salvinorin A, and no studies have looked at the potential for other effects such as teratogenicity.

The psychotropic, and potentially therapeutic effects, elicited by salvinorin A are dependant on the route of exposure. Inhalation and buccal absorption are the most efficient; however, the bioavailability is greatly reduced when ingested without prolonged contact with the oral mucosa.

It is unknown if any potentially therapeutic effects of *Salvia divinorum* /salvinorin A would be achieved via inhalation or ingestion. Although the psychotropic effects appear to be dose-dependent, without more information on the dose-response of the hallucinogenic or therapeutic effects of *Salvia divinorum* or salvinorin A, the risk cannot be fully characterized. However, since the hallucinogenic and potentially therapeutic effects are both dependant on salvinorin A's affinity for the kappa opioid receptor, it is possible that any exposure to the plant or its active constituents, at a dose required for therapeutic use, may result in some degree of psychoactivity. Although selective kappa receptor agonists have been shown to produce analgesic effects, adverse effects such as psychotomimesis, dysphoria and diuresis have been observed in studies investigating their therapeutic use (Barker et al. 2002; Tidgewell et al., 2004). Thus, the potential for psychoactivity, and therefore abuse, with any future therapeutic use of *Salvia divinorum* or salvinorin A, cannot be discounted at the present time.

### **Summary and Conclusions:**

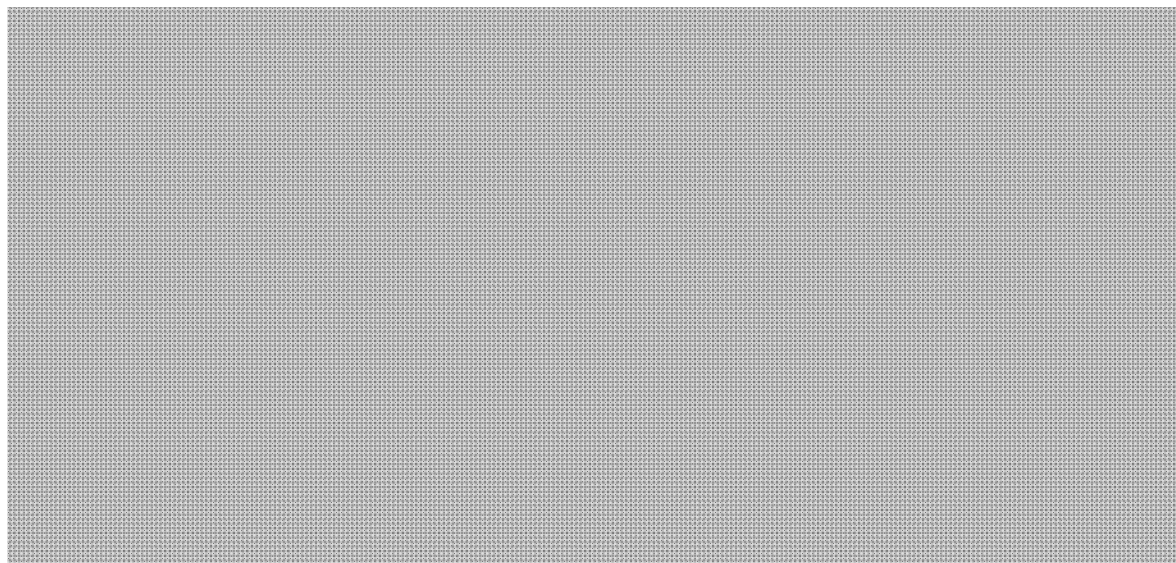
Salvinorin A appears to have low acute and short-term toxicity, although only one limited toxicological study in animals was identified in the scientific literature. No long-term studies have been published, and the long-term safety of this compound has not yet been established. The scientific literature does not support the possibility of developing dependency with *Salvia divinorum* use; however, its use has the potential for misuse or abuse. *Salvia divinorum* and salvinorin A have the ability to induce dose-dependent, moderate to severe hallucinogenic effects in humans, depending on the route of administration.

The fact that a clear dose-response has not been established for the potential therapeutic benefits of salvinorin A, and that the psychotropic and potentially therapeutic actions rely on the same mechanism of action, suggest that any therapeutic activity established in the future may also produce unwanted psychotropic effects. Therefore, the psychotropic activity of *Salvia divinorum* and salvinorin A may lead to the abuse of any health products proposed in the future.

In addition to the above, one of the potential therapeutic uses of salvinorin A is in the treatment of addiction to illicit drugs such as cocaine and heroin. Such potential use should be carried out under the supervision of a qualified physician.

#### Recommendations:

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#### Authors:

Marketed Health Products Directorate: Dr. Shahid Perwaiz, Dr. Scott Jordan  
Natural Health Products Directorate: XXXXXXXX

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## APPENDIX

### CAUSALITY ASSESSMENTS OF ADVERSE REACTIONS

Updated May 22, 2007

#### FINAL

Natural Health Product: *Salvia divinorum*

**Purpose of the assessment:**

To review the adverse reactions<sup>1</sup> associated with the use of *Salvia divinorum*. (Domestic case reports are reviewed with respect to causality<sup>2</sup> and seriousness<sup>3</sup>)

**Date of review commenced:**

May 2005 - ongoing monitoring

**Medical evaluator(s):**

[REDACTED]

**Approved:**

Dr. M. Murty (Sept. 9/05; revised May 22, 2007)

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<sup>1</sup>Natural Health Product Regulations: <http://canadagazette.gc.ca/partII/2003/20030618/html/sor196-e.html>

An **adverse reaction** is defined as a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function. (*réaction indésirable*)

<sup>2</sup> Based on the WHO causality algorithm unless otherwise specified. (*See appendix for WHO algorithm*)

<sup>3</sup>Natural Health Product Regulations: <http://canadagazette.gc.ca/partII/2003/20030618/html/sor196-e.html>

A **serious adverse reaction** means a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death. (*réaction indésirable grave*):

Search Strategy:

Adverse reactions suspected to be associated with *Salvia divinorum* were searched, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to May 3, 2005)]

Executive summary:

There are 4 domestic Canadian case reports of neuropsychiatric adverse effects associated with the use of *Salvia divinorum* (3 "non-serious" cases associated with inhalation route of administration and 1 "serious" case associated with oral ingestion).

The 'serious' case of psychosis associated with oral use was confounded by concomitant alcohol and therefore, the causality assignment is "Possible".

One of the inhaled cases was assessed as 'probable' but the reaction was not 'serious'.

Conclusion: In the serious case, Salvia was sold in a drug form, a tablet containing 57 or 72 mg of Salvinorin-A. In this case concomitant use of Salvia and alcohol most likely contributed to the adverse reaction of psychosis.

In the 3 non serious cases, there was disorientation and hallucination after taking one "puff" of Salvia divinorum.

From a clinical perspective, the main concern is the easy access, availability in retail outlets to adolescents without controls and the potential for misuse, as suggested by the AR case report of prolonged psychoses in an adolescent. Additionally, the hallucinogenic effects of Salvia may put individuals in life-threatening situations for themselves and others (driving while under the influence of Salvia). Although the case was confounded by alcohol and details of "intervention" were not specified in the report, it is likely that the Salvia component had contributed significantly to the psychoses, requiring restraint, observation/monitoring prior to the incarceration. Psychoses is a medically significant event and causality remains "Possible" and "Serious".

It is important to note that CADRMP is not the proper tool for monitoring the risk associated with Salvia in this context, because CADRMP is not designed or promoted for the collection of street drug effects. Rather, CADRMP is designed and promoted for the collection of adverse reactions associated with health products, and Salvia used in the current context would not be considered a health product.

Further monitoring and public education are necessary to regulate and possibly restrict Salvia divinorum.

Total domestic AR case reports associated with the use of *Salvia divinorum* up to May 31, 2005

Source of ADRs	# of cases report	route		psychosis	hallucination disorientation	Causality certain	Causality probable	Causality possible	Serious	Fatal outcome
		oral	inhalation							
CADRMP	4	oral	1	1				1	1	0
		inhalation	3		3		1	2	0	0

Summary of Causality Assessment of reaction associated with the use of *Salvia divinorum*

Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177866 consumer Jan 12, 2005	27yr/F	-Unknown - Disorientation, hallucination, not recognizing people around her.	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No	Recovered (Effect lasted 5 minutes)	Probable	No

Case summary no 0177866

A 27 year old woman experienced disorientation, not recognizing people in the room, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. Patient reported prior use of mescaline and LSD and that the effect of those were not as bad ("moins pires"). The patient was on no other medications. This is not an unexpected reaction to *Salvia divinorum*. There is no evidence from the case report that she had recently taken other hallucinogenic substances.

The causality was assigned as probable.  
The adverse reaction judged as not serious.

Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177865 consumer Jan 12, 2005	28yr/M	-Unknown -Disorientation, hallucination, - foaming at the mouth	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No -no other medications -past med history - unknown	Recovered (Effect lasted 5 minutes)	Possible	No

Case summary no 0177865

A 28 year old man experienced disorientation, foaming at the mouth, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. There was no concomitant medication. Past medical history is unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.  
The adverse reaction judged as not serious.



Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
179969 consumer Feb. 17, 2005	56yr/F	-Unknown -Disorientation, hallucination, does not recognize husband	<i>Salvia divinorum</i> Al sasia encens special	Inhalation	1 puff taken	Unknown	Recovered (total effect 30 minutes)	Possible	No

Case summary no 0179969

A 56 year old woman experienced 30 minutes of disorientation and vivid hallucination after taking 1 puff of *Salvia divinorum*. The reaction was very intense for 10 minutes and then decreased in intensity. The past medical history, concomitant medication and NHP usage are unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.

The adverse reaction judged as not serious.

Case ID reporter date received	Age/ gender/ weight	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
0185128 Consumer (parent) May 31, 2005	16yr/M  150lbs	March 29, 2005/ -drug induced psychosis -incoherent -suicidal -restrained -threatened to kill police officers -amnesia (does not remember any of these events) -jailed	Salvia/ aka Maria Pastora	oral/ 1 tablet "the 30\$ pill" 57mg*	single dose	Yes  <u>Concomitant intake of:</u> Alcohol ("few drinks")  <u>Concomitant condition:</u> ADD	Recovered	Possible	Yes

Case summary no 0185128:

On March 23, 2005, a 16 year old male experienced drug induced psychosis: was incoherent, was suicidal, needed to be restrained, threatened to kill police officers, was jailed and had amnesia of these events after taking a single tablet of *Salvia* ( aka Maria Pastra). He had also consumed a few drinks of alcohol. He had an underlying Attention Deficit Disorder (ADD) but was not receiving medication for this. He had previously taken *Salvia* "on its own" (route of administration unknown) with no adverse reaction.

Additional information obtained through the ADR specialist:

\* Follow up request for more information obtained July 28 2005, confirmed that the tablet was oral "30 \$ pill" purchased "behind the counter" at [REDACTED]

This outlet sells a *Salvia* 10x containing 57 mg of Salvinorin-A for 29.98\$ and a *Salvia* 20x containing 72 mg of Salvinorin-A for 39.98\$.

Further information received August 18 2005: When *Salvia* was taken previously, it was the same dose (30\$ pill orally). The only thing different was that on previous occasions, the patient did not have alcohol with it.

This is a case where there was no adverse reaction with previous use of *Salvia* (same dosage, same distributor, same route of administration) but when associated with alcohol, it had a severe adverse reaction.

[REDACTED]

The causality was assigned as possible with alcohol as a confounder.  
The adverse reaction was judged as serious because it required intervention.

#### Appendix

#### WHO algorithm of Causality Categories:

1	Probably/Likely:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
2	Possible:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
3	Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
4	Conditional/Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.
5	Unassessible/Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.



Health Canada Santé Canada

Health Products and Food Branch  
Direction générale des produits de santé et des aliments

## Health Risk Assessment of *Salvia divinorum* as a Health Product

Marketed Biologicals, Biotechnology and Natural Health Products Bureau  
Marketed Health Products Directorate  
and  
Bureau of Product Review and Assessment,  
Natural Health Products Directorate

June 7, 2007

### **Issue:**

In the last several years, Health Canada has become aware of the use of the plant *Salvia divinorum* as a recreational hallucinogen, and as a “legal alternative” to illicit drugs. In certain parts of North America, this plant has been traditionally used for religious, as well as for health purposes. *Salvia divinorum* meets the criteria for regulation under the *Natural Health Products Regulations*; however, as a hallucinogen, it may also meet the criteria of a substance regulated under the *Controlled Drugs and Substances Act*, or the *Food and Drug Regulations*.

This risk assessment was undertaken to determine the potential risks from the use of *Salvia divinorum* as a health product, and will help determine potential compliance actions to be taken on products available on the Canadian market, containing *Salvia divinorum* or its active constituents.

### **Background:**

*Salvia divinorum* is a plant from the mint family. It is also known by a number of common names such as Diviners Sage, Magic Sage, Mexican Sage, Sage of the Seers, and Herba Maria (Natural Medicines Comprehensive Database, 2007). The plant has been used in traditional and spiritual practices by the Mazatec Indians of Oaxaca, Mexico, to produce “mystical” or hallucinogenic experiences (Diaz, 1976).

Health Canada has received four reports of adverse reactions involving psychotropic effects, associated with the use of *Salvia divinorum*. There have been several reports (scientific articles, case reports, media enquiries/articles) which indicate that *Salvia divinorum* has the potential for abuse, and is being used by adolescents and young adults for its hallucinogenic properties. In

addition, *Salvia* is being widely touted on internet sites aimed at these population groups, as a “legal” alternative to street drugs.

In Canada, neither the herb *Salvia divinorum*, nor its active constituents such as salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act* (CDSA), nor any Schedule of the *Food and Drugs Act and Regulations*. *Salvia divinorum* meets the definition of a natural health product (NHP) if marketed in Canada with health claims. However, the current use and advertising of *Salvia divinorum* as a recreational hallucinogen does not meet the intent of the functional component of the definition of a natural health product. In addition, as a hallucinogen and potential drug of abuse, Health Canada’s Office of Controlled Substances (OCS) has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, the OCS will collect relevant information specific to this herb and its active constituents, in relation to its psychotropic use.

Since *Salvia divinorum* in some circumstances meets the definition of a NHP and is not listed in any Schedule to the CDSA, nor any Schedule of the *Food and Drugs Act* or its Regulations, it is appropriate to assess the health risk associated with the use of *Salvia divinorum*, when used as a health product.

#### **Traditional Use:**

##### Non-Psychoactive Use:

When consumed orally, *Salvia divinorum* has been used traditionally to treat diarrhoea, constipation, anaemia, headache, rheumatism and alcohol addiction, as well as for regulation of urination. It is also used topically in traditional settings for treating ulcers of the skin (Natural Medicines Comprehensive Database, 2007; Valdes et al., 1982).

##### Psychoactive Use:

*Salvia divinorum* has been used traditionally by the Mazatec people of Oaxaca, Mexico, for religious ceremonies, in order to produce “mystical” and hallucinogenic experiences. The psychoactive effects can be produced by chewing the leaves, or by inhalation of the smoke from the leaves.

#### **Non-Traditional Use:**

##### Non-Psychoactive Use:

No information is available on *Salvia divinorum*-containing products currently marketed for health-related purposes. Some research, however, suggests therapeutic potential for salvinorin A (see Therapeutic Potential section, below).

### Psychoactive Use:

The main non-traditional use of *Salvia divinorum* relates to its psychoactive properties and use as a street drug. The hallucinogenic properties can be achieved by a variety of means, and products available commercially for such purposes include dried leaves, extracts, plant cuttings, tinctures, tablets, essence and leaf juice. Products can be taken orally (tablets, leaves extract), sublingually (tincture) and by inhalation (smoking of dried leaves, extract), to experience hallucinogenic effects.

### **Hazard Assessment and Characterisation:**

#### Pharmacokinetics:

The main active constituent of *Salvia divinorum*, both from the perspective of psychoactive and potential therapeutic use, appears to be the diterpene salvinorin A.

The pharmacokinetics of salvinorin A have not been studied extensively; however, it is apparent that when taken orally, the hallucinogenic effects depend on absorption by the oral mucosa, as salvinorin A is largely inactivated in the gastrointestinal tract (Siebert, 1994). Although some psychotropic activity has been noted after drinking the leaf juice, the effects are much more mild compared to the chewing of the leaves (Siebert, 1994). Siebert (1994) administered 2 mg of encapsulated salvinorin A to human subjects. Swallowing the capsules produced no detectable psychotropic activity. Thus, the most effective way (orally) to use the plant or its purified constituents to achieve hallucinogenic effects is to ensure the salvinorin A remains in the mouth for a period of time, allowing buccal absorption. Other studies on the pharmacokinetics and potential therapeutic effects of salvinorin A have relied on non-oral routes of exposure (Schmidt et al., 2005; McCurdy et al., 2006).

It should be noted that since salvinorin A is postulated as the phytochemical in *Salvia divinorum* that has potential therapeutic effect, the plant and its extracts may only be effective when administered non-orally. More research is required to clarify the potential therapeutic uses of *Salvia divinorum*. More detail is provided below.

#### Toxicology studies on *Salvia divinorum* and salvinorin A:

No studies appear to have been performed to determine the adverse effects of *Salvia divinorum*, or its chemical constituents, in humans.

With regard to animal toxicity studies, only one published report is available. Mowry et al. (2003) examined the short term effects of salvinorin A in rats. Swiss-Webster rats of both sexes, 4-6 months of age, were administered salvinorin A by intraperitoneal injection at doses of 0 (vehicle control), 400, 800, 1600, 3200 and 6400 ug/kg/day for 14 days. A total of 114 animals were used, specific numbers in each group were not reported. The authors did not observe any effects on cardiac conduction (PR or QT intervals), heart rate, body temperature or galvanic skin response. In a separate study, a nonsignificant rise in pulse pressure was observed after 20 and 40 minutes of salvinorin A exposure in anesthetized rats administered a single dose of 1600

ug/kg. In the repeat-dose study, no histologic differences were noted at any salvinorin A doses for either sex in the liver, spleen, kidney, bone marrow or brain tissue. The authors concluded that while salvinorin A is a potent hallucinogen, it has relatively low toxicity.

Mowry et al. (2003) also noted a literature report of a single dose of 1g/kg bw of an extract of *Salvia divinorum*, injected in mice (specific route unknown), where no toxic effects were noted. The actual reference provided by Mowry et al. for this study (Valdes et al., 1984), does not make mention of the actual dose, route of administration, or animal species employed, but notes that this administration produced behavioural patterns resembling the intoxication in humans.

Longer terms studies on the potential toxic effects of salvinorin A, or the whole plant, are not available, and no specialized studies (eg. teratology studies) appear to have been published in the scientific literature to date.

#### Psychotropic effects and mechanism of action:

The psychotropic effects induced by salvinorin A include altered perception, hallucinations, ataxia, depersonalization, hysterical laughter, incoherent speech and unconsciousness (Siebert DJ, 1994). Onset and intensity of the effects of salvinorin A depend on the dose and route of administration. A route that avoids the hepatic first-pass effect (sublingual, inhalation) produces rapid and intense effects.

The effects of *Salvia divinorum* can last up to two hours after absorption through the oral mucosa, while effects of inhaled salvia can last up to 30 minutes. A minimum dose of 200-500 µg of purified salvinorin A, or 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled (Bucheler et al., 2005).

Various studies have claimed that the psychotropic effects of *Salvia divinorum* closely resemble the symptoms of schizophrenia induced by other drugs such as LSD, phencyclidine or ketamine (Hansen et al., 1988; Javitt and Zukin, 1991; Valdes, 1994).

Salvinorin A has been shown to be a potent agonist of the kappa-opioid receptor (Chavkin et al., 2004). Research has shown that the hallucinogenic effects of salvinorin A are mediated through its kappa-opioid receptor agonist activity (Zhang et al, 2005).

Salvinorin A is structurally different from other naturally occurring classical hallucinogens such as mescaline, psilocybin and lysergic acid diethylamide. Typical doses of other hallucinogens (LSD, mescaline and psilocybin) required to produce hallucinogenic effects are 50-250 ug, 100 mg and 5 mg, respectively (Wolowich et al., 2006), while a minimum dose of 200-500 µg of purified salvinorin A can produce intense psychoactive affects, when vapourised and inhaled (Natural Medicines Comprehensive Database, 2007). Therefore, salvinorin A has more potency compared to mescaline and psilocybin, both of which are controlled substances in Canada. The Natural Medicines Comprehensive Database (2007) notes that "salvinorin A is the most potent hallucinogen known."

Adverse reactions associated with the use of *Salvia divinorum*:

Domestic reports: See the appendix for detailed causality assessments of the adverse reaction reports submitted to Health Canada. Health Canada has received four reports of adverse reactions (ARs) associated with the use of *Salvia divinorum*. All of these ARs involved psychotropic effects. Out of the four AR reports, three cases involving inhalation were associated with hallucinogenic effects and were considered to be non-serious reactions. The fourth case, however, was considered serious and was associated with the oral use of the chemical constituent salvinorin A. As well, it should be noted that, in this case report, salvinorin A was consumed in a therapeutic drug form (one tablet containing 57 mg of salvinorin A), although this commercially available product was meant to provide psychotropic, rather than therapeutic, effects. In this particular case, the product produced the effects when combined with alcohol.

Summary of Canadian domestic AR cases associated with *Salvia divinorum* or salvinorin A

Total number of cases	4
Route of exposure	Oral (1) & Inhalation (3)
Age range	16 yrs - 56 yrs
Gender	2 male, 2 female
Causality	oral - 1 possible; inhalation - 2 possible, 1 probable

International reports: Two case reports of salvia abuse have been published in the scientific literature.

- (1) An international case report involving *Salvia divinorum* was published in which a young man (19 years of age) described his perceptions after inhaling the smoke from *Salvia divinorum*. The peak psychotropic effects, including prickling of the skin, fever-like hot flashes, muscular tremor, and depersonalization, were reached in less than five minutes after inhalation of an unknown amount of dried leaves (Bucheler et al., 2005).
- (2) Most recently, another published case of *Salvia divinorum* abuse involved a 15-year-old male who presented to psychiatric emergency services with acute onset of paranoia, déjà vu, blunted affect, thought blocking and slowed speech, after smoking *Salvia divinorum* over an unknown period of time. During his hospitalization all symptoms improved significantly except the feeling of déjà vu. Based on this case presentation, the author suggested that the feelings of déjà vu may be considered long-term effects of Salvia use (Singh, 2007). However, given that this is the only case report in which déjà vu was



associated with the use of *Salvia divinorum*, more reports are needed to substantiate this finding.

In addition to the above-mentioned case reports, in 2006, a case report was reported in the US in which a 17-year-old boy committed suicide after smoking *Salvia divinorum* for unknown period of time (<http://www.kvbc.com/Global/story.asp?S=4893692>). Alcohol and general depression were the main confounders in this case. As a result of this case, however, the state of Delaware passed a law outlawing *Salvia divinorum*, and classifying it as a Schedule I controlled substance with other hallucinogenic substances (<http://www.jointogether.org/news/headlines/inthenews/2006/youths-death-inspires.html>). It should be noted that suicidal symptoms were also observed in one of the four domestic cases of *Salvia divinorum* abuse reported to Health Canada.

#### Dose-response assessment

The dose-response for non-psychoactive adverse effects of *Salvia divinorum* or salvininorin A, by any route of administration, either in animals or humans, is unknown. No statistically significant findings were noted in the only available study (Mowry et al., 2003), in which NOELs of 1600 ug/kg bw and 6400 ug/kg bw/day were noted for acute physiologic effects, and short-term histological effects, respectively, using intraperitoneal injection. No longer term studies are available.

The intensity of the psychotropic effects in humans, induced by *Salvia divinorum*, has been noted as dose-dependent; however, a quantitative dose-response assessment has not been carried out. It is known, however, that the minimum dose required to produce hallucinogenic effects by inhalation is about 200 ug salvininorin A (Bucheler et al., 2005).

#### Potential for Dependence, Addiction, and Abuse

It is well known that *Salvia divinorum* or purified salvininorin A can produce various psychotropic effects (altered perception, hallucinations, ataxia, hysterical laughter, and incoherent speech) in humans. As noted above, the intensity of the psychological effects induced by salvininorin A is dose-dependent: high doses can produce extreme effects, such as depersonalisation with loss of reality, and intense psychosis which could be enough for users to harm themselves or others unintentionally (Siebert, 1994). In addition, the symptoms associated with *Salvia divinorum* are expected to be similar to those seen with other hallucinogens, although the duration of effects can be much shorter, depending on the route of exposure (inhalation vs. buccal absorption).

Drug dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal; it can be of two types, physical and/or psychological. Dependence can be influenced by certain receptor types, such as opioid receptors. The existence of three major groups of opioid receptors (mu, delta and kappa) in the central nervous system is well

documented (Suzuki and Misawa 1997). There exist complicated interactions among opioid receptor types. The activation of the kappa opioid receptor suppresses physical and psychological dependence produced by mu and delta opioid receptor agonists, but the activation of the delta opioid receptor potentiates the dependence of mu opioid receptor agonists. Various studies provide arguments to support substantial roles for mu-opioid receptors and the possible involvement of delta-opioid receptors in the development of physical and psychological dependence produced by morphine (Narita et al. 2001; Suzuki and Misawa 1997).

Most of the drugs used clinically that are mu-opioid analgesics are habit-forming. While both receptor types (delta and mu) provide analgesia, only stimulation of the mu-opioid receptors lead to tolerance and dependency. Opioid agonists (stimulators) such as morphine and other drugs (meperidine, diphenoxylate, methadone, dexamethorpan, codeine, fentanyl, heroin, and tetrahydrocannabinol) exert their activity mainly at the mu receptor (Gaveriaux-Ruff and Kieffer 2002; Narita et al. 2001; Pasternak 2003; Suzuki and Misawa 1997). Using in vitro methods, Margolis et al. (2003) demonstrated that the mechanism of action of kappa opioid receptor agonists may involve direct inhibition of midbrain (ventral tegmental area) dopaminergic neurons, that play a critical role in motivation and reinforcement of goal-directed behaviours, and are excited by addictive substances such as morphine. It is well known that mu and delta opioid receptor agonists produce psychological dependence, while kappa opioid receptor agonists produce an aversive effect, i.e. dysphoria rather than euphoria (Kumor et al. 1986; Rothman et al. 2000). The activation of kappa-receptors also leads to the suppression of mu/delta-mediated side effects such as dependence and respiratory depression.

Salvinorin A is unique in that it is a potent, non-nitrogenous, selective kappa opioid agonist, distinct in its actions from other known opioid receptor agonists. It appears to be devoid of the mainly mu receptor-mediated side effects such as dependence and respiratory depression associated with morphine and its analogues. It may, thus, be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, depressive illness, and even excessive marijuana use. Being defined by its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative to addictive drugs. It may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001).

Although *Salvia divinorum* does not appear to cause dependency, it has the potential for abuse/misuse, especially by young adults. Health Canada has received four domestic case reports of adverse reactions (ARs) associated with the use of *Salvia divinorum* (three inhaled and one oral). In addition, Health Canada is aware of several media reports published on the issue of *Salvia divinorum*, specifically its presence on the market as a legal alternative to illicit drugs. This has prompted the concern of police (eg. Saskatoon Star-Phoenix, December 21, 2006). Furthermore, there are two international cases of salvia abuse published in scientific journals. However, it is important to note that accumulated case reports cannot be used to determine the incidence of a reaction, nor the risk associated with use of a product, because of the unknown number of individuals exposed to the product and because of the significant under-reporting of ARs. In any case, it should be noted that the Canadian Adverse Drug Reaction Monitoring

Program is not an appropriate tool to obtain information concerning adverse reactions associated with the use of *Salvia divinorum* as a street drug.

It has been suggested that *Salvia divinorum* is the most marketed herbal substances available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Siemann et al., 2006; Dennehy et al., 2005). In 2000, a large number of *Salvia divinorum* plants were seized at a large scale plantation in Switzerland, which suggest that its use is increasing as a recreational drug in Europe (Giroud et al, 2000). Several countries (Australia, Denmark, Finland, Italy, Norway, Sweden and some states of the US) have either banned or included *Salvia divinorum* in their list of *controlled substances*.

The above evidence would suggest that any therapeutic products containing *Salvia divinorum* and/or salvinorin A could be misused or abused for their potential psychotropic activities.

### **Therapeutic potential of *Salvia divinorum* and salvinorin A**

Recent studies have suggested that salvinorin A acts at kappa opioid receptor sites (Chavkin et al. 2004; Valdes 1994; Roth et al. 2002). Selective kappa receptor agonists have been shown to produce analgesic effects with potential for reduced tolerance and dependence (Tidgewell et al., 2004). Animal studies have shown that salvinorin A has short-acting anti-nociceptive effects which operate via kappa opioid receptors (McCurdy et al., 2006). Considering the functional interaction between opioid receptor types noted above, the co-administration of morphine-like compounds with kappa-receptor agonists, such as salvinorin A, may constitute a preferable and superior approach to the treatment of pain with fewer side effects (Narita et al., 2001).

There have been significant advances in studies on the role of kappa opioid receptor agonists in producing aversive effects and in the potential modulation of withdrawal from other substances such as morphine, cocaine, THC, alcohol, and in other non-opioid addictions (Cui et al. 2000; Hahn et al. 2000; Mori et al. 2002; Raffa et al. 2003; Rosin et al. 1999; Rothman et al. 2000; Schenk et al. 1999; Tao et al. 1994). As noted above, it may, thus, be possible to use salvinorin A to treat heroin, cocaine, alcohol and amphetamine dependency, clinical depression, and even excessive marijuana use. Because of its selectivity for the kappa class of opioid receptor, salvinorin A has the potential to offer a non-habit forming alternative to these drugs, and may also reduce the effects of physical and emotional dependence by its antidepressive action (Hanes, 2001). Nevertheless, salvinorin A is a well recognised hallucinogen in its own right.

One study suggests that the salvinorin A may be used as a novel molecular candidate for the development of antipsychotic drugs and could be used to treat psychiatric (schizophrenia, bipolar depression) and neuropsychiatric disorders (Alzheimer's disease, dementia) (Sheffler and Roth, 2003).

It should be noted that the above-mentioned therapeutic potentials of *Salvia divinorum* are extrapolated from the results of preliminary investigations, and therefore, much more evidence is needed to substantiate the therapeutic use of *Salvia divinorum* or salvinorin A.

### **Exposure Assessment:**

It is not feasible to assess the exposure to *Salvia divinorum* or salvinorin A from the use of health products, as such products do not appear to exist in Canada, currently. Based on currently available information, however, it is possible that any therapeutic doses of this plant or its active constituents may produce adverse psychoactive effects (see below).

### **Risk Characterization:**

Although little scientific information exists regarding dose-response for *Salvia divinorum* or salvinorin A, risks associated with their use can be assessed in a qualitative manner.

The single toxicological study in animals alludes to the low toxicity of salvinorin A, at least with respect to certain physiological and histological effects. No information, however, is available on the potential long-term effects of exposure to *Salvia divinorum* or salvinorin A, and no studies have looked at the potential for other effects such as teratogenicity.

The psychotropic, and potentially therapeutic effects, elicited by salvinorin A are dependant on the route of exposure. Inhalation and buccal absorption are the most efficient; however, the bioavailability is greatly reduced when ingested without prolonged contact with the oral mucosa.

It is unknown if any potentially therapeutic effects of *Salvia divinorum* /salvinorin A would be achieved via inhalation or ingestion. Although the psychotropic effects appear to be dose-dependent, without more information on the dose-response of the hallucinogenic or therapeutic effects of *Salvia divinorum* or salvinorin A, the risk cannot be fully characterized. However, since the hallucinogenic and potentially therapeutic effects are both dependant on salvinorin A's affinity for the kappa opioid receptor, it is possible that any exposure to the plant or its active constituents, at a dose required for therapeutic use, may result in some degree of psychoactivity. Although selective kappa receptor agonists have been shown to produce analgesic effects, adverse effects such as psychotomimesis, dysphoria and diuresis have been observed in studies investigating their therapeutic use (Barker et al. 2002; Tidgewell et al., 2004). Thus, the potential for psychoactivity, and therefore abuse, with any future therapeutic use of *Salvia divinorum* or salvinorin A, cannot be discounted at the present time.

### **Summary and Conclusions:**

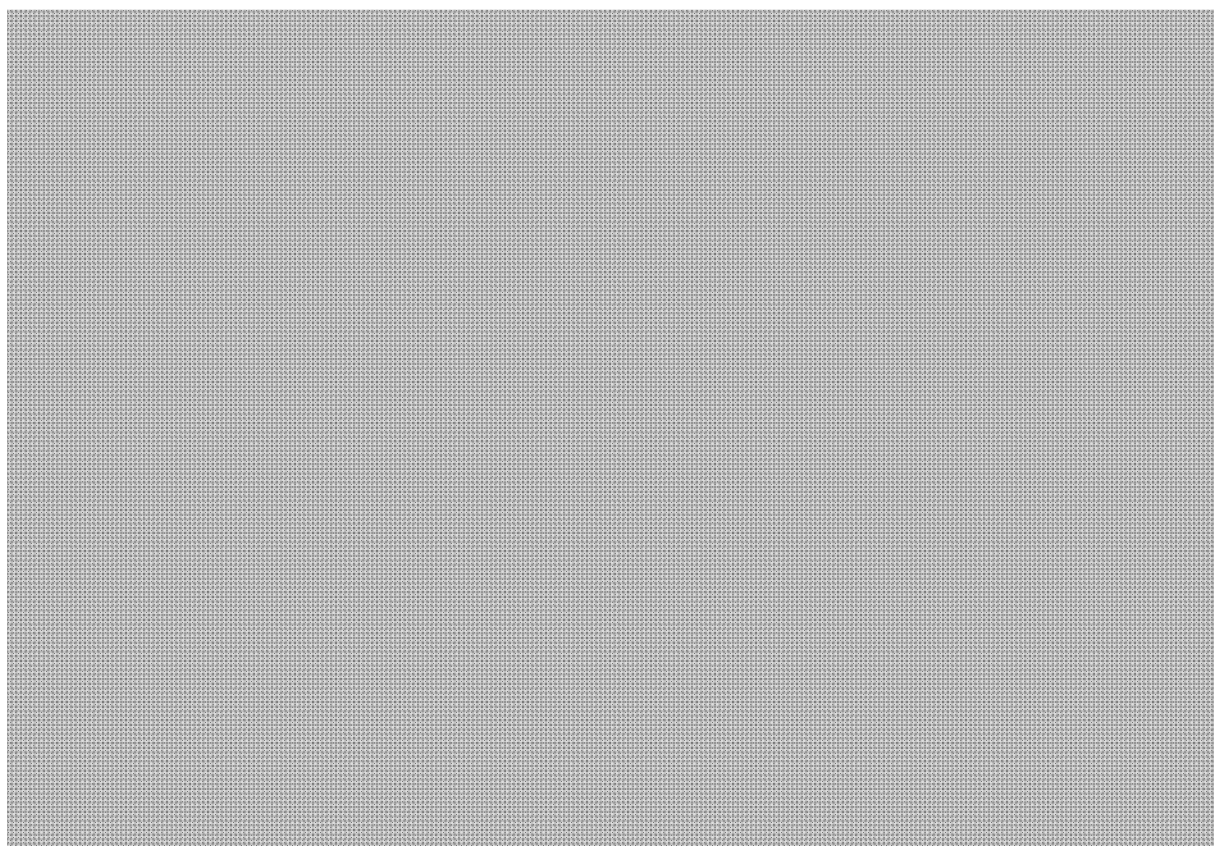
Salvinorin A appears to have low acute and short-term toxicity, although only one limited toxicological study in animals was identified in the scientific literature. No long-term studies have been published, and the long-term safety of this compound has not yet been established. The scientific literature does not support the possibility of developing dependency with *Salvia divinorum* use; however, its use has the potential for misuse or abuse. *Salvia divinorum* and salvinorin A have the ability to induce dose-dependent, moderate to severe hallucinogenic effects in humans, depending on the route of administration.

The fact that a clear dose-response has not been established for the potential therapeutic benefits of salvinorin A, and that the psychotropic and potentially therapeutic actions rely on the same mechanism of action, suggest that any therapeutic activity established in the future may also produce unwanted psychotropic effects. Therefore, the psychotropic activity of *Salvia divinorum* and salvinorin A may lead to the abuse of any health products proposed in the future.

In addition to the above, one of the potential therapeutic uses of salvinorin A is in the treatment of addiction to illicit drugs such as cocaine and heroin. Such potential use should be carried out under the supervision of a qualified physician.

Recommendations:

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Natural Health Products Directorate:

## References:

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## APPENDIX

### CAUSALITY ASSESSMENTS OF ADVERSE REACTIONS

Updated May 22, 2007

#### FINAL

Natural Health Product: *Salvia divinorum*

**Purpose of the assessment:**

To review the adverse reactions<sup>1</sup> associated with the use of *Salvia divinorum*. (Domestic case reports are reviewed with respect to causality<sup>2</sup> and seriousness<sup>3</sup>)

**Date of review commenced:**

May 2005 - ongoing monitoring

**Medical evaluator(s):**

**Approved:**

Dr. M. Murty (Sept. 9/05; revised May 22, 2007)

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<sup>1</sup>Natural Health Product Regulations: <http://canadagazette.gc.ca/partII/2003/20030618/html/sor196-e.html>

An **adverse reaction** is defined as a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function. (*réaction indésirable*)

<sup>2</sup> Based on the WHO causality algorithm unless otherwise specified. (*See appendix for WHO algorithm*)

<sup>3</sup>Natural Health Product Regulations: <http://canadagazette.gc.ca/partII/2003/20030618/html/sor196-e.html>

A **serious adverse reaction** means a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death. (*réaction indésirable grave*):

Search Strategy:

Adverse reactions suspected to be associated with *Salvia divinorum* were searched, using the search term *Salvia divinorum* in the Canadian Adverse Drug Reaction Monitoring Program (includes reports received and entered into the database from January 01, 1997 to May 3, 2005)]

Executive summary:

There are 4 domestic Canadian case reports of neuropsychiatric adverse effects associated with the use of *Salvia divinorum* (3 “non-serious” cases associated with inhalation route of administration and 1 “serious” case associated with oral ingestion).

The ‘serious’ case of psychosis associated with oral use was confounded by concomitant alcohol and therefore, the causality assignment is “Possible”.

One of the inhaled cases was assessed as ‘probable’ but the reaction was not ‘serious’.

Conclusion: In the serious case, Salvia was sold in a drug form, a tablet containing 57 or 72 mg of Salvinorin-A. In this case concomitant use of Salvia and alcohol most likely contributed to the adverse reaction of psychosis.

In the 3 non serious cases, there was disorientation and hallucination after taking one “puff” of *Salvia divinorum*.

From a clinical perspective, the main concern is the easy access, availability in retail outlets to adolescents without controls and the potential for misuse, as suggested by the AR case report of prolonged psychosis in an adolescent. Additionally, the hallucinogenic effects of Salvia may put individuals in life-threatening situations for themselves and others (driving while under the influence of Salvia). Although the case was confounded by alcohol and details of "intervention" were not specified in the report, it is likely that the Salvia component had contributed significantly to the psychoses, requiring restraint, observation/monitoring prior to the incarceration. Psychosis is a medically significant event and causality remains "Possible" and "Serious".

It is important to note that CADRMP is not the proper tool for monitoring the risk associated with Salvia in this context, because CADRMP is not designed or promoted for the collection of street drug effects. Rather, CADRMP is designed and promoted for the collection of adverse reactions associated with health products, and Salvia used in the current context would not be considered a health product.

Further monitoring and public education are necessary to regulate and possibly restrict *Salvia divinorum*.

Total domestic AR case reports associated with the use of *Salvia divinorum* up to May 31, 2005

Source of ADRs	# of cases report	route		psychosis	hallucination disorientation	Causality certain	Causality probable	Causality possible	Serious	Fatal outcome
CADRMP	4	oral	1	1				1	1	0
		inhalation	3		3		1	2	0	0

Summary of Causality Assessment of reaction associated with the use of *Salvia divinorum*

Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177866 consumer Jan 12, 2005	27yr/F	-Unknown - Disorientation, hallucination, not recognizing people around her.	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No	Recovered (Effect lasted 5 minutes)	Probable	No

Case summary no 0177866

A 27 year old woman experienced disorientation, not recognizing people in the room, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. Patient reported prior use of mescaline and LSD and that the effect of those were not as bad ("moins pires"). The patient was on no other medications. This is not an unexpected reaction to *Salvia divinorum*. There is no evidence from the case report that she had recently taken other hallucinogenic substances.

The causality was assigned as probable.  
The adverse reaction judged as not serious.

Case ID reporter  date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
177865  consumer  Jan 12, 2005	28yr/M	-Unknown -Disorientation, hallucination, - foaming at the mouth	<i>Salvia divinorum</i> Puff encens spécial	Inhalation	1 puff taken	No -no other medications -past med history - unknown	Recovered (Effect lasted 5 minutes)	Possible	No

Case summary no 0177865

A 28 year old man experienced disorientation, foaming at the mouth, hallucination for a duration of approximately 5 minutes after taking one puff of *Salvia divinorum*. The product called *Puff encens spécial* obtained from a boutique called [REDACTED] was inhaled thru a pipe. There was no concomitant medication. Past medical history is unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.  
The adverse reaction judged as not serious.

Case ID reporter date received	Age/ gender	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
179969 consumer Feb. 17, 2005	56yr/F	-Unknown -Disorientation, hallucination, does not recognize husband	<i>Salvia divinorum</i> Al sasia encens special	Inhalation	1 puff taken	Unknown	Recovered (total effect 30 minutes)	Possible	No

Case summary no 0179969

A 56 year old woman experienced 30 minutes of disorientation and vivid hallucination after taking 1 puff of *Salvia divinorum*. The reaction was very intense for 10 minutes and then decreased in intensity. The past medical history, concomitant medication and NHP usage are unknown. This is not an unexpected reaction to *Salvia divinorum*.

The causality was assigned as possible.

The adverse reaction judged as not serious.

Case ID reporter  date received	Age/ gender/ weight	Date/ Adverse reaction (AR)	Suspect drug/ Product name	Route/ Dose/ Freq.	Time to onset AR/ Exposure time period	Possible Confounders	Outcome	Causality	Serious (Y/N)
0185128  Consumer (parent)  May 31, 2005	16yr/M  150lbs	March 29, 2005/ -drug induced psychosis -incoherent -suicidal -restrained -threatened to kill police officers -amnesia (does not remember any of these events) -jailed	Salvia/ aka Maria Pastora	oral/ 1 tablet "the 30\$ pill" 57mg*	single dose	Yes  <u>Concomitant intake of:</u> Alcohol ("few drinks")  <u>Concomitant condition:</u> ADD	Recovered	Possible	Yes

Case summary no 0185128:

On March 23, 2005, a 16 year old male experienced drug induced psychosis: was incoherent, was suicidal, needed to be restrained, threatened to kill police officers, was jailed and had amnesia of these events after taking a single tablet of *Salvia* ( aka Maria Pastra). He had also consumed a few drinks of alcohol. He had an underlying Attention Deficit Disorder (ADD) but was not receiving medication for this. He had previously taken *Salvia* "on its own" (route of administration unknown) with no adverse reaction.

Additional information obtained through the ADR specialist:

\* Follow up request for more information obtained July 28 2005, confirmed that the tablet was oral "30 \$ pill" purchased "behind the counter" at [REDACTED]

This outlet sells a *Salvia* 10x containing 57 mg of Salvinorin-A for 29.98\$ and a *Salvia* 20x containing 72 mg of Salvinorin-A for 39.98\$.

Further information received August 18 2005: When *Salvia* was taken previously, it was the same dose (30\$ pill orally). The only thing different was that on previous occasions, the patient did not have alcohol with it.

This is a case where there was no adverse reaction with previous use of *Salvia* (same dosage, same distributor, same route of administration) but when associated with alcohol, it had a severe adverse reaction.

[REDACTED]

The causality was assigned as possible with alcohol as a confounder.  
The adverse reaction was judged as serious because it required intervention.

#### Appendix

##### WHO algorithm of Causality Categories:

1	Probably/Likely:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
2	Possible:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
3	Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
4	Conditional/Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.
5	Unassessible/Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.



Carole Bouchard  
2006-10-13 01:07 PM

To: Hans Yu/HC-SC/GC/CA@HWC  
cc: Ana Mayorga/HC-SC/GC/CA@HWC, Chad Sheehy/HC-SC/GC/CA@HWC, Jenna Griffiths/HC-SC/GC/CA@HWC, Jim Daskalopoulos/HC-SC/GC/CA@HWC, MBBNHPB\_Support Staff,  
Subject: Re: DONE Re: HFA: revised SALVIA DIVINORUM QP□

Sorry about the delay in getting back to you . I was in meetings and also working on an issue related to salvia . I will be speaking with a reporter from CBC radio this afternoon only on the criteria used to assess substances against CDSA.

My only comment is in the background. Please see below (strikeout information on watch list) . Carole

Hans Yu

Hans Yu  
2006-10-12 04:43 PM

To: Jim Daskalopoulos/HC-SC/GC/CA@HWC  
cc: Ana Mayorga/HC-SC/GC/CA@HWC, Carole Bouchard/HC-SC/GC/CA@HWC, Chad Sheehy/HC-SC/GC/CA@HWC, Jenna Griffiths/HC-SC/GC/CA@HWC, Jim Daskalopoulos/HC-SC/GC/CA@HWC, MBBNHPB Support Staff, Patricia Maynard/HC-SC/GC/CA@HWC  
Subject: Re: DONE Re: HFA: revised SALVIA DIVINORUM QP□

Hi, all

Here it is per Jim's request:

H

*Working Draft / Document de travail*

QUESTION PERIOD NOTE  
NOTES POUR LA PÉRIODE DE QUESTIONS

Classification: HPFB PROTECTED/PROTÉGÉ DGPSA

Requested/Demandée

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

**MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Salvia divinorum is a herb which belongs to the mint family that has been used in traditional and spiritual practices by the Aboriginal peoples of Mexico to produce hallucinogenic experiences. It is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating this issue in light of

the risks of *Salvia divinorum* to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of *Salvia divinorum*?

## KEY MESSAGES - MESSAGES CLÉS

English:

- Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level.

*Salvia divinorum* has not been authorized for sale in Canada. If marketed, *Salvia divinorum* would pose a risk for abuse, likely to lead to harmful non-medicinal use, and thus, would be subject to immediate compliance action by the Health Products and Food Branch Inspectorate.

- Health Canada is assessing the potential for regulatory control of *Salvia divinorum* and will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its availability and use.

Français:

On October 6, 2006, the Health Products and Food Branch Inspectorate (HPFBI), Ontario Region received an enquiry from MP Joe Preston's office (Elgin-Middlesex, London, Ontario riding). A constituent had inquired why the hallucinogenic product, *Salvia divinorum*, was available as an over-the-counter product.

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* has traditional medicinal uses among the Aboriginal peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1983). *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious kappa-opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

#### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*, that would remove it from the purview of the *Natural Health Products Regulations*.

Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act*, although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

#### Current Situation in Canada

*Salvia divinorum* and salvinorin A meet both the functional and substance portions of the definition of a natural health product and are not currently subject to any regulatory exclusions, and therefore, they would be considered natural health products in Canada. However, since *Salvia divinorum* and salvinorin A are subject to the *Natural Health Products Regulations* and the *Food and Drugs Act*, and present a risk for abuse that is likely to lead to harmful non-medicinal use, they are subject to immediate compliance action by the HPFBI according to Compliance and Enforcement Policy (POL-0001).

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS ~~has placed *Salvia divinorum* on their 'watch list', meaning, they~~ will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and international regulatory status as monitored by MHPD. Additionally, if the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

#### Health Canada Actions

HPFBI is investigating the product identified by MP Joe Preston's constituent, and will take appropriate compliance and enforcement actions. Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

#### Remarks/ Remarques:

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub

2005 Sep 13.

Díaz JL. 1976. Propiedades Terapéuticas Atributas a Plantas Mexicanas, Primera Parte: Nombre Botánico y Usos. Instituto Mexicano para el Estudio de las Plantas Medicinales, Mexico.

Valdés LJ, Díaz JL, Paul AG. 1983. Ethnopharmacology of *Ska María Pastora* (*Salvia divinorum* , Epling and Játiva-M.). J. Ethnopharmacology 7(3): 287-312.

\* HECS-OCS was consulted on this QP - Oct 11, 2006

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**\*Date Prepared/**

**Date préparé:** 2006-10-12

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Marketed Biologicals, Biotechnology and Natural Health Products Bureau/Bureau des produits b  
biotechnologiques et de santé naturels commercialisés

**Contact Signed/  
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**Date Signed/ Date signé:**

Date will be entered automatically when signed and saved.

**D.G. Approved/  
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**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/  
Date de l'approbation du DG:**

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/  
Approbation par le SMA :**

Neil Yeates - HPFB/DGPSA (957-1804)

**Branches/  
Directions générale:** HPFB/ DGPSA

**Departments/ Ministères:** Health Canada / Santé Canada

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Jenna Griffiths Oct 12, 2006 - 04:28:17 PM updating  
Jenna Griffiths Oct 12, 2006 - 03:47:13 PM updating  
Shahid Perwaiz Oct 12, 2006 - 10:32:39 AM editing

**Created By:** Louise Carriere/HC-SC/GC/CA **Date Created:** October 12, 2006  
**Modified By:** Jenna Griffiths/HC-SC/GC/CA **Date Modified:** October 12, 2006

Jim Daskalopoulos



**Jim Daskalopoulos**  
2006-10-12 04:40 PM

**To:** Hans Yu/HC-SC/GC/CA@HWC  
**cc:** Ana Mayorga/HC-SC/GC/CA@HWC, Carole  
Bouchard/HC-SC/GC/CA@HWC, Jenna  
Griffiths/HC-SC/GC/CA@HWC, MBBNHPB Support Staff, Patricia  
Maynard/HC-SC/GC/CA@HWC, Chad Sheehy/HC-SC/GC/CA@HWC,  
Jim Daskalopoulos/HC-SC/GC/CA@HWC  
**Subject:** Re: DONE Re: HFA: revised SALVIA DIVINORUM QP☐

Hans,

I do not have access to the QP database and therefore cannot read your note; please send me a copy. I have also copied Trish and Chad from our Ottawa office to provide input.

Thank you,

Jim

---

Jim Daskalopoulos,  
A/Manager, Ontario Operational Centre  
Health Products and Food Program - Inspectorate  
Ontario Region  
Public Affairs, Consultation and Regions Branch - Health Canada  
Phone: (416) 973-1466 Fax (416) 973-1954  
email: Jim\_Daskalopoulos@hc-sc.gc.ca  
Hans Yu

**Hans Yu**  
2006-10-12 04:28 PM

**To:** Jenna Griffiths/HC-SC/GC/CA@HWC, Jim  
Daskalopoulos/HC-SC/GC/CA@HWC, Carole  
Bouchard/HC-SC/GC/CA@HWC  
**cc:** Ana Mayorga/HC-SC/GC/CA@HWC, MBBNHPB Support Staff  
**Subject:** DONE Re: HFA: revised SALVIA DIVINORUM QP☐

Hi, Jenna

s.19(1)

s.21(1)(b)

Thanks  
H

---

Hans H. Yu  
Acting Director/Directeur intérimaire  
Marketed Biologicals, Biotechnology and Natural Health Products Bureau  
Bureau des produits biologiques, biotechnologiques et de santé naturels commercialisés  
Marketed Health Products Directorate  
Direction des produits de santé commercialisés  
200 Tunney's Pasture Driveway (AL 0701A)  
Ottawa, Ontario, K1A 0K9  
Phone: (613) 952-8301  
Cell: [REDACTED]  
Fax: (613) 952-6011  
Assistant: Ana Mayorga (613) 946-5068

Jenna Griffiths



**Jenna Griffiths**  
2006-10-12 03:54 PM

To: Hans Yu/HC-SC/GC/CA@HWC  
cc: Ana Mayorga/HC-SC/GC/CA@HWC, MBBNHPB Support Staff  
Subject: HFA: revised SALVIA DIVINORUM QP

Hi Hans,  
Please review the attached QP which Shahid and I have revised.

We suggest that once approved by you, this be sent to HPFBI (Jim Daskalopoulos) and OCS (Carole Bouchard) for review prior to being sent up the line.



Thanks.  
Jenna  
Ana Mayorga

**Ana Mayorga**  
2006-10-12 08:23 AM

To: Shahid Perwaiz/HC-SC/GC/CA@HWC  
cc: MBBNHPB Management, MBBNHPB Support Staff  
Subject: For action please: Shahid please follow-up re. HPFBI's info re. SALVIA DIVINORU

Good morning Shahid,

The information provided by HPFBI needs to be incorporated in the QP using red font.

Once it has been approved by Management and A/Director, I will prepare the binder.

Thank you

(Please let me know if you need help incorporating the info).

Ana

----- Forwarded by Ana Mayorga/HC-SC/GC/CA on 2006-10-12 08:20 AM -----



**Louise Carrière**  
2006-10-12 08:05 AM

To: Ana Mayorga/HC-SC/GC/CA@HWC  
cc: MBBNHPB Management, MBBNHPB Support Staff, Shahid  
Perwaiz/HC-SC/GC/CA@HWC, MHPD\_DPSC DGO Assistants  
Subject: Re: Shahid please follow-up re. HPFBI's info re. SALVIA DIVINORU

Hi Ana,

Please update the QP (in red text) and re-submit the revised QP via regular process (red binder).

Let me know if you cannot update, I may need to move the QP back to the working database.

Merci.

Louise Carrière  
Director General's Office/Bureau du directeur général  
Marketed Health Products Directorate (MHPD)/ A.L. 0701B  
Direction des produits de santé commercialisés (DPSC)  
Tel./Tél.: 613-948-6136  
Fax/Télécopieur: 613-952-7738  
Ana Mayorga

**Ana Mayorga**  
2006-10-11 03:38 PM

To: Louise Carriere/HC-SC/GC/CA@HWC  
cc: MBBNHPB Management, MBBNHPB Support Staff, Shahid  
Perwaiz/HC-SC/GC/CA@HWC  
Subject: Shahid please follow-up re. HPFBI's info re. SALVIA DIVINORU

Hi Louise,

Please see below Dr. Jenna Griffiths' email. Please advise next step in order to follow proper procedures.

Thanks,

Ana

----- Forwarded by Ana Mayorga/HC-SC/GC/CA on 2006-10-11 03:35 PM -----



**Jenna Griffiths**  
2006-10-11 03:21 PM

To: Shahid Perwaiz/HC-SC/GC/CA@HWC  
cc: Ana Mayorga/HC-SC/GC/CA@HWC, Hans Yu/HC-SC/GC/CA@HWC,  
Scott Jordan/HC-SC/GC/CA@HWC  
Subject: Shahid please follow-up re. HPFBI's info re. SALVIA DIVINORU

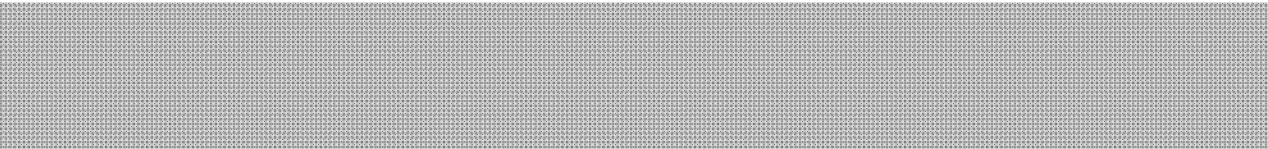
Shahid,

Please revise the QP including HPFBI info. This was the trigger for the QP note!

As NHPs, *Salvia divinorum* and salvinorin A are subject to the **Compliance Policy for Natural Health Products**. According to the Policy's "A Risk-based Approach", any NHP that poses an unacceptable risk to consumers will be subject to immediate compliance action. *Salvia divinorum* and salvinorin A present an identifiable risk for abuse with respect to the safety.



The caller will be advised to submit a complaint to our office identifying where this product is being sold so that we may follow-up and take the necessary compliance and enforcement actions.



Thanks  
Jenna

----- Forwarded by Jenna Griffiths/HC-SC/GC/CA on 2006-10-11 03:13 PM -----

**Ana Mayorga**  
2006-10-11 02:20 PM

To: MBBNHPB Management  
cc: Louise Carriere/HC-SC/GC/CA@HWC, Shahid Perwaiz/HC-SC/GC/CA@HWC  
Subject: HPFBI's input - Re: REQUEST : QP Note - DRUGS - SALVIA DIVINORUM

Merci Louise.

\*\*\*\*\*

Management/Shahid: FYI/action.

Thanks.

Ana

----- Forwarded by Ana Mayorga/HC-SC/GC/CA on 2006-10-11 02:15 PM -----



**Louise Carriere**  
2006-10-11 02:12 PM

To: Brenda Lajeunesse/HC-SC/GC/CA@HWC  
cc: Shahid Perwaiz/HC-SC/GC/CA@HWC, MBBNHPB Support Staff  
Subject: HPFBI's input - Re: REQUEST : QP Note - DRUGS - SALVIA DIVINORUM

Thanks Brenda, I've copied our Bureau on this e-mail.

Louise Carrière  
Director General's Office/Bureau du directeur général  
Marketed Health Products Directorate (MHPD)/ A.L. 0701B  
Direction des produits de santé commercialisés (DPSC)  
Tel./Tél.: 613-948-6136  
Fax/Télécopieur: 613-952-7738  
Brenda Lajeunesse

**Brenda Lajeunesse**  
2006-10-11 02:08 PM

To: Louise Carriere@HWC  
cc:  
Subject: Re: REQUEST : QP Note - DRUGS - SALVIA DIVINORUM

Hi Lou - somehow Jim Daskalopoulos was copied on Marianne's email below and he provided info to Patricia Maynard. I'm not sure if you require his info but thought I would pass to you as MHPD (Shahid Perwais) has written QPs on this issue? Thanks

----- Forwarded by Brenda Lajeunesse/HC-SC/GC/CA on 2006-10-11 02:06 PM -----



**Patricia Maynard**  
2006-10-10 04:39 PM

To: Brenda Lajeunesse/HC-SC/GC/CA@HWC  
cc:  
Subject: Re: REQUEST : QP Note - DRUGS - SALVIA DIVINORUM

Patricia Maynard  
Manager, Drug Compliance Verification and Investigations Unit  
Health Products and Food Branch Inspectorate  
250 Lanark ave, AL 2003B  
Ottawa, Ontario K1A 0K9  
tel 613-952-9906  
fax 613-946-5636

----- Forwarded by Patricia Maynard/HC-SC/GC/CA on 10/10/2006 04:39 PM -----



**Chad Sheehy**  
10/10/2006 04:37 PM

To: Patricia Maynard/HC-SC/GC/CA@HWC  
cc:  
Subject: Re: REQUEST : QP Note - DRUGS - SALVIA DIVINORUM

MHPD has written QPs on this. Shahid Perwaiz was the author.  
Patricia Maynard



**Patricia Maynard**  
10/10/2006 04:36 PM

To: Jim Daskalopoulos/HC-SC/GC/CA@HWC, Brenda  
Lajeunesse/HC-SC/GC/CA@HWC  
cc: Diana Dowthwaite/HC-SC/GC/CA@HWC, Chad  
Sheehy/HC-SC/GC/CA@HWC  
Subject: Re: REQUEST : QP Note - DRUGS - SALVIA DIVINORUM

Brenda, have we received a request for this?

Patricia Maynard  
Manager, Drug Compliance Verification and Investigations Unit  
Health Products and Food Branch Inspectorate  
250 Lanark ave, AL 2003B  
Ottawa, Ontario K1A 0K9  
tel 613-952-9906  
fax 613-946-5636  
Jim Daskalopoulos



**Jim Daskalopoulos**  
10/10/2006 04:32 PM

To: Patricia Maynard/HC-SC/GC/CA@HWC  
cc:  
Subject: REQUEST : QP Note - DRUGS - SALVIA DIVINORUM

Trish,

I don't have access to the QP Database. Here is what I completed for this MP inquiry. Is this something  
your team can help with?

Jim



MP Contact Report Salvia divinorum.v

Jim Daskalopoulos,  
A/Manager, Ontario Operational Centre  
Health Products and Food Program - Inspectorate  
Ontario Region  
Public Affairs, Consultation and Regions Branch - Health Canada  
Phone: (416) 973-1466 Fax (416) 973-1954  
email: Jim\_Daskalopoulos@hc-sc.gc.ca

----- Forwarded by Jim Daskalopoulos/HC-SC/GC/CA on 2006-10-10 04:31 PM -----

Marianne DeVito  
2006-10-10 04:22 PM

To: Hannah Kahn/HC-SC/GC/CA@HWC  
cc: diane\_laplante@hc-sc.gc.ca, Julien Clavel/HC-SC/GC/CA@HWC, Jim Daskalopoulos/HC-SC/GC/CA@HWC  
Subject: REQUEST : QP Note - DRUGS - SALVIA DIVINORUM



Good afternoon!

MO is looking for an update to an existing QP Note on "salvia divinorum", in light of an MP Request on this issue.

Existing QP Note -> March 23, 2006 :

This updated QP Note is due to me, cc: Julien Clavel by 3:30 PM on Wednesday, October 11, 2006.

Many thanks for your kind attention to this matter!

*-Marianne DeVito-*

Question Period & Private Members' Business Coordinator /  
Coordinatrice de la Période des questions & des affaires émanant des députés  
Parliamentary Relations Office / Bureau des relations parlementaires  
Tél.: (613) 952-7108

**Talking Points for the  
Minister of Health  
on *Salvia divinorum*  
for presentation to the  
Mr. Daryl Kramp (MP-CPC)  
Date - TBD, 2006**

- *Salvia divinorum* is an herb, native to Mexico. It is chewed or smoked and can induce hallucinations.
- *Salvia divinorum* is being widely touted on the Internet as a legal alternative to street drugs.
- Neither *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule to the *Food and Drugs Act and Regulations*.
- *Salvia Divinorum* has not been authorized for sale in Canada.
- *Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Europe, only Finland and Denmark have added *Salvia Divinorum* to their list of controlled plants.
- In the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act*, although it is

included on the Drug Enforcement Administration's list of Chemicals and Substances of Concern. There are no legal implications of this classification; however, some states have put restrictions on its sale.

- *Salvia Divinorum's* mechanism of action is still not fully understood. It has been known to cause hallucinations, out-of-body experiences, unconsciousness and short-term memory loss. There is, consequently, a potential for accidents occurring while the user is under the influence of the substance.
- The plants effects are short acting and no cases of dependency have been reported in the literature. Long-term effects have not yet been observed.
- The Canadian Adverse Drug Reaction Monitoring Program within HC's Marketed Health Products Directorate has received four reports of adverse reactions associated with *Salvia Divinorum*.
- Three cases were associated with inhalation of *Salvia Divinorum* with reported brief hallucinogenic effects.

These cases were considered to be non-serious reactions requiring no medical intervention.

- The fourth case was associated with the oral consumption of *Salvia* tablets and use of alcohol in a 16 year old male, with reported adverse reactions of psychosis and amnesia. This was considered to be serious and required medical intervention.
- Health Canada has no statistics on usage of *Salvia divinorum* in Canada.
- Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level.
- Health Canada is assessing the potential for regulatory control of *Salvia Divinorum* and will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its availability and use.



**Theresa Schopf**  
2006-01-25 04:50 PM

To: Cheryl Tremblay/HC-SC/GC/CA@HWC  
cc:  
Subject: QP - Salvia Divinorum - Please provide input/approval

Hi Cheryl,

Can you please give me the file on SD?

Thanks  
Theresa

----- Forwarded by Theresa Schopf/HC-SC/GC/CA on 2006-01-25 04:50 PM -----

**Carole Bouchard**  
2006-01-25 04:13 PM

To: Theresa Schopf/HC-SC/GC/CA@HWC  
cc: Colleen Simard/HC-SC/GC/CA@HWC, Karen  
Keighley/HC-SC/GC/CA@HWC  
Subject: QP - Salvia Divinorum - Please provide input/approval

Theresa

could you please have someone reviewed the QP prepared by HPFB? Please provide comments or changes required to me by no later than Friday 9 o'clock.

Merci

Sorry for the late submission - too many e-mails.

----- Forwarded by Carole Bouchard/HC-SC/GC/CA on 2006-01-25 04:11 PM -----



**Madeleine Milloy**  
2006-01-24 09:15 AM

To: Carole Bouchard/HC-SC/GC/CA@HWC  
cc: Karen Keighley/HC-SC/GC/CA@HWC  
Subject: QP - Salvia Divinorum - Please provide input/approval

Bonjour Carole,

See below. Please note that Beth will have to give her approval prior to sending. I would appreciate a response by January 27 - 10:00 a.m.

Thank you.

Madeleine  
Madeleine Milloy  
Drug Strategy and Controlled Substances Programme  
Programme de la strategie antidrogue et des substances contrôllées  
613-946-6489

--- Forwarded by Madeleine Milloy/HC-SC/GC/CA on 2006-01-24 09:14 AM -----



**Helene Landers**  
2006-01-24 08:19 AM

To: Madeleine Milloy/HC-SC/GC/CA@HWC  
cc: Ginette Faubert/HC-SC/GC/CA@HWC  
Subject: QP - Salvia Divinorum - Please provide input/approval

Please provide me with your input/approval by Friday NOON January 27, 2006

Thank you



*Helene*

952-3684

----- Forwarded by Helene Landers:HC-SC/GC/CA on 2006-01-24 08:18 AM -----

**Jacqueline Seck**  
2006-01-23 03:31 PM

To: Ginette Faubert/HC-SC/GC/CA@HWC  
cc: Louise Maisonneuve/HC-SC/GC/CA@HWC  
Subject: QP - Salvia Divinorum - Please provide input/approval

Ginette,

Attached is a QP that needs your approval or input as required. Please consult with Office of Controlled Substances.

Jacqueline  
952-2266

----- Forwarded by Jacqueline Seck:HC-SC/GC/CA on 01/23/06 03:29 PM -----

Working Draft / Document de travail

QUESTION PERIOD NOTE  
NOTES POUR LA PÉRIODE DE QUESTIONS

Classification: HPFB PROTECTED/PROTÉGÉ DGPSA

\* Anticipatory/Anticipée

English:

**SALVIA DIVINORUM, A HALLUCINOGENIC PLANT IS BEING PROMOTED ON INTERNET SITES AS A LEGAL ALTERNATIVE TO STREET DRUGS**

### **MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Salvia divinorum is a hallucinogenic plant which is being widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating these reports in light of the risks of Salvia divinorum to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

## KEY MESSAGES - MESSAGES CLÉS

English:

- Health Canada is aware of the recent media reports and scientific publications which indicate the abuse potential of *Salvia divinorum* among adolescents and young adults, and is taking appropriate actions to manage this issue and mitigate any potential risk to Canadians.
- Products containing *Salvia divinorum* have not been authorized for sale in Canada. The Office of Controlled Substances of Health Canada has placed *Salvia divinorum* on their watch list, and is monitoring this issue.
- The Marketed Health Products Directorate investigated the trend of *Salvia divinorum* use at the national and international level and provided results of their investigation to the Office of Controlled Substances for their potential action.
- Health Canada has received four reports of adverse reactions involving *Salvia divinorum* as a suspected agent, and has provided details of their assessment to the Office of Controlled Substances.

Français

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### BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, that is smoked as a hallucinogen. The main active ingredient of *Salvia divinorum* is salvinorin A. *Salvia divinorum* is being widely touted on Internet sites aimed at young adults and adolescents, as a "legal" alternative to street drugs. Salvinorin A is a highly efficacious *kappa*-opioid receptor agonist of clinical interest for treatment and

etiological studies of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 g of purified salvinin A, or 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug. The American Drug Enforcement Agency (DEA) has also placed *Salvia divinorum* on a list of drugs and chemicals "of concern," without legal implications.

A recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults.

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*, that would remove it from the purview of the *Natural Health Products Regulations*. The Canadian Adverse Drug Reaction Monitoring Program has received four reports of adverse reactions involving *Salvia divinorum* as a suspected agent, taken for its hallucinatory effects.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations, and will develop appropriate risk mitigation strategies, if deemed necessary, following consultation with other Directorates. In the meantime, the Office of Controlled Substances (OCS), which is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, has placed *Salvia divinorum* on their watch list. As part of this action, the OCS will maintain a file on *Salvia divinorum* and will collect relevant information specific to this plant and its active constituents. If the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA).

These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

The Health Products and Food Branch and the Office of Controlled Substances (Healthy Environments and Consumer Safety branch) of Health Canada will continue to share relevant information concerning *Salvia divinorum* to determine whether it should be added to appropriate schedules under the *Controlled Drugs and Substances Act*.

Hard copies of the media reports will be provided to the QP note coordinator

**Remarks/ Remarques:**

Bucheler R, Gleiter CH, Schwoerer P, Gaertner I. Use of nonprohibited hallucinogenic plants: increasing relevance for public health? A case report and literature review on the consumption of *Salvia divinorum* (Diviner's Sage). *Pharmacopsychiatry*. 2005 Jan;38(1):1-5.

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother*. Oct;39(10):1634-9. Epub 2005 Sep 13

Giroud C, Felber F, Augsburger M, Horisberger B, Rivier L, Mangin P. 2000. *Salvia divinorum*: an hallucinogenic mint which might become a new recreational drug in Switzerland. *Forensic Science International* 112: 143-150.

Prisinzano T E. 2005. Psychopharmacology of the hallucinogenic sage *Salvia divinorum*, Minireview. *Life Sciences* 78: 527-531.

National review of medicine, Nov. 15, 2005  
[www.nationalreviewofmedicine.com/issue/2005/11\\_15/2\\_patients\\_practice06\\_19.html](http://www.nationalreviewofmedicine.com/issue/2005/11_15/2_patients_practice06_19.html)

Radio-Canada, Nov. 22, 2005, <http://radio-canada.ca/radio/sansfrontieres/66659.shtml>

**Contact Information / Personnes-Ressource**

<b>*Primary/Primaire:</b> Shahid Perwaiz	<b>*Telephone/Téléphone:</b> (613) 948-8540 <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b> <b>Title/Titre:</b> Director General	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b>
<b>Secondary/Secondaire:</b> Jenna Griffiths	<b>Telephone/Téléphone:</b> 346-6507 <b>Mobile/Cellulaire:</b>		

**\*Date Prepared/**

Date préparé: 11/29/2005

**\*Director-Contact/  
Directeur-personne  
ressource:**

Duc Vu

**\*Phone Number/  
Téléphone:** 613-952-8301

**\*Directorate & Bureau/  
Direction et bureau:**

Marketed Natural Health Products Division/Divison des produits de santé naturels commerciaux

**Contact Signed/  
Signature par la  
personne-ressource:**

Contact Signed: Signature de la personne ressource

**Date Signed/ Date signé:** 12/28/2005

Date will be entered automatically when signed and saved.

**D.G. Approved/  
Approuvé par le DG:**

D.G. Approved/Approbation par le D.G.

**Approved by/ Approuvé par:** Dr. Chris Turner

**Date D.G. Approved/  
Date de l'approbation du DG:** 12/28/2005

Date will be entered automatically when verified and saved: La date s'inscrira au moment de la signature et de la sauvegarde

**\*Directorates/ Directions:** Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/  
Approbation par le SMA :** Diane Gorman - HPFB/DGPSA (613-957-1804)

**Branches/  
Directions générale:** HPFB/ DGPSA

**Departments/ Ministères:** Health Canada / Santé Canada

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**Edit History:**

Jacqueline Seck	Jan 23, 2006 - 03:29:11 PM	Revisions
Jacqueline Seck	Jan 3, 2006 - 03:40:33 PM	Revisions
Jacqueline Seck	Jan 3, 2006 - 03:33:34 PM	Revisions
Louise Carriere	Dec 29, 2005 - 08:05:58 AM	DG approval
Jenna Griffiths	Dec 22, 2005 - 03:42:46 PM	editing
Scott Jordan	Dec 22, 2005 - 12:28:35 PM	edits
Shahid Perwaiz	Dec 21, 2005 - 03:52:06 PM	edits
Shahid Perwaiz	Dec 21, 2005 - 03:47:46 PM	revision
Scott Jordan	Dec 20, 2005 - 11:12:32 AM	edits

**Created By:** Shahid Perwaiz/HC-SC/GC/CA  
**Modified By:** Jacqueline Seck/HC-SC/GC/CA

**Date Created:** November 29, 2005  
**Date Modified:** January 23, 2006

**QUESTION PERIOD NOTE**  
**NOTE POUR LA PÉRIODE DE**  
**QUESTIONS**

Date: November 22, 2006

Classification

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**SUBJECT - SUJET**

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

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English:

Salvia divinorum is a herb which belongs to the mint family that has been used in traditional and spiritual practices by the Aboriginal peoples of Mexico to produce hallucinogenic experiences. It is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating this issue in light of the risks of Salvia divinorum to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

---

**ANTICIPATED QUESTION - QUESTION PRÉVUE**

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

Français:

Quelles mesures Santé Canada prend-il pour protéger les Canadiens contre les effets indésirables possibles liés à l'utilisation de la Salvia divinorum?

---

English:

- Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level including continuous monitoring of adverse reaction reports involving *Salvia divinorum* submitted to the Canadian Adverse Drug Reaction Monitoring Program.
- Health Canada's Office of Controlled Substances has placed *Salvia divinorum* on its list of substances to monitor. As part of this action, Health Canada will work with its partners, including law enforcement agencies and international counterparts to collect relevant information on this herb.
- Based on all information received, Health Canada will assess the potential for regulatory control of *Salvia divinorum* and will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its sale and use.

Français:

- Santé Canada évalue actuellement la tendance de l'utilisation de la *Salvia divinorum*, à l'échelle nationale et internationale, et surveille également de façon continue les déclarations d'effets indésirables associées à la *Salvia divinorum* qui sont soumises dans le cadre du Programme canadien de surveillance des effets indésirables des médicaments.
- Le Bureau des substances contrôlées de Santé Canada a inscrit la *Salvia divinorum* sur sa liste des substances à surveiller. À cette fin, Santé Canada collaborera avec ses partenaires, notamment les organismes d'application de la loi et ses homologues internationaux, en vue de recueillir des

renseignements pertinents sur cette plante.

- En se fondant sur l'information obtenue, Santé Canada évaluerait la possibilité de réglementer la *Salvia divinorum* et prendrait les mesures nécessaires pour protéger les Canadiens contre les risques éventuels, notamment la communication des risques au public ou l'imposition de restrictions relatives à sa vente et à son utilisation.

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## BACKGROUND - CONTEXTE

### English:

On November 16, 2006, Le Journal de Montréal published a report entitled "Un hallucinogène légal Santé Canada a cependant la *Salvia divinorum* à l'oeil" which indicated that Health Canada is evaluating the possibility of imposing restrictions over the sale and use of *Salvia divinorum*, similar to those of certain countries. Given that *Salvia* does not have long-term adverse effects or the risk of dependence, the article suggests that Health Canada does not consider the short-term hallucinogenic effects to be sufficiently significant health risks to impose restrictions over its sale. In fact, according to the article, *Salvia divinorum* has been sold in certain Quebec retail outlets since 2000, as a hallucinogen. The article quotes an RCMP officer in saying that prevention of *Salvia divinorum*'s use is necessary. Additionally, the article quotes Jean-Sébastien Roy, in saying that Quebec's law enforcers' hands are tied because Health Canada has not categorized *Salvia divinorum* as a controlled substance, despite its effects being comparable to the illicit drugs cannabis and LSD. Additionally, he indicated that if an individual were stopped for erratic driving under *Salvia divinorum*'s influence, they would be charged for driving while impaired. Since *Salvia divinorum* is not included in the Controlled Drugs and Substance Act, Health Canada's ability to carry out enforcement activities concerning *Salvia divinorum*, could only occur if the drug were marketed with health claims. Under these circumstances, the Health Products and Food Branch Inspectorate (HPFBI) could remove *Salvia divinorum* from the market, due to its known safety concerns. In fact, on October 6, 2006, the HPFBI Ontario Region received an enquiry from MP Joe Preston's office (Elgin-Middlesex, London, Ontario riding). A constituent inquired why the hallucinogenic product, *Salvia divinorum*, was available as an over-the-counter product. HPFBI requested that a complaint be submitted to the HPFBI office in Toronto for the product identified by MP Joe Preston's constituent, identifying the location of the retailer and the product. HPFBI is currently reviewing this complaint.

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* has traditional medicinal uses among the Aboriginal peoples of Mexico, e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1983). *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as an alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious  $\kappa$ -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of



the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

### **Regulatory Control of *Salvia divinorum***

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*, that would remove it from the purview of the *Natural Health Products Regulations*.

Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act*, although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

### **Current Situation in Canada**

In July of 2005 Health Canada completed a review of the information currently available on the potential risks and benefits of *Salvia divinorum* use in humans. *Salvia divinorum* has traditional medicinal uses among the native peoples of Mexico where it grows naturally, so a product with such health claims could meet the definition of a natural health product and therefore be subject to the *Food and Drugs Act* and the *Natural Health Products Regulations*. One of the advantages of these Regulations is the mandatory assessment of every product for its safety, effectiveness with regard to the claims on the label, and quality issues such as ensuring that it is the correct herb and that it is free of contamination by pesticides, toxic metals such as lead, bacteria and molds.

However, it is highly unlikely that a *Salvia divinorum* product would be licensed as a natural health product due to its safety issues. Despite the fact that it is being used as a hallucinogen, the potential for *Salvia divinorum* to cause addiction or dependence is likely to be very low since it affects the brain in way that is quite different from other hallucinogens such as heroin or LSD. Nevertheless, *Salvia divinorum* alters perception and could potentially trigger withdrawal symptoms in people suffering from other addictions, it is subject to abuse as a street drug, and it acts on the brain in ways that are quite novel and for which the consequences have not yet been fully established.

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing

legislation, regulations, policies and operations regarding the movement of controlled substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS will work with its partners within the department, other government departments, law enforcement agencies and its international counterparts to collect relevant information specific to this herb and its active constituents. If the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

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**Date Prepared/Préparé le :** 2008-02-06

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Bureau/Bureau des produits biologiques, biotechnologiques et de santé  
naturels commercialisés

**Date Contact Signed/  
Signature de la personne  
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**D.G. Verification/  
Vérification par le D.E. :** Dr. Chris Turner  D.G. Approved / Approuvé D.E.

**Date D.G. Verified/  
Date vérifié par le D.E. :**

**Programme :** Marketed Health Products Directorate/Direction des Produits de Santé  
Commercialisés

**ADM Approved/ Approbation  
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( )

**Branch/ Direction générale :** HPFB/ DGPSA

**Department/ Ministère :** Health Canada / Santé Canada

## QUESTION PERIOD NOTE

### NOTE POUR LA PÉRIODE DE QUESTIONS

Date:	January 25, 2007
Classification :	<b>HECS PROTECTED - SESC PROTÉGÉ</b>

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#### SUBJECT - SUJET

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

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#### MEDIA ANALYSIS - ANALYSE DES MÉDIAS

English:

Media interest in Salvia Divinorum is recurrent but mild. Questions around this substance, to date, have always been about its legality. There have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties.

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#### ANTICIPATED QUESTION - QUESTION PRÉVUE

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

Français:

Quelles mesures Santé Canada prend-il pour protéger les Canadiens contre les effets indésirables possibles liés à l'utilisation de la Salvia divinorum?

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English:

- Health Canada is currently monitoring the trend of Salvia divinorum use at the national and international level including continuous monitoring of adverse reaction reports involving Salvia divinorum.
- Health Canada has placed Salvia divinorum on its list of substances to monitor. As part of this action, Health Canada will work with its partners, including law enforcement agencies and international counterparts to collect relevant information on this herb.
- Should there be evidence of a significant risk to health and safety, Health Canada will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its sale and use.

●  
Français:

Santé Canada évalue actuellement la tendance de l'utilisation de la Salvia divinorum, à l'échelle nationale et internationale, et surveille également de façon continue les déclarations d'effets indésirables associées à la Salvia divinorum qui sont soumises dans le cadre du Programme canadien de surveillance des effets indésirables des médicaments.

Le Bureau des substances contrôlées de Santé Canada a inscrit la Salvia divinorum sur sa liste des substances à surveiller. À cette fin, Santé Canada collaborera avec ses partenaires, notamment les organismes d'application de la loi et ses homologues internationaux, en vue de recueillir des renseignements pertinents sur cette plante.

S'il y aura de l'évidence d'un risque substantielle, Santé

Canada prendra les mesures nécessaires pour protéger les Canadiens. Ces mesures peuvent inclure la communication des risques au public ou l'imposition de restrictions relatives à sa vente et à son utilisation.

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## BACKGROUND - CONTEXTE

English:

### BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico. *Salvia divinorum* is traditionally smoked among the Aboriginal peoples of Mexico and has been used for medical purposes e.g. for the treatment of topical ulcers (Díaz 1976), to help normalize eliminatory functions (diarrhoea/constipation and urination), anemia, headaches, rheumatism, and alcohol addiction, in addition to its use as a hallucinogen in divination rituals (Valdés et al. 1983). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious  $\kappa$ -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* has been shown to produce intense psychoactive effects when inhaled.

*Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as an alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005).

#### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*. This means that *Salvia divinorum* can be imported and sold legally in Canada provided that no health claim has been made. If *Salvia divinorum* is associated with a health claim, it would be subject to the *Natural Health Products Regulations* and would be subject to the mandatory assessment for its safety, effectiveness with regard to the claims on the label, and quality issues such as ensuring that it is the correct herb and that it is free of contaminants such as pesticides and toxic metals.

At the present time, *Salvia divinorum* is not listed under the United Nations Drug Control Conventions which means that it is not required to be regulated as a controlled substance in any of the countries that are signatories to these Conventions. However, some countries have decided to control *Salvia divinorum* on their own. In Australia, Belgium, Denmark, Sweden, Italy, Finland, and North Korea, the possession and sale of *Salvia divinorum* is illegal. In Spain, its sale is prohibited, but possession or use is not. In Norway, *Salvia divinorum* cannot be imported without a prescription, and Japan has recently passed a law that will take effect in April 2007 which totally bans all activities with *Salvia divinorum*. *Salvia divinorum* is not controlled by the US Drug Enforcement Administration; however, some states such as Missouri, Louisiana, Tennessee and Delaware have implemented laws restricting its use, sale and/or distribution.

#### Current Situation in Canada


In July of 2005 Health Canada completed a review of the information currently available on the potential risks and benefits of *Salvia divinorum* use in humans. At that time there was insufficient evidence to warrant the introduction of any regulatory controls. The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) had received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. Three of the reports were considered to be non-serious reactions requiring no medical intervention, the fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol and was considered to be serious and required medical intervention.

Health Canada continues to monitor the trend of *Salvia divinorum* use at the national and international level. Information is collected from multiple sources including the internet, international agencies such as the World Health Organization, the Inter-American Drug Abuse Control Commission (CICAD), the International Narcotics Control Board (INCB), Health Canada's regulatory counterparts in other jurisdictions, and law enforcement agencies.

Should ongoing monitoring reveal that *Salvia divinorum* poses a significant risk to Canadians, Health Canada will develop appropriate risk mitigation strategies, such as introducing regulatory controls regarding its sale and distribution in Canada, or via other mechanisms such as the release of a product advisory by the Health Products and Food Branch or other notices.

OCS is responsible for developing legislation, regulations, policies and operations regarding the movement of controlled substances in Canada, and has placed *Salvia divinorum* on its list of substances to monitor. If the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

ATTACHMENTS / PIÈCE(S)-JOINTE(S)	
	
media lines salvia divinorum_may_2005.v	

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Signature de la personne  
ressource :**

Contact Signed - Signé

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Beth Pieterston

D.G. Approved / Approuvé D.E.

**Date D.G. Verified/  
Date vérifié par le D.E. :**

**Programme :** Drug Strategy and Controlled Substances

**ADM Approved/ Approbation  
par le SMA :** Susan Fletcher, ADM (HECS/SESC)  
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**Branch/ Direction générale :** HECS/SESC

**Department/ Ministère :** Health Canada / Santé Canada



**FOR A MEETING**

07-113157-398

**BRIEFING NOTE**

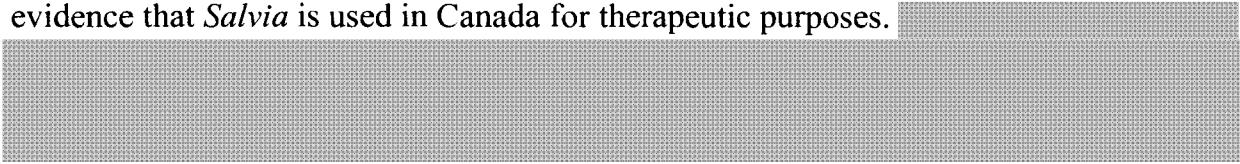
Meeting with Susan Fletcher, Assistant Deputy Minister, Healthy Environment and  
Consumer Safety Branch (HECSB) to discuss *Salvia divinorum*

**ISSUE:**

To determine the most effective strategy to mitigate the public health and safety risks  
associated with the recreational use and abuse of *Salvia divinorum* and its active  
constituents.

**BACKGROUND:**

The health and safety risks associated with *Salvia divinorum*<sup>1</sup> result from its use as a  
recreational drug and substance of abuse. The Health Products and Food Branch (HPFB)  
cannot address the risks associated with *Salvia*'s abuse; HPFB can only address issues  
concerning the health risks associated with use of *Salvia* as a health product. In this  
regard, the Marketed Health Products Directorate (MHPD) conducted a Health Risk  
Assessment (HRA) of *Salvia divinorum* when used as a health product. Currently, *Salvia  
divinorum* may be considered a natural health product (NHP), because it meets the  
substance and function components of the NHP definition (e.g., it is a plant/plant material  
being manufactured, sold, or represented for use in modifying organic function in  
humans). However, the Natural Health Products Directorate (NHPD) has not reviewed  
any claims associated with products containing *Salvia*, nor has NHPD received any  
submissions for *Salvia*'s therapeutic use. It should be noted, that to date, there is no  
evidence that *Salvia* is used in Canada for therapeutic purposes.



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<sup>1</sup>For the purpose of this document '*Salvia divinorum*' includes the herb as well as  
its active constituents.

- 2 -

HPFB could classify *Salvia*, used for therapeutic purposes, as a Schedule F substance, since it meets Schedule F criteria A, C, and H (A- requirement for direct practitioner supervision; C - potential or known undesirable or severe side effects at normal therapeutic dose; H - possesses a dependence or abuse potential that is likely to lead to harmful non-medicinal use). However, while such restriction would mitigate the health risks associated with *Salvia* when used as a health product, it would not address the health and safety risks associated with *Salvia*'s use as a recreational substance. Additionally, the scheduling process involving submission to Canada Gazette (CG) Part I and II would take an average of 6 to 8 months. Given the current health risks identified, the case could be made that this issue should go directly to CG II, but this process would still take approximately 3 months. The issue of access to and use by the public would remain unaddressed over the scheduling process time interval. Additionally, it should be noted that the process of scheduling *Salvia* as a prescription substance would likely be impeded because *Salvia* is not currently market authorized in any form. As well, it is anticipated that there would be scientific and legal challenges associated with adding *Salvia* to Schedule F, similar to the challenges associated with providing qualifiers to the naturally sourced substances currently on Schedule F. Specifically, in the absence of product submissions or claims for *Salvia*, the minimum dosage required for a therapeutic effect is unknown, both for the different forms (raw herb, extract, tincture) and routes of administration (inhaled, sublingual). It should also be noted, that even if *Salvia* were to be a Schedule F substance, use of this substance would still be considered legal, and law enforcers would still have no grounds for carrying out compliance/enforcement actions among abusers.

The HRA classified the risk of using *Salvia* as a 'Type II' (e.g., there is a reasonable probability that the use of, or exposure to, a product, will cause moderate or mild adverse health consequences). According to the NHP Compliance Policy's risk-based approach, given the Type II risk, the Health Products and Food Branch Inspectorate (HPFBI) could request manufacturers of *Salvia* to stop-sale and recall their product. This, however, would require that HPFBI be notified about specific *Salvia* manufacturers. The Type II risk would also enable the Customs Border Services Agency (CBSA) to refuse *Salvia* importation, or those products containing the active constituents of *Salvia*. For this strategy to be somewhat effective, it would have to be decided that any *Salvia*, would be subject to compliance/enforcement actions, and not specifically *Salvia* bearing a health claim. This would enable CBSA to refuse bulk shipments of the raw herb, as well as HPFBI to seize *Salvia*, or those products containing the active constituents of *Salvia* from the retail level. However, this strategy would not prevent access to Internet sales of *Salvia*, and use of *Salvia* would still be considered a legal alternative to illicit drugs.

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- 3 -

Normally, in the case of a Type II health risk, HPFB would issue a public notice advising of the risk to health, HPFB's actions to mitigate this risk, and HPFB's recommendations to the public to mitigate the potential health risk. Again, HPFB would be restricted to communicating the risks associated with use of *Salvia* used for its therapeutic effects. Such an advisory would indicate that, because of its hallucinogenic properties, HPFB had taken steps to restrict *Salvia*'s use as a health product; such a message would also convey that use of the substance was not considered illegal. Communication of this sort would likely have a promotional effect by increasing the curiosity of *Salvia*'s main user population, into experiencing the effects of *Salvia*. This would likely result in more adolescents seeking out *Salvia* from its currently easy access.

It has been suggested that the four adverse reactions (ARs), reported to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP), comprise Health Canada's only solid evidence of *Salvia*'s risk as a street drug. However, it needs to be clarified that CADRMP is not the appropriate tool for monitoring the risk of a substance used recreationally; CADRMP is responsible for collecting and assessing adverse reaction reports for health products. As such, the reports concerning *Salvia divinorum* do not constitute true ARs because the suspect product in question was not used for its therapeutic use, but rather for recreational purposes. It is important to note, that there have been no reported ARs associated with *Salvia* use as a health product, either in Canada or internationally.

**Organization:**

Office of Controlled Substances (OCS, HECSB)

**Previous meeting (s):**

OCS convened a working group meeting (May 16, 2007) in response to requests from HPFB-ADMO. Proposed actions involving HPFB comprised of formulating a HRA (attached) to classify the health risk associated with *Salvia divinorum* when used as a health product in order to enable HPFBI compliance/enforcement actions, and public risk communications. Further consideration by HPFB directorates concluded that *Salvia divinorum* and its active constituents present a Type II health risk, making it subject to the risk-based compliance approach in accordance to the Compliance Policy for NHPs, and the HPFB Inspectorate and Enforcement Policy (POL-0001). This means that the Inspectorate can act against importation and retail sale. However, it should be noted that most sale of *Salvia divinorum* is on the street, not in the retail environment.

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- 4-

### **Recent Correspondence:**

June 6, 2007: (1) Jocelyn Kula (OCS) emailed the working group to confirm the action plan. (2) Jenna Griffiths (MHPD) advised Jocelyn that certain components of the plan had been drafted e.g., Issue Summary, HRA. However, there were issues concerning the public communication aspect, and Neil Yeates would communicate with Susan Fletcher about the file, over the coming weeks.

### **Consultation(s):**

MHPD has consulted with NHPD, HPFBI, and the Therapeutic Products Directorate (TPD) on the draft HRA, Briefing Note, and Speaking Points. The concerns expressed have been incorporated.

### **CONSIDERATIONS:**

*Salvia divinorum* (and its constituents) is a substance with hallucinogenic properties, which is subject to abuse primarily among adolescents and young adults. Since it is not restricted in Canada, *Salvia* and its active constituents are touted as a legal herbal alternative to illicit drugs. Currently, HPFBI has the authorization to remove this product from retail sales and stop importation of the product into Canada. However, the majority of *Salvia divinorum* sold in Canada is done so illicitly, and would not be captured by compliance activity conducted by the Inspectorate. The CBSA does not refuse bulk importations of the raw herb, and law enforcers cannot charge abusers of the substance, due to their lack of regulatory capacity. As a result, *Salvia* is widely accessible to Canadians in retail outlets and via the Internet, and harmful incidents involving *Salvia*'s effects including psychotic symptoms and driving under its influence occur without imposed legal boundaries. Various countries and states in the US have categorized *Salvia* as a controlled substance. Although HECSB believes that HPFB can most efficiently mitigate the health risk associated with *Salvia* use, it is HPFB's opinion that any actions taken by HPFB to communicate *Salvia*'s health risk or to restrict *Salvia*'s use would not appropriately address the safety issues inherent in *Salvia*'s abuse as a street drug.

### **Meeting Strategy:**

This is an opportunity to share information concerning HPFB's limited capacity to address the health and safety risks associated with *Salvia divinorum*. HPFB's risk mitigation and communication strategies are restricted to addressing health risks associated with therapeutic use of health products. Given that NHPD has received no submissions for *Salvia divinorum*, HPFB has no evidence to suggest that *Salvia*

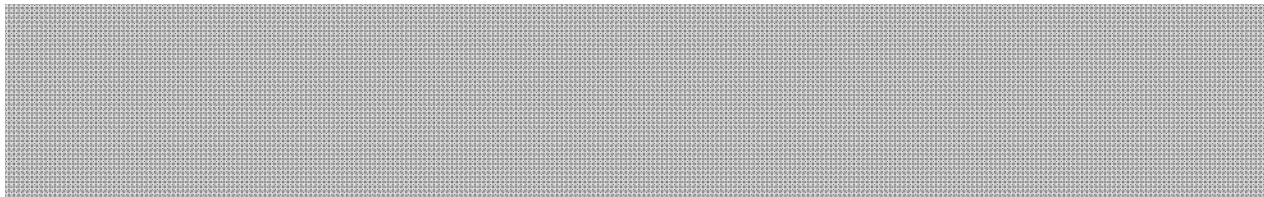
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s.21(1)(b)

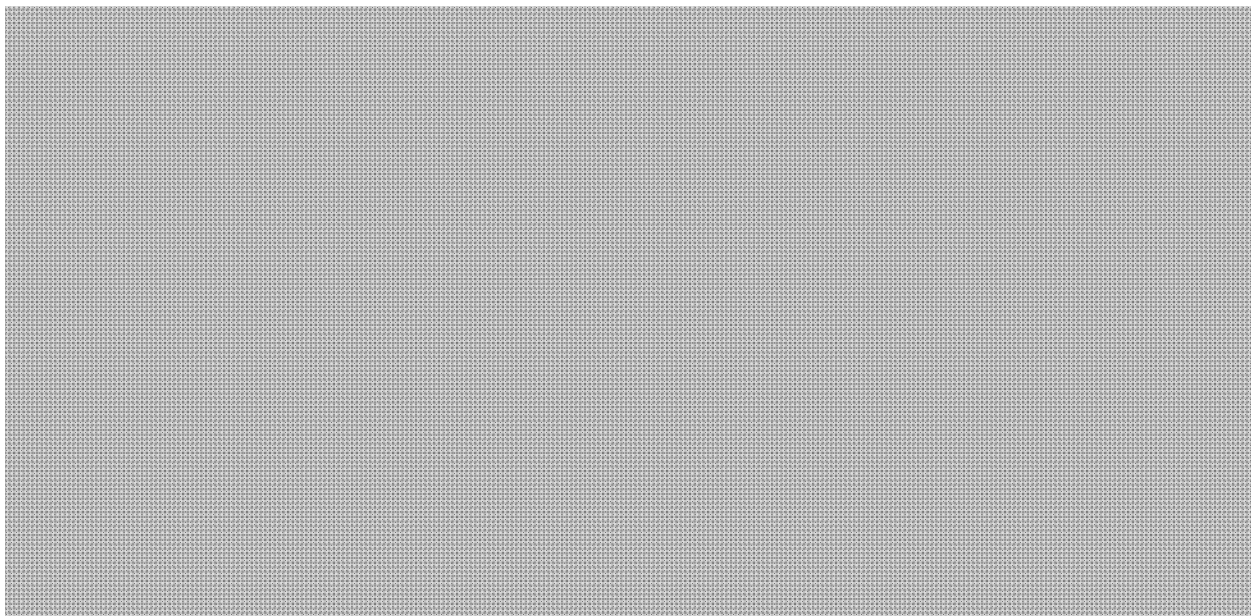
-5-

*divinorum* is currently used for its therapeutic potential. Additionally, there have been no documented ARs associated with *Salvia* when used for therapeutic purposes. As such, HPFB cannot effectively contribute to restricting *Salvia*'s use as a substance of abuse, nor communicate the potential risks associated with *Salvia*'s use as a health product.

**Proposal(s)/Issue(s):**



**CONCLUSIONS/NEXT STEP(S):**



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Attachment(s): APPENDIX A - MHPD Health Risk Assessment  
APPENDIX B - NHPD Casualty Assessments of Adverse Reactions  
APPENDIX C - MHPD/NHPD Issue Anlysis Summary

**FOR INFORMATION**

07-119974-627

**BRIEFING NOTE**

Regulatory Status of *Salvia divinorum* in Canada

**ISSUE:**

To provide you with further information about the regulatory status of *Salvia divinorum*, further to correspondence from Patricia Davidson, M.P for Sarnia-Lambton (CPC).

**BACKGROUND:**

*Salvia divinorum* is a species of sage belonging to the mint family that is chewed or smoked in order to induce its drug-like effects. These effects, which are reported to include out-of-body experiences, hallucinations, unconsciousness and short-term memory loss, are short-acting in nature. Despite its use in Mexico as a traditional medicine in the treatment of such varied conditions as diarrhoea, constipation, anaemia, headache, rheumatism and alcohol addiction, there are no approved medical uses for *Salvia divinorum* in Canada, and it is not currently marketed as a health product.

While limited clinical studies have indicated that *Salvia divinorum* may be of clinical interest in the treatment of depression, substance abuse, and pain, its mechanism of action is still not fully understood<sup>1</sup>. Though some studies have claimed that its psychotropic effects resemble those induced by other drugs such as LSD, phencyclidine, or ketamine, *Salvia divinorum* is structurally different from other naturally occurring hallucinogens and affects the brain in a way that is quite different from heroin or LSD. It has also been reported as producing a quite unpleasant high, leaving some users with sensations of introversion and feelings of anxiety.

**CURRENT STATUS:**

At the present time, neither the plant *Salvia divinorum*, nor its active ingredient

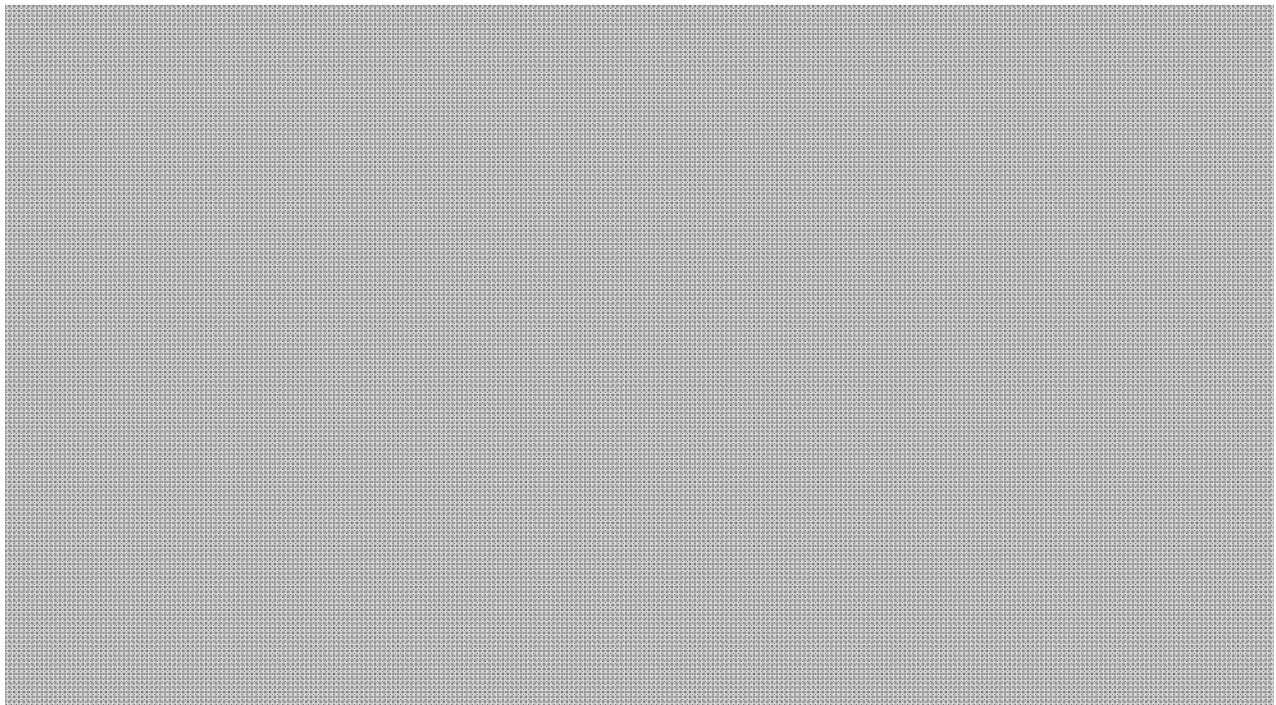
.../2

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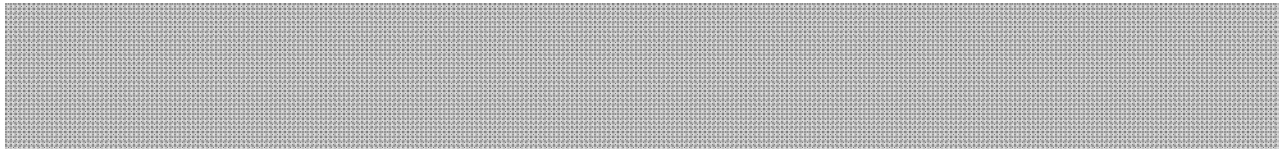
<sup>1</sup>Marketed Health Products Directorate and Natural Health Products Directorate. *Health Risk Assessment of Salvia divinorum as a Health Product*. Ottawa: Health Canada. June 2007.

Salvinorin A, are regulated as controlled substances under the *Controlled Drugs and Substances Act* (CDSA), nor are they regulated under the *Controlled Substances Act* in the United States<sup>2</sup>.

*Salvia divinorum* is not listed under the United Nations Drug Control Conventions and only a few countries (Australia, Denmark, Sweden, Italy, Spain, Belgium, Finland and South Korea) have taken steps to control its import and/or sale. Finally, *Salvia divinorum* cannot be considered to be a natural health product (NHP) unless it were to be manufactured, sold, or represented as an NHP (where a health claim is clear representation as an NHP), in which case it would be subject to the *Natural Health Products Regulations*.




**CONCLUSION:**



.../3

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<sup>2</sup>Certain individual states have taken steps to restrict the use and/or sale of *Salvia divinorum* but it is not regulated as a controlled substance at the national level.



Branch Head/RDG: Andrew Adams  
Telephone: 613-946-6484

Contact: Jocelyn Kula  
Telephone: 613-946-0125

Originator: Erin Kingdom  
Telephone: 613-948-8948



**Page(s) 000363 to\à 000368**

**Is(Are) exempted pursuant to section(s)  
est(sont) exemptée(s) en vertu de(s)(l')article(s)**

**21(1)(a), 21(1)(b)**

**of the Access to Information Act  
de la Loi sur l'accès à l'information**

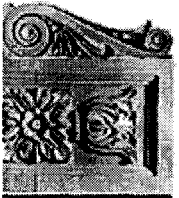


**Jocelyn Kula/HC-SC/GC/CA**  
2008-02-06 09:27 AM

To Jenifer Collette/HC-SC/GC/CA@HWC  
cc Carmen Berube/HC-SC/GC/CA@HWC, Tiana Branch/HC-SC/GC/CA@HWC, Jocelyn Kula/HC-SC/GC/CA@HWC  
bcc  
Subject Fw: VERY URGENT!!! Fw: QP REQUEST - Fw: QP Note on DRUGS - SALVIA DIVINORUM

---

Jocelyn Kula  
A/Manager, Policy and Regulatory Affairs Division  
Office of Controlled Substances  
Healthy Environments and Consumer Safety Branch  
Health Canada  
Tel: (613) 946-0125 Fax: (613) 946-4224  
----- Forwarded by Jocelyn Kula/HC-SC/GC/CA on 2008-02-06 09:10 AM -----



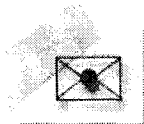
**Carmen Berube/HC-SC/GC/CA**  
2008-02-06 09:08 AM

To Jocelyn Kula/HC-SC/GC/CA@HWC, Tiana Branch/HC-SC/GC/CA@HWC, Isabel Shanahan/HC-SC/GC/CA@HWC  
cc  
Subject Fw: VERY URGENT!!! Fw: QP REQUEST - Fw: QP Note on DRUGS - SALVIA DIVINORUM

Here is the HPFB note.

Carmen

----- Forwarded by Carmen Berube/HC-SC/GC/CA on 2008-02-06 09:07 AM -----



**Helene Landers/HC-SC/GC/CA**  
2008-02-06 09:07 AM

To Paula Robert/HC-SC/GC/CA@HWC  
cc Carmen Berube/HC-SC/GC/CA@HWC, Geoff Barrett/HC-SC/GC/CA@HWC  
Subject Fw: VERY URGENT!!! Fw: QP REQUEST - Fw: QP Note on DRUGS - SALVIA DIVINORUM

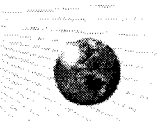
Bonjour Paula,

As discussed please find attached below the note prepared by HPFB, please add your input in red and return to me a.s.a.p

Thank you

---

Hélène Landers  
Tel: 613-952-3684/ Fax: 613-946-6666  
----- Forwarded by Helene Landers/HC-SC/GC/CA on 2008-02-06 09:01 AM -----



**Kathleen Lafleur/HC-SC/GC/CA**  
2008-02-06 08:54 AM

To Patrice Milord/HC-SC/GC/CA@HWC, Helene Landers/HC-SC/GC/CA@HWC  
cc Carole Bouchard/HC-SC/GC/CA@HWC, Jocelyn



Kula/HC-SC/GC/CA@HWC, Kyra  
Paterson/HC-SC/GC/CA@HWC, Nancy  
Richards/HC-SC/GC/CA@HWC, Robin  
Marles/HC-SC/GC/CA@HWC, Scott  
Jordan/HC-SC/GC/CA@HWC, Jenna  
Griffiths/HC-SC/GC/CA@HWC, Andrea  
MacTavish/HC-SC/GC/CA@HWC, MHPD\_DPSC DGO  
Assistants, Joan Kennedy/HC-SC/GC/CA@HWC, Marianne  
DeVito/HC-SC/GC/CA@HWC  
Subject VERY URGENT!!! Fw: QP REQUEST - Fw: QP Note on  
DRUGS - SALVIA DIVINORUM

Hi

On behalf of Dr. Scott Jordan, could you please review the anticipated QP note hereunder and send your comments to Scott asap. Please be advised that we need your input by 9:15, so that we can get this to our DGO by 9:30.

Thank you,

Kathleen Lafleur  
Administrative Assistant / Adjoint  
Marketed Biologicals, Biotechnology & Natural Health Products Bureau  
Bureau des produits biologiques, biotechnologiques et de santé naturels commercialisés  
(ph) 613 - 948-6011 - (fax) 613 - 954-2354

----- Forwarded by Kathleen Lafleur/HC-SC/GC/CA on 2008-02-06 08:48 AM -----

Scott Jordan/HC-SC/GC/CA

2008-02-06 08:41 AM



To Kathleen Lafleur/HC-SC/GC/CA@HWC

cc Jenna Griffiths/HC-SC/GC/CA@HWC, Shahid  
Perwaiz/HC-SC/GC/CA@HWC, Andrea  
MacTavish/HC-SC/GC/CA@HWC, MBBNHPB Support Staff

Subject

Hi Kathleen.

For forwarding to HECS and NHPD, for comments. Please let them know we need their input by 9:15, so that we can get this to our DGO by 9:30.

Thanks!

- Scott.

----- Forwarded by Scott Jordan/HC-SC/GC/CA on 2008-02-06 08:40 AM -----

\* Indicates a Mandatory Field/ Indique un champ obligatoire

*Working Draft / Document de travail*

QUESTION PERIOD NOTE  
NOTES POUR LA PÉRIODE DE QUESTIONS

Classification: HPFB PROTECTED/PROTÉGÉ DGPSA

000370

\*  Anticipatory/Anticipée  Requested/Demandée

## \*SUBJECT - SUJET

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

## MEDIA ANALYSIS - ANALYSE DES MÉDIAS

English:

~~Salvia divinorum, a herb which belongs to the mint family, is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating these reports in light of the risks of Salvia divinorum to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.~~ **USE MEDIA ANALYSIS PROVIDED BY PRO THIS MORNING**

## \*ANTICIPATED QUESTION - QUESTION PRÉVUE

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de Salvia divinorum?

## KEY MESSAGES - MESSAGES CLÉS

A Key Message must not be longer than 300 characters (350 for French text) per bullet and a maximum of 4 bullets. Les messages clés ne devraient pas dépasser 300 caractères (350 pour le texte français) par point et un maximum de 4 points.

English:

Bullet 1:

- ~~Salvia divinorum is not authorized for sale in Canada, but meets the definition of a natural health product. As such, its importation and sale could be restricted under the Food and Drugs Act. To be authorized for sale, products are required to be~~

~~assessed for safety, quality and effectiveness.~~ While *Salvia divinorum* meets the definition of a natural health product, Health Canada has not yet elected to take compliance actions under the *Food and Drugs Act* or its Regulations. Health Canada has also not yet decided to regulate *Salvia divinorum* under the *Controlled Drugs and Substances Act* .

Bullet 2:

- Health Canada is currently collecting information about the plant and its active ingredient, Salvinorin A from national and international sources, and assessing the risk that the unrestricted sale of the plant poses to Canadians, including its abuse and dependence potential.

Bullet 3:

- If the information collected warrants further action, Health Canada will assess the potential for regulatory control, and take all necessary actions to safeguard Canadians from potential risks from *Salvia*. These actions may include public risk communications or ~~restriction of availability and use.~~ imposing restrictions over its sale and use.

Bullet 4:

.

Français:

Point 1:

●

Point 2:

●

Point 3:

●

Point 4:

---

#### SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

English:

Français:

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## BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious  $\kappa$ -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations* that would remove it from the purview of the *Natural Health Products Regulations*. In addition, although *Salvia divinorum* meets the definition of a natural health product, Health Canada has not yet elected to take compliance actions under the *Food and Drugs Act* or its Regulations.

Similarly, in the United States, *Salvia Divinorum* is not included-regulated under the in their *Controlled Substances Act*, although it is included on the Drug Enforcement Administration Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few other jurisdictions. countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, it is illegal to the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and as both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. Other jurisdictions that have placed controls on *Salvia* are Finland, Denmark and Norway. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

### Current Situation in Canada

As of December, 2007, the Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year old female, 56 year old female, 28 year old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16-year-old male, with reported adverse reactions of psychosis and amnesia which were

~~considered to be serious and required medical intervention.~~

~~Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. While *Salvia divinorum* meets the definition of a Natural Health Product (NHP), no products have been authorized by Health Canada, and *Salvia divinorum* does not appear to be sold as a "health product." Also, proposed use as a recreational substance would not be permitted under the *NHP Regulations*. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on its list of substances of concern. their list of substances to monitor. As part of this action, the OCS has placed *Salvia divinorum* on their 'watch list', meaning, they will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and international regulatory status as monitored by MHPD. Additionally, If the information collected warrants further action, the OCS will may assess *Salvia divinorum* against for scheduling under the *Controlled Drugs and Substances Act* (CDSA) these criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:~~

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

~~Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.~~


**ATTACHMENTS / PIÈCE(S)-JOINTE(S)**


**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13

**\* HECS-OCS was consulted on this QP - Oct 11, 2006**

**Contact Information / Personnes-Ressource**

*Primary/Primaire: Joan Kennedy	*Telephone/Téléphone: xxx-xxxx-xxxx Mobile/Cellulaire:	Approved by/Approuvé par: Dr. Chris Turner  Title/Titre:	Telephone/Téléphone: 613-941-8889 Mobile/Cellulaire:
------------------------------------	--	--	--

		Director General	
<b>Secondary/Secondaire:</b>	<b>Telephone/Téléphone:</b>		
	<b>Mobile/Cellulaire:</b>		

**\*Date Prepared/**

Date préparé: 2008-02-05

**\*Director-Contact/  
Directeur-personne  
ressource:**

Hans Yu

**\*Phone Number/  
Téléphone:** 613-952-8301**\*Directorate & Bureau/  
Direction et bureau:****Contact Signed/  
Signature par la  
personne-ressource:****Date Signed/ Date signé:**

Date format: yyyy-mm-dd

Date will be entered automatically when signed and saved.

**D.G. Approved/****Approuvé par le DG:****Approved by/ Approuvé par:** Dr. Chris Turner**Date D.G. Approved/****Date de l'approbation du DG:**

Date format: yyyy-mm-dd

Date will be entered automatically when verified and saved/ La date s'inscrira au moment de la signature et de la sauvegarde.

**\*Directorates/ Directions:**

Marketed Health Products Directorate/Direction des Produits de Santé Commercialisés

**ADM Approved/****Approbation par le SMA :**

Neil Yeates - HPFB/DGPSA (957-1804)

**Branches/****Directions générale:**

HPFB/ DGPSA

**Departments/ Ministères:**

Health Canada / Santé Canada

**Edit History:**

Scott Jordan

Feb 6, 2008 - 08:10:09 AM

Updating

**Created By:** Joan Kennedy/HC-SC/GC/CA**Date Created:** February 5, 2008**Modified By:** Scott Jordan/HC-SC/GC/CA**Date Modified:** February 6, 2008



Carmen  
Berube/HC-SC/GC/CA  
2008-02-29 08:08 AM

To Daniel Galarneau/HC-SC/GC/CA@HWC, Brad  
Shapansky/HC-SC/GC/CA@HWC, Jenifer  
Collette/HC-SC/GC/CA@HWC

cc

bcc

Subject Fw: Salvia Divinorum

Do we have anything to add to this QP?

Since it's Friday, this note must be prepared and sent to DGO at 8:45 AM.

Carmen

----- Forwarded by Carmen Berube/HC-SC/GC/CA on 2008-02-29 08:06 AM -----

Helene  
Landers/HC-SC/GC/CA  
2008-02-29 07:56 AM

To Bronwyn Cline/HC-SC/GC/CA@HWC,  
HECS\_DSCS\_Directors, HECS\_DSCS\_Directors\_cc, Ray  
Edwards/HC-SC/GC/CA@HWC, Stephanie  
Mitchell/HC-SC/GC/CA@HWC, Stephanie  
Szick/HC-SC/GC/CA@HWC

cc Christine von Arx/HC-SC/GC/CA@HWC, Denis  
Arsenault/HC-SC/GC/CA@HWC, Geoff  
Barrett/HC-SC/GC/CA@HWC, Heidi  
Jackson/HC-SC/GC/CA@HWC

Subject Salvia Divinorum

As per my previous email, please see the note below that we prepared in collaboration with HPFB. Merci

Hélène Landers  
Tel: 613-952-3684/ Fax: 613-946-6666

## ADVICE TO THE MINISTER

English:

### DRUGS - SALVIA DIVINORUM

Français:

### DROGUES - SALVIA DIVINORUM

#### MEDIA ANALYSIS / ANALYSE DES MÉDIAS

English:

Media interest in Salvia divinorum is recurrent. To date questions around this substance have always been about its legality and what, if any, regulatory actions Health Canada is taking. There have been several reports from scientific and media sources, that indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties.

#### ANTICIPATED QUESTION / QUESTION PRÉVUE

English:

What is Health Canada doing to protect Canadians from the potential adverse effects

associated with the use of *Salvia divinorum*?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de *Salvia divinorum*?

**KEY MESSAGES / MESSAGES CLÉS**

English:

- The importation and sale of *Salvia divinorum* could either be restricted under the *Food and Drugs Act* or the *Controlled Drugs and Substances Act*. Health Canada is currently discussing the issue of *Salvia divinorum* and will take appropriate action.
- My Department is currently collecting information about the plant and its active ingredient, Salvinorin A from national and international sources, and assessing the risk that the unrestricted sale of the plant poses to Canadians, including its abuse and dependence potential.
- If the information collected warrants further action, we will take all necessary actions to safeguard Canadians from potential risks from *Salvia*. These actions may include public risk communications or imposing restrictions over its sale and use.

Français:

- L'importation et la vente de *Salvia divinorum* pourraient être contrôlées en vertu de la *Loi sur les aliments et drogues* ou de la *Loi réglementant certaines drogues et autres substances*. Santé Canada étudie actuellement ce dossier et prendra les mesures qui s'imposent.
- Santé Canada recueille actuellement de l'information de source canadienne et étrangère sur cette plante et son ingrédient actif, la salvinorine A. Il évalue également les risques, notamment le

potentiel d'abus et de dépendance, que la vente non contrôlée de la plante présente pour les Canadiens.

- S'il juge qu'il doit intervenir d'après l'information qu'il a obtenue, SC prendra toutes les mesures qui s'imposent pour protéger la santé des Canadiens contre les risques potentiels de *Salvia divinorum* . Il pourrait notamment communiquer au public de l'information sur les risques associés à cette plante ou en contrôler la vente et l'utilisation.

---

**SUPPLEMENTARY MESSAGES / MESSAGES SUPPLÉMENTAIRES**

English:

Français:

---

## BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious *kappa*-opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*. In addition, although *Salvia divinorum* meets the definition of a natural health product, Health Canada has not yet elected to take compliance actions under the *Food and Drugs Act* or its Regulations.

Similarly, in the United States, *Salvia Divinorum* is not regulated under the *Controlled Substances Act*, although it is included on the Drug Enforcement Administration list of Chemicals and Substances of Concern. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few other jurisdictions. In Australia, it is illegal to possess *Salvia divinorum* as both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. Other jurisdictions that have placed controls on *Salvia* are Finland, Denmark and Norway.

### Current Situation in Canada

As of December, 2007, the Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

While *Salvia divinorum* meets the definition of a Natural Health Product (NHP), no products have been authorized by Health Canada, and *Salvia divinorum* does not appear to be sold as a "health product." *Salvia divinorum* could also be scheduled under the *Controlled Drugs and Substances Act*; however, more information and analysis is required. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within

the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on its list of substances of concern.—If the information collected warrants further action, the OCS may assess *Salvia divinorum* against for scheduling under the *Controlled Drugs and Substances Act* (CDSA) these criteria used for adding substances to the appropriate schedules of the CDSA. These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

\*Date Received: 10-JAN-05 Inquiry : N Incident Nature: VENUE PSN - RISQUE A LA SANTE  
 Source: C CONSUMER COMPLAINT Source System Id: N/A  
 REPORTED?: \*ILLNESS: N \*ALLERGY: N \*SABOTAGE/TAMPER: N \*Summary: N FOR PICK-UP?: \*SPECIMEN: N

Inc. Type: D DRUGS  
 Priority : REGULAR  
 Opened by : STEPHANE GELINAS

PART A. CLIENT INFORMATION: ID #:

Correspondence : FRENCH

Type	Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
R							CANADA

PART B. PRODUCT INFORMATION

Code	Product Name	Brand Name	Size	Lot#	Purchased
ZZZZ	UNKNOWN	SALVIA DIVINORUM	SACHET	n/a	n/a

Common Name	Distribution	DIN/GP	MAN PROD NO.	Model#	Serial#	Lot Size
SALVINORIN A	N/A			N/A	N/A	N/A

UPC	Expiry Date
N/A	N/A

Enterprise associated with the product

V VENDOR/RETAILER

Type	Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
B							CANADA

ACTION(S) TAKEN

Product	Enterprise	Action Date/Comment	Code Compliance Action	Depth Of Recall	Effectiveness
ZZZZ	9092	03-NOV-05 achat echantillon	F Specimen	NA NOT APPLICABLE	NA NOT APPLICABLE

Enterprise associated with the product

V VENDOR/RETAILER

Type	Address	City	Post/Zip Code	Phone	Fax	Province/State	Country
B							CANADA

ACTION(S) TAKEN

Product	Enterprise	Action Date/Comment	Code Compliance Action	Depth Of Recall	Effectiveness
---------	------------	---------------------	------------------------	-----------------	---------------

INCIDENT STATUS HISTORY

Code	Status	Effective Date	Expiry Date	User Name
OP	OPEN INCIDENT	10-JAN-05	18-FEB-05	STEPHANE GELINAS
IA	INVESTIGATOR ASSIGNED	18-FEB-05	30-NOV-05	STEPHANE GELINAS
CL	CLOSE INCIDENT	13-JAN-06	13-JAN-06	F. MEN

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REPORT ISR51

Incident number: 4 625

INCIDENT TEXT

03-MAY-05 09:07:21 O OPEN INCIDENT STEPHANE GELINAS

10-Jan-05: Ouverture incident

L'inspectorat a reçu une plainte téléphonique de la part de Mme [REDACTED]. Elle nous informe qu'elle et sa mere ont vu la semaine precedente, une emission a TQS-Quebec qui parlait de la Salvia Divinorum comme etant benefique contre les chaleurs provoques par la menopause mais qui aurait aussi des proprietes hallucinogenes.

Le vendredi 7 janvier 2005, sa mere, [REDACTED] a achete le produit pour verifier ses effets. Elle s'est rendue a la boutique [REDACTED] au [REDACTED] a [REDACTED]. Elle a demande a la vendeuse si elle pouvait avoir de la Salvia. La vendeuse lui a dit qu'elle avait de la Salvia "forte", "moyenne" et "douce". Elle a demande a avoir 4 sachets de force "moyenne". La vendeuse a pris les sachets derriere son comptoir. Les sachets sont identifies comme etant de [REDACTED].

Il n'y aucune mention de Salvia Divinorum sur l'etiquette du sachet, ni aucune reclame. [REDACTED] et leurs conjoints ont fume le produit a l'aide d'une pipe a hasch. [REDACTED] n'aurait pris qu'une seule inhalation. Tous auraient eu des reactions adverses importantes. Aucune des quatre personnes n'a consulte un medecin. Etant donne qu'ils ont fume les quatre sachets, elle ne peut nous fournir d'echantillon, ni l'emballage.

Sa mere [REDACTED] aurait communique avec TQS-Quebec pour les informer de la vente de ce produit qu'elle considere dangereux. Elle leur aurait montre les sachets vides.

[REDACTED] a une autre succursale situee au [REDACTED].

Mme [REDACTED] a ete avise de communiquer avec le Bureau des reactions indesirables de Sante Canada pour rapporter cet incident.

03-MAY-05 09:07:43 I INVESTIGATIVE STEPHANE GELINAS

20-AVR-05: Recherche sur site Web

L'Inspectorat du Centre Operationnel du Quebec a deja refuse une importation commerciale de 100 Kg de Salvia Divinorum destinee a [REDACTED] sise au [REDACTED].

Une recherche a l'aide du site WhitePages.com, en utilisant cette adresse, nous donne le nom de [REDACTED].

Une seconde recherche sur le site de CIDREQ, en utilisant le nom de [REDACTED] nous donne le nom de [REDACTED] comme etant l'actionnaire majoritaire des 2 etablissements de [REDACTED] de la region de [REDACTED] soit: [REDACTED].

03-MAY-05 09:07:59 I INVESTIGATIVE STEPHANE GELINAS

25-AVR-05: Courriel a Jenny et Marie

J'ai envoye un courriel a Jenny McLaughlin et Maire Morrisey afin de savoir si une evaluation du danger a la sante (HHE) a ete faite et si oui, quel etait le niveau de risque. Une demande de classification du produit a ete faite le 26 mai 2004 et la Salvia Divinorum ainsi que son principe actif Salvinorin A sont classifies comme etant un PSN.

03-MAY-05 09:08:12 I INVESTIGATIVE STEPHANE GELINAS

02-Mai-05: Reponse de Jenny

Jenny m'a repondu par courriel et m'avise qu'il n'y a pas eu de HHE de fait.

30-NOV-05 03:54:34 I INVESTIGATIVE STEPHANE GELINAS

06-Mai-05: BSC avise

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## INCIDENT STATUS HISTORY

Code	Status	Effective Date	Expiry Date	User Name
RV	REVIEW	13-JAN-06	13-JAN-06	F. MENARD

## WORK ASSIGNMENT INFORMATION

Reg/Dis	Started	Completed	Work Spec Code	Gm Unit	Negotiated Unit	Time	Region	Organizational Unit
M IV	12-JAN-05	13-JAN-06	DDOC	DILA			QUEBEC	INVESTIGATIONS UNIT

Type	User Name	Date Assigned	Date Complete
I	STEPHANE GELINAS	18-FEB-05	30-NOV-05

000383



REPORT ISRS1

Incident number: 4 626

INCIDENT TEXT

Jenny a rapporte au Bureau des Substances Controlees (BSC OCS) a Ottawa que le centre operationnel du Quebec a ete informe de la vente de Salvia Divinorum dans 2 boutiques de la ville de [REDACTED]

30-NOV-05 03:57:03 I INVESTIGATIVE STEPHANE GELINAS

11-Mai-05: Courriel de Jenny  
Jenny nous informe qu'elle veut organiser une rencontre avec BSC/Inspectorat/NHPD et Services legaux pour determiner comment le produit devrait etre reglemente et les actions appropriees a prendre dans ce dossier.

30-NOV-05 03:57:17 I INVESTIGATIVE STEPHANE GELINAS

08-Sep-05: Courriel a Jenny  
J'ai envoye un courriel a Jenny pour savoir s'il y a du nouveau dans ce dossier.  
Jenny m'informe qu'il n'y a pas de mis a jour pour le statut de la Salvia Divinorum. Cependant, BSC / OCS a place la Salvia Divinorum sur sa "Watch list" et suit de pres l'utilisation de la Salvia au Canada.

30-NOV-05 03:57:33 I INVESTIGATIVE STEPHANE GELINAS

03-Nov-05: Achat de Salvia  
Le 3 novembre 2005, j'ai fait un achat incognito de Salvia Divinorum a [REDACTED] situee au [REDACTED] Apres avoir demande s'il avait de la Salvia a vendre, le prepose au comptoir m'a demande si je voulais de la 5X, 10X, 15X ou 20X et quel poids que je desirais. J'ai demande au prepose de m'expliquer ce que veut dire 5X, par exemple. Il m'a repondu que la 5X est 5 fois plus forte que la plante mere qui est consideree 1X.  
Le prepose m'a indique que 0,1 gramme de Salvia equivaut a 1 "trip" et que je devais essayer la 5X ou 10X mais pas plus fort que ca puisque c'est la premiere fois que je vais l'essayer. Il m'a mentionne que la matiere premiere est importee du Mexique. Rendu au [REDACTED] il extrait le principe actif de la plante et l'ajoute a des feuilles sechees de la plante qui sert de substrat.  
J'ai procede a l'achat de 0,1 gramme de Salvia 5X au cout de 5,00 dollars (taxable) et de 0,1 gramme de Salvia 10X au cout de 10,00 dollars (taxable).  
Sur le coupon de caisse, il est indique "Encens". Sur l'etiquette des sachets, il est indique: <<Salvia Divinorum Encens naturel non destinee a la consommation / Not for human consumption>>. Une adresse internet est egalement indiquee sur l'etiquette du produit: [REDACTED]

30-NOV-05 03:57:50 G GENERAL STEPHANE GELINAS

30-Nov-05: Fermeture dossier  
Puisque que la Salvia Divinorum rencontre seulement la partie "substance" de la definition d'un produit de sante naturel (la partie "fonction" n'est pas rencontree puisque "hallucinogene" n'est pas acceptable pour un PSN), que le Bureau des substances controlees a ete avise du fait de la vente de Salvia dans la region de la [REDACTED] que le BSC a place la substance sur sa "watch list", que la Salvia n'est pas une substance controlee, et que le produit n'est pas represente pour consommation humaine et ne fait aucune reclame therapeutique, aucune autre action n'est jugee necessaire pour le moment dans ce dossier. La plaignante a ete avisee par courrier du resultat de sa plainte.

\*\*\*\*\* END OF REPORT ISRS1 \*\*\*\*\*

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QUESTION PERIOD NOTE  
NOTE POUR LA PÉRIODE DE QUESTIONS

Date: March 24, 2006  
Classification: HPFB PROTECTED/ PROTÉGÉ DGPSA

## **SUBJECT - SUJET**

English:

**SALVIA DIVINORUM, A PLANT WITH HALLUCINOGENIC PROPERTIES, IS BEING PROMOTED ON INTERNET SITES AS A LEGAL ALTERNATIVE TO STREET DRUGS**

## **MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Salvia divinorum, a plant which belongs to the mint family, is being widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating these reports in light of the risks of Salvia divinorum to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

## **ANTICIPATED QUESTION - QUESTION PRÉVUE**

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

## **KEY MESSAGES - MESSAGES CLÉS**

English:

- Health Canada is aware of the recent media reports and scientific publications which indicate the abuse potential of Salvia divinorum among adolescents and young adults, and is taking appropriate actions to manage this issue and mitigate any potential risk to Canadians.
- This action includes investigating the use of Salvia divinorum at the national and international level and taking any necessary steps to protect Canadians. These actions could result in

communicating information to Canadians on this plant or imposing more controls on its availability and use.

- Products containing *Salvia divinorum* have not been authorized for sale in Canada under the Food and Drug Regulations. Neither *Salvia Divinorum*, nor its main ingredient, Salvinorin A, are controlled under the United Nations Drug Control Conventions or in the United States.
- Four reports of adverse reactions involving *Salvia divinorum* or Salvinorin A as suspected agents have been reported to Health Canada, the three involving the plant were considered to be non serious, the fourth which involved tablets of Salvinorin A was serious.

Français:

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#### SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

English:

Français:

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#### BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, that is smoked as a hallucinogen. The main active ingredient of *Salvia divinorum* is salvinorin A. *Salvia divinorum* is being widely touted on Internet sites aimed at young adults and adolescents, as a "legal" alternative to street drugs. Salvinorin A is a highly efficacious *kappa* -opioid receptor agonist of clinical interest for treatment and etiological studies of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 g of purified salvinorin A, or 0.1 - 0.5 g of dried leaves of *Salvia divinorum*

were shown to produce intense psychoactive affects when inhaled.

In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug. The American Drug Enforcement Agency (DEA) has also placed *Salvia divinorum* on a list of drugs and chemicals "of concern," without legal implications.

A recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults.

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*, that would remove it from the purview of the *Natural Health Products Regulations*. The Canadian Adverse Drug Reaction Monitoring Program has received four reports of adverse reactions involving *Salvia divinorum* as a suspected agent, taken for its hallucinatory effects.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations, and will develop appropriate risk mitigation strategies, if deemed necessary, following consultation with other Directorates. In the meantime, the Office of Controlled Substances (OCS), which is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS will maintain a file on *Salvia divinorum* and will collect relevant information specific to this plant and its active constituents. If the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA).

These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

The Health Products and Food Branch and the Office of Controlled Substances (Healthy Environments and Consumer Safety branch) of Health Canada will continue to share relevant information concerning *Salvia divinorum* to determine whether it should be added to appropriate schedules under the *Controlled Drugs and Substances Act*.

Internationally, *Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled, to various degrees in a few countries. Australia and Denmark regard *Salvia*

*Divinorum* as a controlled substance, whereas in other countries *Salvia Divinorum* has been given prescription status. *Salvia Divinorum* is not included in the *Controlled Substances Act* in the United States although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern. Some states have put restrictions on its sale.

Health Canada has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum* . All the reported adverse reactions relate to neuro-psychological effects. Three cases (27 year old female, 56 year old female, 28 year old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects which were considered to be non serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablet and concomitant use of alcohol in a 16 year old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

**ATTACHMENTS / PIÈCE(S)-JOINTE(S)**  
 Hard copies of the media reports will be provided to the QP note coordinator

**Remarks/ Remarques:**

Bucheler R, Gleiter CH, Schworer P, Gaertner I. Use of nonprohibited hallucinogenic plants: increasing relevance for public health? A case report and literature review on the consumption of *Salvia divinorum* (Diviner's Sage). *Pharmacopsychiatry*. 2005 Jan;38(1):1-5.

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother*. Oct;39(10):1634-9. Epub 2005 Sep 13

Giroud C, Felber F, Augsburg M, Horisberger B, Rivier L, Mangin P. 2000. *Salvia divinorum* : an hallucinogenic mint which might become a new recreational drug in Switzerland. *Forensic Science International* 112: 143-150.

Prisinzano T E, 2005. Psychopharmacology of the hallucinogenic sage *Salvia divinorum*, Minireview. *Life Sciences* 78: 527-531.

National review of medicine, Nov. 15, 2005, [www.nationalreviewofmedicine.com/issue/2005/11\\_15/2\\_patients\\_practice06\\_19.html](http://www.nationalreviewofmedicine.com/issue/2005/11_15/2_patients_practice06_19.html)

Radio-Canada, Nov. 22, 2005, <http://radio-canada.ca/radio/sansfrontieres/66659.shtml>

Contact Information / Personnes-Ressource			
<b>Primary/Primaire:</b> Shahid Perwaiz	<b>Telephone/Téléphone:</b> (613) 948-8540 <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b> Dr. Chris Turner <b>Title/Titre:</b> Director General	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b> [REDACTED]
<b>Secondary/Secondaire:</b> Jenna Griffiths	<b>Telephone/Téléphone:</b> 946-6507 <b>Mobile/Cellulaire:</b>		

QUESTION PERIOD NOTE  
NOTE POUR LA PÉRIODE DE QUESTIONS

Date: October 11, 2006  
Classification: HPFB PROTECTED/ PROTÉGÉ DGPSA

## **SUBJECT - SUJET**

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

## **MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Salvia divinorum, a herb which belongs to the mint family, is widely promoted on various Internet sites as a legal alternative to illicit drugs of abuse. Health Canada has received four reports of adverse reactions associated with the use of Salvia divinorum. In addition, there have been several reports from scientific and media sources, which indicate that Salvia divinorum has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties. Health Canada is investigating these reports in light of the risks of Salvia divinorum to human health and safety. Depending on the outcome of this investigation, Health Canada will determine appropriate strategies to mitigate the risk.

## **ANTICIPATED QUESTION - QUESTION PRÉVUE**

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of Salvia divinorum?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de Salvia divinorum?

## **KEY MESSAGES - MESSAGES CLÉS**

English:

- Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level.
- *Salvia divinorum* has not been authorized for sale in Canada.
- Health Canada is assessing the potential for regulatory control of *Salvia divinorum* and will take necessary actions to safeguard Canadians against potential risks. These actions may include public risk communications, or imposing restrictions over its

## availability and use

Français:

Santé Canada surveille actuellement la tendance dans l'utilisation de *Salvia divinorum* à l'échelle nationale et internationale.

*Salvia divinorum* n'est pas autorisée pour la vente au Canada.

Santé Canada évalue s'il est possible de réglementer *Salvia divinorum* et prendra les mesures nécessaires pour protéger les Canadiens contre les risques éventuels. Santé Canada pourrait communiquer des renseignements au public sur les risques ou imposer des restrictions à sa disponibilité et à son utilisation.

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### SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

English:

Français:

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### BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious  $\kappa$ -opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*, nor any Schedule of the *Food and Drugs Act and Regulations*, that would remove it from the purview of the *Natural Health Products Regulations*.

Similarly, in the United States, *Salvia Divinorum* is not included in their *Controlled Substances Act*, although it is included on the Drug Enforcement Agency's list of Chemicals and Substances of Concern, but there are no legal implications of this classification. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few countries. Australia regards *Salvia Divinorum* as a controlled substance. In Australia, the possession of *Salvia divinorum* is illegal due to its unknown addictive potential and long term effects, and both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. In Europe, only Finland and Denmark have added *Salvia* to their list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of psychoactive drug.

#### Current Situation in Canada

The Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

Health Canada is currently monitoring the trend of *Salvia divinorum* use at the national and international level through MHPD's ongoing environmental scan of media and the Internet, as well as through contacts with other regulatory organizations. It should be noted that *Salvia divinorum* when used as a recreational substance, would not meet the functional definition of a Natural Health Product (NHP). Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on their list of substances to monitor. As part of this action, the OCS has placed *Salvia divinorum* on their 'watch list', meaning, they will collect relevant information specific to this herb and its active constituents. Such information will include adverse reaction reports and international regulatory status as monitored by MHPD. Additionally, if the information collected warrants further action, the OCS will assess *Salvia divinorum* against the criteria used for adding substances to the appropriate schedules of the *Controlled Drugs and Substances Act* (CDSA). These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;



- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. Ann Pharmacother. Oct;39(10):1634-9. Epub 2005 Sep 13

\* HECS-OCS was consulted on this QP - Oct 11, 2006

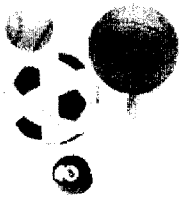
<b>Contact Information / Personnes-Ressource</b>			
<b>Primary/Primaire:</b> Dr. Shahid Perwaiz	<b>Telephone/Téléphone:</b> (613)-948-8540 <b>Mobile/Cellulaire:</b>	<b>Approved by/Approuvé par:</b> Dr. Chris Turner	<b>Telephone/Téléphone:</b> 613-941-8889 <b>Mobile/Cellulaire:</b>
<b>Secondary/Secondaire:</b> Dr. Jenna Griiffiths	<b>Telephone/Téléphone:</b> (613)-946-6507 <b>Mobile/Cellulaire:</b>	<b>Title/Titre:</b> Director General	

**Brenda Lajeunesse/HC-SC/GC/CA**  
2007-06-11 11:03 AM

To Jean Saint Pierre/HC-SC/GC/CA@HWC, Jenny McLaughlin/HC-SC/GC/CA@HWC  
cc Sharon Mullin/HC-SC/GC/CA@HWC, Chantal Stead/HC-SC/GC/CA@HWC, Jason Andrus/HC-SC/GC/CA@HWC, Annette  
bcc  
Subject Fw: URGENT - FOR CONSULTATION // Briefing Note and Speaking Points re: Salvia Divinorum

For your review and comments on draft briefing note prepared by MHPD - need to get back with DG approval by noon today. Thanks

----- Forwarded by Brenda Lajeunesse/HC-SC/GC/CA on 2007-06-11 11:00 AM -----



**Louise Carriere/HC-SC/GC/CA**  
2007-06-08 05:01 PM

To Philip Waddington/HC-SC/GC/CA@HWC, Supriya Sharma/HC-SC/GC/CA@HWC, Diana Douthwaite/HC-SC/GC/CA@HWC  
cc Helene Amyot/HC-SC/GC/CA@HWC, Joanne Regnier/HC-SC/GC/CA@HWC, TPD-DGO Corr/HC-SC/GC/CA@HWC, Brenda Lajeunesse/HC-SC/GC/CA@HWC, Brenda Barber/HC-SC/GC/CA@HWC, MHPD\_DPSC DGO Division, MBBNHPB Support Staff, MBBNHPB Management  
Subject URGENT - FOR CONSULTATION // Briefing Note and Speaking Points re: Salvia Divinorum

~ Sent on behalf of Dr. Chris Turner ~

**FOR CONSULTATION**

TO: NHPD  
TPD  
HPFBI

As requested by Dr. Chris Turner, DG of MHPD, **could you please review the attached draft Briefing Note and provide your input (in colour if any) and sign-off on the approval slip by sending to: MHPD DPSC DGO Assistants by noon, Monday June 11th.**

Sorry for the short turnaround on this one.



Approval Slip: AS\_07-113157-398.wpd



Briefing Note: 07-113157-398\_Salvia Briefing Note June 8.07.wpd  
(revised in DGO and saved on i:\corresp\Briefing Notes\MBBNHPB\....

Attachment: TO BE ATTACHED

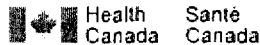


Speaking Points: Salvia Speaking points June8.07.wpd

Thank you.

Louise Carrière  
Director General's Office (DGO) / Bureau du directeur général (BDG)  
Marketed Health Products Directorate (MHPD) / Direction des produits de santé commercialisés (DPSC)  
A.L. 0701B / I.A. 0701B  
Tel / tél.: 613.948.6136 Fax / télécopieur: 613.952.7738

----- Forwarded by Louise Carriere/HC-SC/GC/CA on 2007-05-31 10:56 AM -----



**Health Products and Food Branch**  
**Direction générale des produits de la santé et des aliments**  
**ACTION REQUEST - DEMANDE D'ACTION**

\* Number - Numéro: AR/07-0188

\* MECS No.: 07-113157-398

* DIRECTORATE - DIRECTION <b>MHPD/DPSC</b>	* ATTENTION <b>Louise Carriere, Georgette Franklin</b>
---	---

c.c.: Heather Throop, Kathy A Young, Johanne Fortin, Jennifer-Anne McNeill, Pat Corbett, Marie Morrissey, Diane Laplante, Natalie Racine, Joan Kennedy, Tania Chevalier, Gretha Jean-Gilles, Brook Bertrand, Brenda Barber, Brenda Lajeunesse, Jenna Griffiths

* SUBJECT - OBJET <b>ADM requires Speaking Points for his discussion with Susan Fletcher re: Salvia Divinorum</b>
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* DEADLINE - ÉCHÉANCE <b>2007-06-07</b>	DEADLINE - ÉCHÉANCE <b>03:00 PM</b>
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* REQUESTED FORMAT - FORMAT DEMANDÉ <b>Talking Points/Points De Discussion</b>	DATE <b>2007-05-30</b>
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\* REQUEST - DEMANDE  
The ADM will be meeting with Susan Fletcher, ADM of HECS Branch, to discuss Salvia Divinorum, a substance which is not currently banned under the Controlled Drugs and Substances Act. The date and time for this meeting have yet to be determined.

To prepare the ADM for this meeting, please provide the following:

- Speaking Points (bullet form)



TEMPLATE - Speaking Points.wpd

- Briefing Note - For a Meeting (include background information and HPFB's concerns).

**Briefing Note - For a meeting**



Template: ADM's BRIEFING NOTE - MEETING\_eng.Guidelines:



ADM's Guidelines for BN for Mtg\_Apr\_2006

The ADM requires clear recommendations on the following questions:

- 1) What are the appropriate Next Steps on this file (who should have the lead on what, is it appropriate for HPFB to be leading this?)
- 2) Is an advisory the most appropriate risk communications tool?
- 3) Is CADRMP appropriate for this particular substance?

To assist you in the preparation of this request, we have attached a recent IAS (may not be the most updated version) and some draft background information. You may include these in the package if you deem it appropriate to do so.

Input must be gathered from NHPD, Inspectorate, and HPFB Communications, who have been c.c.'d on this Action Request.

REQUEST ORIGIN - ORIGINE DE LA DEMANDE

**Assistant Deputy Minister's Office/Bureau du Sous-ministre adjoint**

LANGUAGE - LANGUE

**English / Anglais**

BRANCH CONTACT - AGENT DE LIASON DE LA DIRECTION GÉNÉRALE

**Jonathan Loan**

TELEPHONE NUMBER - NUMÉRO DE TÉLÉPHONE

**(613) 957-6809**

COMMENTS - COMMENTAIRES



Salvia D.wpd



NHPD-MHPD Salvia IAS Nov 2006.doc

\* Status - Étape: **Active / Non complétée**

\* Priority - Priorité: **Regular (see date) / Régulière (voir date)**

## Speaking Points

### Salvia divinorum

Date:

Time:

Location:

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The ADM requires clear recommendations on the following questions:

- 1) What are the appropriate Next Steps on this file (who should have the lead on what, is it appropriate for HPFB to be leading this?)
- 2) Is an advisory the most appropriate risk communications tool?
- 3) Is CADRMP appropriate for monitoring the safety of this particular substance?



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<sup>1</sup>For the purpose of this document 'Salvia divinorum' includes the herb as well as its active constituents.



QUESTION PERIOD NOTE  
NOTE POUR LA PÉRIODE DE QUESTIONS

Date: February 6, 2008  
Classification: HPFB PROTECTED/ PROTÉGÉ DGPSA

## **SUBJECT - SUJET**

English:

**DRUGS - SALVIA DIVINORUM**

Français:

**DROGUES - SALVIA DIVINORUM**

## **MEDIA ANALYSIS - ANALYSE DES MÉDIAS**

English:

Media interest in *Salvia divinorum* is recurrent. To date questions around this substance have always been about its legality and what, if any, regulatory actions Health Canada is taking. There have been several reports from scientific and media sources, that indicate that *Salvia divinorum* has the potential for abuse, and is used by adolescents and young adults for its hallucinogenic properties.

## **ANTICIPATED QUESTION - QUESTION PRÉVUE**

English:

What is Health Canada doing to protect Canadians from the potential adverse effects associated with the use of *Salvia divinorum*?

Français:

Que fait Santé Canada pour protéger les Canadiens contre les effets indésirables associés à l'utilisation de *Salvia divinorum*?

## **KEY MESSAGES - MESSAGES CLÉS**

English:

- The importation and sale of *Salvia divinorum* could either be restricted under the *Food and Drugs Act* or the *Controlled Drugs and Substances Act*. Health Canada is currently discussing the issue of *Salvia divinorum* and will take appropriate action.
- Health Canada is currently collecting information about the plant and its active ingredient, Salvinorin A from national and international sources, and assessing the risk that the unrestricted sale of the plant poses to Canadians, including its abuse and dependence potential.

- If the information collected warrants further action, Health Canada will take all necessary actions to safeguard Canadians from potential risks from *Salvia*. These actions may include public risk communications or imposing restrictions over its sale and use.



Français:

- L'importation et la vente de *Salvia divinorum* pourraient être contrôlées en vertu de la *Loi sur les aliments et drogues* ou de la *Loi réglementant certaines drogues et autres substances*. Santé Canada étudie actuellement ce dossier et prendra les mesures qui s'imposent.
- Santé Canada recueille actuellement de l'information de source canadienne et étrangère sur cette plante et son ingrédient actif, la salvinorine A. Il évalue également les risques, notamment le potentiel d'abus et de dépendance, que la vente non contrôlée de la plante présente pour les Canadiens.
- S'il juge qu'il doit intervenir d'après l'information qu'il a obtenue, SC prendra toutes les mesures qui s'imposent pour protéger la santé des Canadiens contre les risques potentiels de *Salvia divinorum*. Il pourrait notamment communiquer au public de l'information sur les risques associés à cette plante ou en contrôler la vente et l'utilisation.

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SUPPLEMENTARY MESSAGES/ MESSAGES SUPPLÉMENTAIRES

English:

Français:



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## BACKGROUND / CONTEXTE

*Salvia divinorum* is a herb, native to Mexico, where it is traditionally smoked as a hallucinogen. *Salvia divinorum* is being widely touted on Internet sites, in various dosage forms, as a "legal" alternative to street drugs. In fact, a recently published article reported *Salvia divinorum* to be one of the most prevalently marketed herbal dietary supplements available for use as a legal alternative to illicit drugs of abuse, among adolescents and young adults (Dennehy et al., 2005). The main active ingredient of *Salvia divinorum* is salvinorin A. Salvinorin A is a highly efficacious *kappa*-opioid receptor agonist, and as such, this substance has been used to investigate the pharmacological contribution of this opioid system to the etiology of depression, dementia, bipolar disorder, and schizophrenia. A minimum dose of 200-500 mcg of purified salvinorin A, or inhalation of the smoke from 0.1 - 0.5 g of dried leaves of *Salvia divinorum* were shown to produce intense psychoactive affects when inhaled.

### Regulatory Control of *Salvia divinorum*

In Canada neither the herb, *Salvia divinorum*, nor its active ingredient salvinorin A, are listed in any Schedule to the *Controlled Drugs and Substances Act*. In addition, although *Salvia divinorum* meets the definition of a natural health product, Health Canada has not yet elected to take compliance actions under the *Food and Drugs Act* or its Regulations.

Similarly, in the United States, *Salvia Divinorum* is not regulated under the *Controlled Substances Act*, although it is included on the Drug Enforcement Administration list of Chemicals and Substances of Concern. Some states, however, have put restrictions on its sale.

*Salvia Divinorum* is not controlled under the United Nations Drug Conventions. It is controlled to various degrees in a few other jurisdictions. In Australia, it is illegal to possess *Salvia divinorum* as both the herb and its active constituents are listed on schedule 9 of Australia's Standard for the Uniform Schedule of Drugs & Poisons. Other jurisdictions that have placed controls on *Salvia* are Finland, Denmark and Norway.

### Current Situation in Canada

As of December, 2007, the Canadian Adverse Drug Reaction Monitoring Program within the Marketed Health Products Directorate (MHPD) has received four reports of adverse reactions (ARs) associated with *Salvia divinorum*, used for its hallucinatory effects. MHPD has conducted causality assessments on the four Canadian case reports associated with the use of *Salvia divinorum*. All the reported ARs relate to neuropsychological effects. Specifically, three cases (27 year-old female, 56 year-old female, 28 year-old male) were associated with inhalation of *Salvia divinorum* with reported brief hallucinogenic effects, which were considered to be non-serious reactions requiring no medical intervention. The fourth case was associated with the oral consumption of *Salvia divinorum* tablets and concomitant use of alcohol in a 16 year-old male, with reported adverse reactions of psychosis and amnesia which were considered to be serious and required medical intervention.

While *Salvia divinorum* meets the definition of a Natural Health Product (NHP), no products have been authorized by Health Canada, and *Salvia divinorum* does not appear to be sold as a "health product." *Salvia divinorum* could also be scheduled under the *Controlled Drugs and*

Substances Act; however, more information and analysis is required. Health Canada will develop appropriate risk mitigation strategies, if deemed necessary upon consultation between the Health Products and Food Branch and the Office of Controlled Substances (OCS), within the Healthy Environments and Consumer Safety Branch. OCS is responsible for developing legislation, regulations, policies and operations that support the control of illicit and controlled drugs and other substances in Canada, and has placed *Salvia divinorum* on its list of substances of concern. If the information collected warrants further action, the OCS may assess *Salvia divinorum* against for scheduling under the *Controlled Drugs and Substances Act* (CDSA) these criteria used for adding substances to the appropriate schedules of the CDSA. These criteria include:

- International requirements and trends in control/scheduling;
- Chemical and pharmacological similarity to other drugs listed in the CDSA;
- Dependence potential;
- Likelihood of abuse/misuse;
- Extent of abuse/misuse in Canada;
- Danger to public health and safety; and,
- Legitimate use in Canada

Health Canada will continue to actively monitor the trends of, and regulatory control over *Salvia divinorum* use at the national and international level, and will take appropriate risk mitigation actions as necessary.

<b>ATTACHMENTS / PIÈCE(S)-JOINTE(S)</b>

**Remarks/ Remarques:**

Dennehy CE, Tsourounis C, Miller AE. 2005. Evaluation of herbal dietary supplements marketed on the internet for recreational use. *Ann Pharmacother.* Oct;39(10):1634-9. Epub 2005 Sep 13

**\* HECS-OCS was consulted on this QP - Feb. 6, 2008**

Contact Information / Personnes-Ressource			
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