Study report

The Volcano® *Medic* cannabis vaporizer:

Effect of repeated use of a single filling

LabAssistent Phytochemical Services
Utrechtse Veer 12b
Leiden, The Netherlands

Partner of PRISNA BV
Product Isolation from Nature

PRISNA

Performed this study for:
Storz&Bickel GmbH
Tuttlingen
Germany

LabAssistent project #:
2009-003b

Study period:
December 2009-February 2010

This report has 33 pages, including this first page

Introduction

The "Volcano *Medic* vaporizer", by Storz & Bickel, will become the world's first officially approved medical cannabinoid inhaler. The device is designed to allow the inhaled administration of pure cannabinoids or cannabis extracts (liquids), as well as the smoke-free inhalation of cannabinoids present in cannabis flowers (plant material).

The earlier models, the non-medically approved Volcano *Classic* and Volcano *Digit* in combination with the Solid Valve filling chamber and balloon, have been evaluated in several clinical studies. The obtained results have given strong indications that the more advanced Volcano *Medic* will be capable of doing what it is designed for. However, the Volcano vaporizer as a medical device is the first of its kind, offering a new route of administration for cannabinoids in medicine. Due to the fact that there are no other devices quite like it, and the Volcano vaporizer offers a new mode of administration for cannabinoids in medicine, it is foreseeable and justified that questions will arise on how reliable and efficient the device is when used according to its operating manual. Therefore, a final validation of the Volcano Medic in combination with the Medic Valve has been performed. The study was performed according to the current draft version of the operating manual.

The operating manual of the Volcano *Medic* has been drafted with the intention to find a compromise between the practical circumstances and experiences of the medical users, and the results of previous scientific studies. However, there are still important issues that have not been addresses in proper research, e.g. the potential cost-reducing aspects of vaporization compared to smoking and other application methods. Beside the medical potency and preferences of the patients, cost-effectiveness is an important factor for the overall success of cannabinoids in medicine. Health insurance companies may be best convinced to pay for a new medicine and a particular administration form, if it can be shown that the new medicine/method is cheaper compared to established medicines/methods already covered by insurance.

One important way to decrease the cost of medicinal cannabis consumption is to use a single load of cannabis or cannabinoids repeatedly to fill more than one balloon with the Volcano vaporizer. According to experienced users, a loading of 0.5 grams of cannabis, variety 'Bedrocan' (flowers with ca 20% THC) may be sufficient to fill up to 10 balloons, all showing clear physiological effects. However, due to the wish to have a reproducible dose, the current draft of the operating manual recommends to use each filling chamber load for only a single balloon filling. In that case, costs may be reduced by reducing the load of cannabis to a minimum, while ensuring to still administer a reasonable amount of cannabinoids into the balloon.

Storz & Bickel GmbH wonders whether, in times of increasing health care costs, such a potential waste of medicine is appropriate for patients and society. We therefore have initiated and financed this study to determine the effects of multiple balloon fillings on the content of cannabinoids in the balloon. Also the minimum load of the Volcano *Medic* was determined with two different types of herbal cannabis, and with a solution of Dronabinol (pure THC).

Considerations for the study design with Cannabis flowers

Today, the Office of Medicinal Cannabis (OMC) of the Netherlands offers three varieties of standardized and controlled Cannabis flowers to patients. They contain the following main active ingredients:

- Bedrocan ® ca. 19% THC, less than 1% CBD
- Bedrobinol ® ca. 12% THC, less than 1% CBD
- Bediol ® ca. 6% THC, 7.5% CBD

Interesting for our study design is variety Bedrocan because of its high relative high THC content and variety Bediol because of its relative high CBD content. THC, and to a lesser extent CBD, are currently regarded as the most promising medical cannabinoids.

Experienced Volcano users report, by vaporizing Cannabis flowers, that a temperature of 185°C should not be exceeded, because higher temperatures have a negative influence on the taste and can cause unnecessary irritation of the airways. In contrast, temperatures below 185°C may cause insufficient vaporization, especially of CBD (which has a boiling point higher than THC). Because Storz & Bickel thinks that patients and doctors should not be confused with a choice of possible temperatures, we recommend to vaporize Cannabis flowers always and only at a temperature setting of 185°C.

The flowers should always been grinded to a fine size with the herbal grinder that comes with every Volcano device. This applies also to the cannabis variety Bediol; even though this material is already granulated, it is not considered fine enough for proper vaporization from our point of view. Because of these recommendations, two of four main factors for proper vapor release have been fixed – temperature and fineness. The other two main factors are quality (potency) and quantity (load) of the cannabis material. The influence of these two factors is the subject of the study presented here.

Naturally, higher quality and quantity of the load of the filling chamber allows for more balloons to be filled compared to a low quality and smaller load. If for example only 0,1 gram of a Cannabis flower with 3,5% THC is used, we don't expect a significant amount of the desired cannabinoids in the second balloon as the first balloon might have nearly exhausted the poor load of the filling chamber.

Interestingly, experienced users report, when repeatedly using the same filling chamber, they experience the strongest effects with the second or third balloon. This may not be surprising, as the plant material in practice contains a certain amount of residual moisture (usually 5-10%), which lowers the temperature in the filling chamber until the moisture has been evaporated into the first balloon. Subsequent balloons are expected to show less and less cannabinoid aerosol in a balloon, as the load increasingly becomes exhausted of its potency (cannabinoid percentage) during the vaporization process.

We expect the low thermal conductivity of hemp fibre to be an important factor responsible for the reluctant vaporization and the only gradual release of cannabinoid aerosol out of cannabis flowers. After all, hemp fibres are known to be an excellent thermal insulation for buildings. To improve the vaporization process, Storz & Bickel developed the Easy Valve and the Medic Valve. The only difference between the Easy Valve and the Medic Valve is the mouthpiece, needed to inhale the balloon after filling is completed. The Medic Valve mouthpiece contains a one-way valve with a diaphragm for hygienic reasons to prevent the user exhaling into the balloon. In this way, no air contaminated with micro-organisms (bacteria, viruses) can enter the balloon.

Also the filling chamber has been improved. While the older Solid Valve filling chamber has the shape of a narrow tube, the new Easy/Medic Valve filling chamber has the shape of a wider disc, thereby offering the hot air stream a larger contact surface. Additionally, the new filling chamber design drives the vapor directly into the balloon without passing a valve, thus minimizing undesirable condensation of vapor within the vaporization system. The Easy/Medic Valve filling chamber allows a load of 0.05 to 0.5 gram of ground up plant material. A load of less than 0.05 gram (just a few crumbs) should not be used, because of potential problems with accurate weighing and reproducibility.

Considerations for the study design with Dronabinol (THC)

Dronabinol for vaporization purposes is available in Germany in an alcoholic solution with 2,5% THC (THC-Pharm GmbH, Frankfurt/Main, Germany). For such preparations, Storz & Bickel developed a "liquid pad", made of a stainless steel wire mesh that has been pressed to a pad with a diameter of 28 mm and a thickness of 4 mm, exactly fitting into the filling chamber of the Medic Valve. The wire of the pad has a length of approx. 28 meters and a surface of approx. 100 cm^2. Up to 20 drops of an alcoholic solution can be absorbed onto the "liquid pad".

The use of an alcoholic Dronabinol solution is slightly more inconvenient for the user than the use of Cannabis flowers, due to the necessary evaporation of the alcohol prior to inhalation (because inhalation of even a slight amount of alcohol vapor results in intense coughing). Therefore, according to our instructions in the operating manual of the Volcano *Medic*, the alcohol has to be evaporated from the filling chamber by placing it, without balloon attached, onto the vaporizer at 100°C. This process may take approx. half a minute. The THC remains in the pad and can be subsequently vaporized with a temperature of 200°C into the balloon. Pure THC can be evaporated at higher temperature than cannabis flowers, because taste and irritation of the airways is not as much of an issue.

The stainless steel wire mesh has a function similar to the natural hemp fibers in Cannabis flowers: it provides enough surface area for a proper vaporization. However, there is an important difference. The thermal conductivity of stainless steel is much higher compared to the thermal conductivity of hemp fibers. Due to the relative high thermal conductivity of the pad, we expect a fast vaporization process. Even with a

load of 20 drops (about 10 mg THC), it may be expected that in a second balloon no significant amount of THC vapor can be detected. In our study, this hypothesis will be validated by proper chemical analysis.

Analytical conditions

Three different substances will be tested in the Volcano Medic: the cannabis plant materials Bedrocan and Bediol, and a pure THC solution in alcohol (2.5%). For each substance, three different loadings will be used (50, 250 and 500 mg plant materials; 1, 5 and 10 mg THC). Subsequently, multiple balloons will be filled for each loading by re-using the filling chamber repeatedly. An overview is given in the table below.

Substance		Load (filling chamber)	# of balloons filled with each load
Bedrocan - 19% THC	A	0.50 gr	10
	B	0.25 gr	6
	C	0.05 gr	2
Bediol - 6% THC, 7.5% CBD	A	0.50 gr	7
	B	0.25 gr	4
	C	0.05 gr	2
Dronabinol - 2,5% THC in ethanol	A	10 mg (ca. 20 drops)	2
	B	5 mg (ca. 10 drops)	2
	C	1 mg (ca. 2 drops)	2

A: high load
B: medium load
C: low load

All experiments indicated in the table will be performed in threefold for better accuracy of results.

The experiments should be done by closely following the operating manual (see Appendix 5) and the practical circumstances of the Volcano Medic user. Furthermore, the following conditions apply:

I. Fixed basic conditions for all substances:

1. The filling chamber always has to have approx. ambient temperature before vaporization
2. The Medic Valve has to be used with a standard balloon (approx. 8 liters, as delivered)
3. The balloon has to be on the filling chamber before the airflow is activated

4. The vapors may stay in the balloon max. 10 min before filtering
5. Each balloon has to be extracted through the Medic Valve mouthpiece
6. Each individual experiment is performed in triplicate for better accuracy

II. Additional conditions for Bedrocan and Bediol (Cannabis flowers):

1. Temperature setting: 185 °C
2. Have to be fine grinded with the Storz & Bickel grinder
3. No additional grinding between balloon fillings

III. Additional conditions for Dronabinol (THC solution):

1. Removal of alcohol with 100°C into ambient air (with no balloon connected to filling chamber)
2. Temperature setting: 200°C
3. Concentration of 2,5 % in alcohol (ethanol)

Experimental

Solvents

All organic solvents were analytical grade and obtained from Merck Biosolve Ltd. Valkenswaard, The Netherlands.

Cannabis plant material

Variety Bedrocan: Batch number *(A1)01.87.011208*; harvest date March 2, 2009.
Variety Bediol: Batch number *(A1)05.23.080908*; harvest date December 1, 2008

Cannabis plant material (female flowertops) was medical grade and obtained from Bedrocan BV (Veendam, The Netherlands). Plants were cultivated under standardized conditions according to the requirements of Good Agricultural Practice (GAP) [Hazekamp 2006b, OMC 2009]. After harvest, the plant material was air-dried in the dark under constant temperature and humidity for 1 week. Materials were stored in a freezer (-20°C) until used in our study. The same cannabis material is officially dispensed through Dutch pharmacies under the Dutch medicinal cannabis program, supervised by the Office of Medicinal Cannabis (OMC).

Cannabis used in the study was grinded with the Storz&Bickel Grinder, as delivered with the Volcano device, and homogenized by mixing with a spoon. Material was used immediately without storage.

THC solution

Pure THC was isolated from herbal cannabis material, obtained through Bedrocan BV, the Neherlands. The methods for isolation and quality control have been published, and are available from LabAssistent. The final THC solution had a concentration of 25 mg/ml (2.5%) in ethanol, and had a purity of ≥98%. Batch number was THC#580. A full Certificate of Analysis is available from LabAssistant. No significant amounts of the THC degradation products delta-8-THC or CBN were present.

Overview of Conditions

The following setting and conditions were selected for using the Volcano *Medic*:

- Volcano type: Medic
- Filling chamber type: Easy valve
- Valve type: Easy valve
- Mouthpiece type: Medic
- Temperature setting: (Bedrocan, Bediol)
    - Bedrocan, Bediol 185°C
    - THC 200°C
- Amount of filling:
    - Bedrocan, Bediol: 500, 250, 50mg
    - THC 10, 5, 1 mg
- Balloon volume: 8 L

Filling of the balloons

Cannabis material

For each experimental condition an exact amount of grinded material was accurately (+/-2 mg) weighed on a calibrated analytical balance and placed in the standard filling chamber of the Volcano. The filling chamber was placed onto a Volcano apparatus set at 185°C and the balloon was filled according to the instructions of the manufacturer. The balloon was then removed from the filling chamber and the vapor was extracted within two minutes. No additional grinding was performed between balloon fillings. After each experiment, the filling chamber had to cool down to room temperature (ca. 10 min) before filling the next balloon.

THC solution

10, 5, 1 mg. Alcohol solution was accurately placed onto the liquid pad present in the filling chamber, by using a precision pipette. Alcohol was evaporated on the Volcano vaporizer at 100°C for 1 minute without a balloon attached to the filling chamber. THC does not evaporate under these conditions. The filling chamber was placed onto a Volcano apparatus set at 200°C and the balloon was filled according to the instructions of the manufacturer. The balloon was then removed from the filling chamber and the vapor was extracted within two minutes. After each experiment, the filling chamber had to cool down to room temperature (ca. 10 min) before filling the next balloon.

After filling the required number of balloons, the liquid pad was removed from the filling chamber and extracted with ethanol. In this way, the amount of residual (non-vaporized) THC present on the liquid pad could be determined.

Preparation of vapor extracts

Cannabinoids were recovered from the vapor inside the balloon by condensation onto glass fiber filters, designed to capture particles >0.1 microns. Glass fiber filters (Cambridge type, borosilicate glass, 92 mm diameter) and tightly fitting filter holders for vapor extraction were obtained from Borgwaldt Technik GmbH (Hamburg, Germany). With the use of a vacuumpump, the vapor was aspired through the glass-fiber filter with a constant flow of 30L/min. The filter was then placed in a 50ml plastic tube and extracted with ethanol (15ml, 10 min, under constant agitation). Extraction was repeated three times and extracts were combined. Ethanol was added to a final volume of exactly 50ml. These final vapor extracts were stored at -20°C until analysis.

The conditions mentioned above for the analysis of cannabinoids in the vapor of the Volcano balloon have been optimized in previous studies [Hazekamp 2006a, Zuurman 2008]. It was shown that the profile of cannabinoids analyzed in the vapor extract is identical to the composition of the original vapor present in the balloon (accuracy of the method is >95%).

Cannabinoid analysis by UPLC

Quantitative analysis was performed with a Waters Acquity Ultra Performance LC (UPLC) system. The UPLC method used for the quantitative analysis of cannabinoids present in the vapor extracts has been fully validated according to ICH guidelines. This method is part of the official Dutch Monography for the quality control of medicinal cannabis distributed through Dutch pharmacies [OMC 2009]. The ethanolic samples (vapor extracts) were diluted 4 times in the mobile phase of the UPLC method (acetonitrile/water 70:30, + 0.1% formic acid), and analyzed by UPLC to determine the cannabinoid composition.
The UPLC system consisted of a Solvent Delivery Pump (Serial number: J05UPB 162M), an Auto Sampler (Serial number: J05UPS 062M), and a Photodiode Array Detector (Serial number: J05UPD 449M). Equipment control, data acquisition and integration were performed with Water Empower 2 software. Chromatographic separation was achieved using a Waters C_{18} analytical column (1.7µm, 2.1x150 mm) protected by a Waters C_{18} guard column. The mobile phase consisted of acetonitrile and water, both acidified with 0.1% formic acid. The gradient elution is shown below:

t(min.)	% water	% acetonitrile
0.0	30	70
6.0	30	70
10.5	0	100
10.7	0	100
11.0	30	70
12.5	30	70

Total runtime was 12.5 minutes. Flow-rate was set to 0.3 ml/min, the injection volume was 10µL, and detection wavelength was 228 nm. For identification of cannabinoids,

full UV-spectra were recorded in the range of 200-400nm. All experiments were carried out at a column temperature of 30°C.

Processing of the data

The primary result of the UPLC analysis is the peak area at 228nm for each cannabinoid analyzed. The proper controls and standards have been analyzed to convert data to quantitative results. All original data (chromatograms and integration data) is available from LabAssistent.

The following cannabinoids were analyzed:

- THC delta-9-tetrahydrocannabinol
- THCA tetrahydrocannabinolic acid
- CBD cannabidiol
- CBDA cannabidiolic acid
- CBN cannabinol (degradation product of THC)
- D8-THC delta-8-tetrahydrocannabinol (degradation product of THC)
- CBG cannabigerol
- CBC cannabichromene

Other cannabinoids were below the threshold of UV-detection.

Results

In total, 138 balloons were filled and analyzed for cannabinoid content. Results of the quantitative UPLC analyses are presented in bar-diagrams in appendices 1-3. Values are expressed as milligrams of cannabinoid present in the balloon. Each bar represents the mean of triplicate measurements. Errorbars indicate standard error (n=3).

Bedrocan & Bediol

Results were divided over several separate diagrams, to prevent them from becoming too crowded with data. The following cannabinoids are presented together in a diagram:

CBDA and CBD	because CBDA converts into CBD upon heating
THCA, THC and CBN	precursor and degradation products of THC
CBG and CBC	other minor cannabinoids

Bar-diagrams are shown on the same scale, to facilitate visual comparison of the amount of cannabinoids present in different samples. As a result, the bars for the low loading conditions (50 mg plant material) may look very small.

For easier interpretation of the results, the total cannabinoid content of 10 balloons filled with 500 mg of Bedrocan was visualized by using Thin Layer Chromatography, see appendix 4.

Dronabinol (THC) solution

The diagrams for the THC experiments are far simpler, because only a single pure cannabinoid was used. Moreover, no degradation into CBN or delta-8-THC could be detected, so the only cannabinoid detected in the vapor was THC itself. To facilitate the visual interpretation of the results, an extra bar is shown indicating the amount of THC initially applied to the liquid pad (1, 5 or 10 mg).

After each experiment, the total recovery of THC was determined by adding up the THC detected in the balloons and the liquid pad (balloon 1 + balloon 2 + residue on liquid pad). By comparing this value to the total amount initially applied to the liquid pad, the recovery of THC could be determined. The results were:

THC milligram applied	**Recovery**
10 mg	63.5%
5 mg	60.0%
1 mg	59.0%

The missing amount of THC is most like present as a condensate on the inside of the balloon. However, this has not been confirmed by analytical testing. It is interesting to note that the recovery % is fairly constant when different amounts of THC are used.

Discussion & Conclusion

This study was performed to determine the effects of repeated use of a single filling (load) of the Volcano vaporizer. The Volcano *Medic* device was used for all experiments. Under fixed conditions (temperature setting, balloon size) different types of samples (plant material, pure THC) were repeatedly vaporized to fill a number of balloons. The number of balloons filled ranged from 2-10, depending on the amount of sample present in the filling chamber. The goals of the study were:

1) Determine the difference in relative composition (cannabinoid profile) between the successive balloons.
2) Determine to absolute composition (concentration of major cannabinoids) of the successive balloons.
3) Use the obtained results to make a recommendation on how many balloons can be filled when using the same load of the filling chamber.
4) Determine the minimum load that leads to therapeutically significant levels of cannabinoids inside the balloon.

When using plant material, which contains a range of different cannabinoids, the following general observations can be made:

- The acidic cannabinoids THCA and CBDA are present at very low levels, and only in the first few balloons. This result shows that the Volcano vaporizer is an efficient device for releasing the therapeutic cannabinoids THC and CBD from plant material, through decarboxylation of their precursors, THCA and CBDA, respectively.

- The concentration of neutral cannabinoids (THC, CBD, CBG and CBC) increases during the first few balloon fillings, and then goes down again Generally, balloon #3 and 4 are the most potent, which confirms the opinion of some experienced users of the Volcano. As discussed in the introduction of this report, a likely reason for this delayed evaporation is a) the fact that decarboxylation needs to take place first, and b) the presence of residual water in the plant material, lowering the temperature in the filling chamber during the first balloon filling.

- Even in balloon # 10 (load: 500 mg Bedrocan) cannabinoids could be detected, but levels were insignificant for therapeutic effects. In general terms, it seems that 3-4 balloons can be filled before the concentration of cannabinoids becomes too low. Moreover, according to experienced users, the taste of the vapor after balloon filling #3-4 becomes increasingly irritant to the lungs.

- Small amounts of CBN (oxidation product of THC) could be detected in the samples obtained with plant material (Bedrocan and Bediol). However, levels of CBN never exceeded 5% compared to the total level of THC. No delta-8-THC could be detected in any of the balloons, indicating that degradation of THC is no major concern when using the Volcano Medic.

- The use of only 50 mg of plant material results in detectable amounts of cannabinoids inside the balloon, but levels seem to be too low for therapeutic effects.

When using the pure THC solution, the following can be noticed:

- The first balloon is much more potent than the second one, unlike the results obtained for the plant material. Most likely, this is the result of the higher (and therefore more efficient) vaporizing temperature used to vaporize THC (200°C, versus 185°C for plant material). Also, no decarboxylation step (conversion from THCA into THC) is needed, and no water needs to evaporate when pure THC is used. All these factors result in a more efficient and rapid evaporation of THC.

- It seems that the vaporizing of the pure compound THC, even at higher temperatures, does not lead to degradation. In a previous study it was already shown that no significant degradation of THC occurs during evaporation with the Volcano [Hazekamp 2006a]. Also in the current study, no delta-8-THC (thermal degradation product of THC) or CBN (oxidation product of THC) could be detected in any of the samples. These results further confirm that the Volcano vaporizer is a reliable and efficacious device to deliver pure THC via the pulmonal administration route.

- Only about 60% of the applied dose of THC could be recovered from the balloon, independent of the load (1, 5, 10 mg). The remaining amount of THC is most likely lost as a condensate inside the balloon, which indeed becomes visible as a brown sticky material after using the same balloon repeatedly. However, in a previous study it was shown that this condensation process does not change the concentration of THC or other cannabinoids inside the balloon. It is currently recommended to use a single balloon for up to 14 days, 5 times daily.

The obtained results clearly indicate that multiple balloons can be filled with a single load, especially when a larger amount of plant material of THC solution is used. Degradation of cannabinoids (THC in particular) is not an issue of concern when using the recommended temperature settings.

In conclusion, the generalized recommendations based on the obtained results are:

- For plant materials, about 3-4 balloons can be filled when a load of 250-500 mg is used.

- For Dronabinol (THC) solution, only a single balloon can be filled with a load of 5-10 mg.

This report was prepared in Leiden, The Netherlands, by Arno Hazekamp:

Signed:

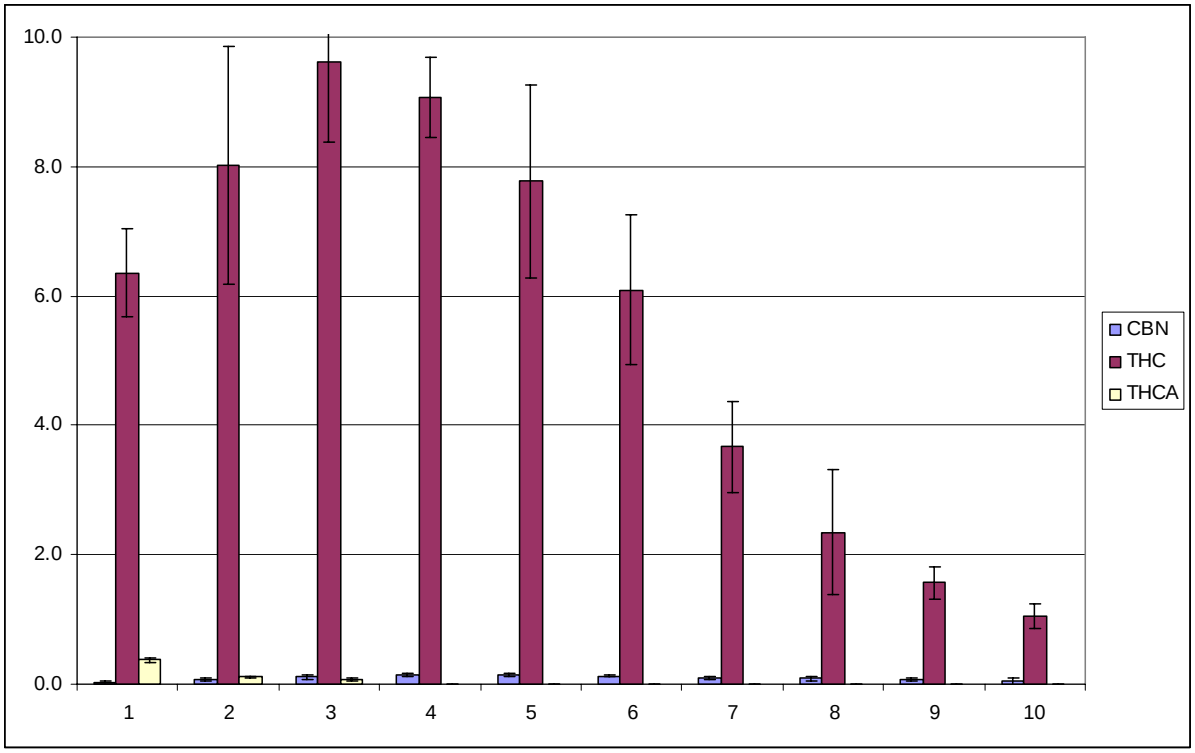
Dr. Arno Hazekamp
Study director
LabAssistent

Leiden, 10 February 2010

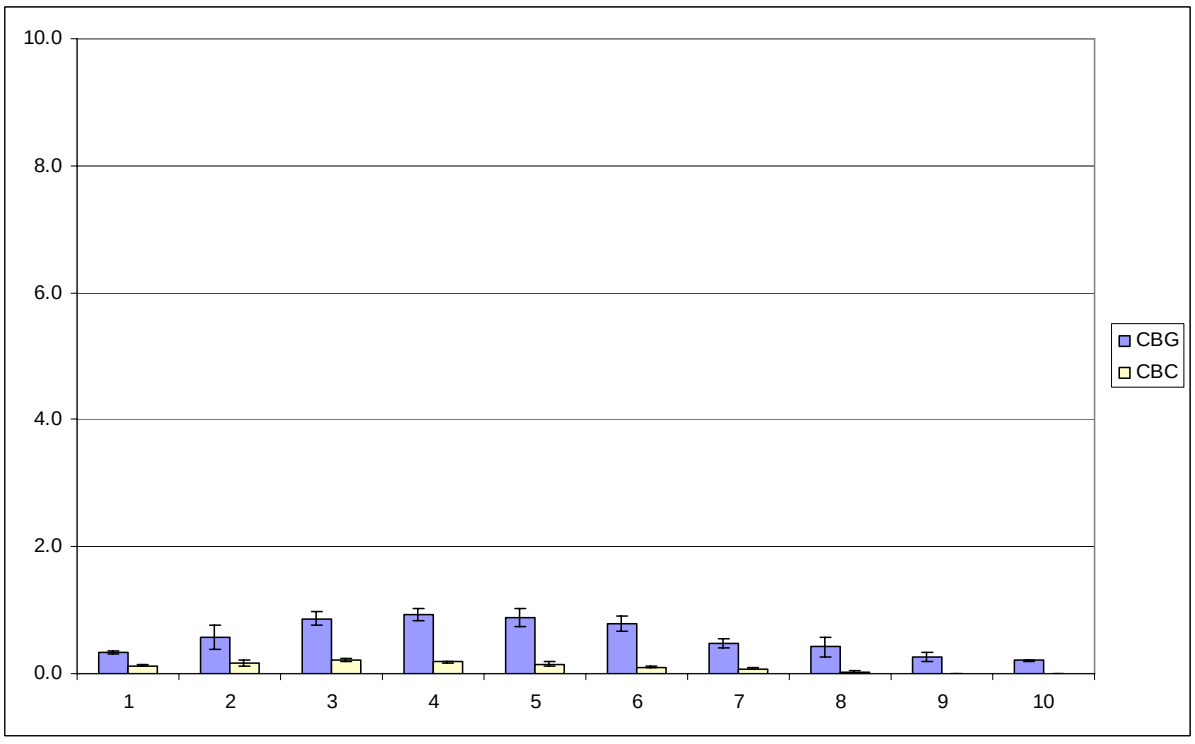
APPENDIX 1: results obtained with Bedrocan plant material. Bars show milligrams of cannabinoids detected in the balloon after vaporizing the indicated load.

Bedrocan: 500 mg load (10 balloons filled)

THC, THCA and CBN

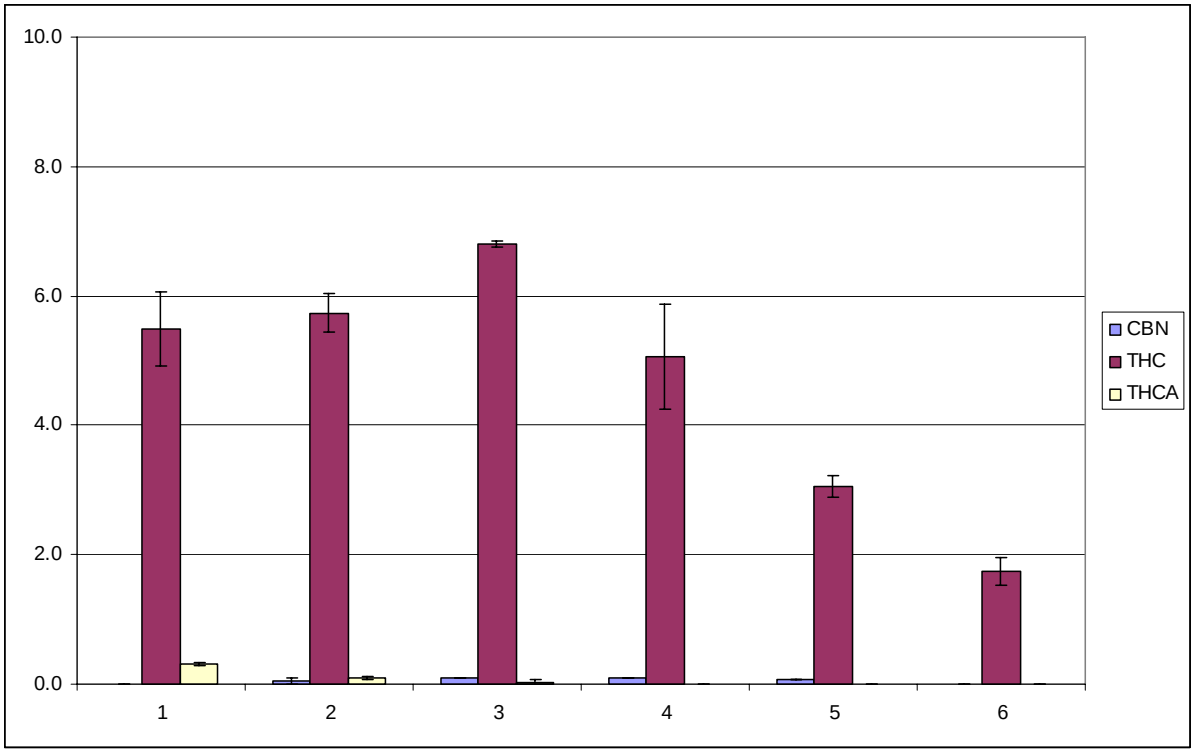


CBG and CBC

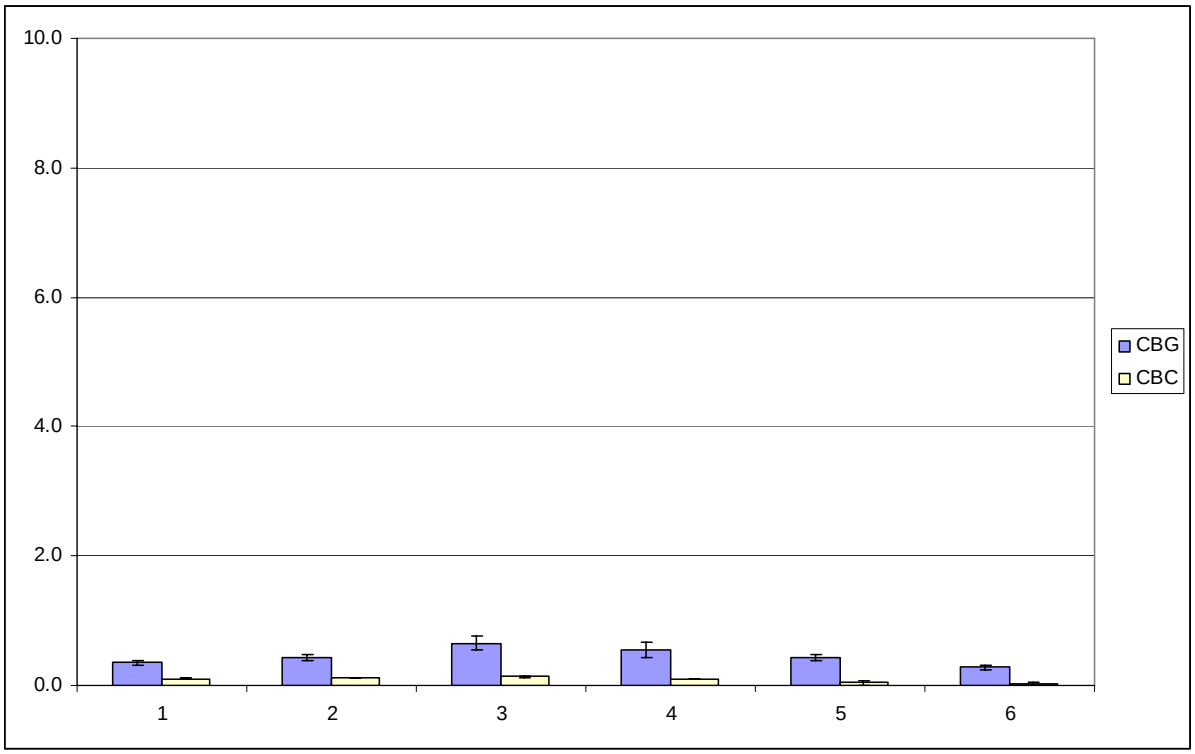


Bedrocan: 250 mg load (6 balloons filled)

THC, THCA and CBN

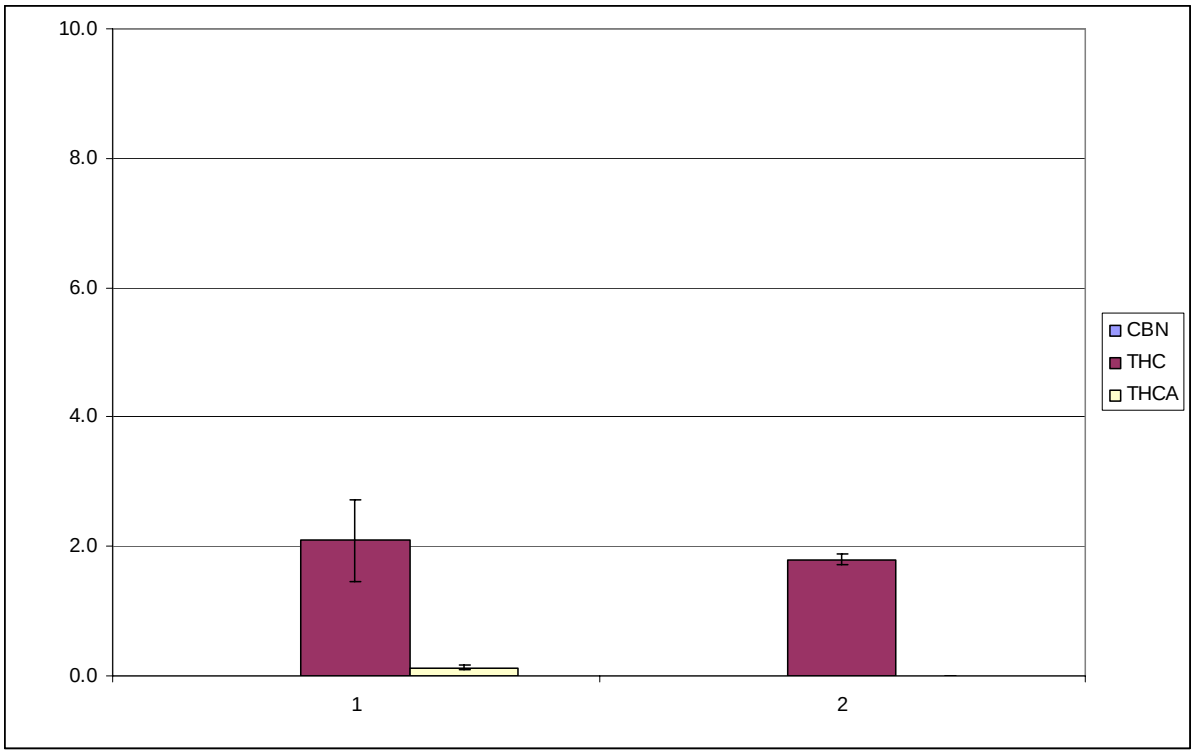


CBG and CBC

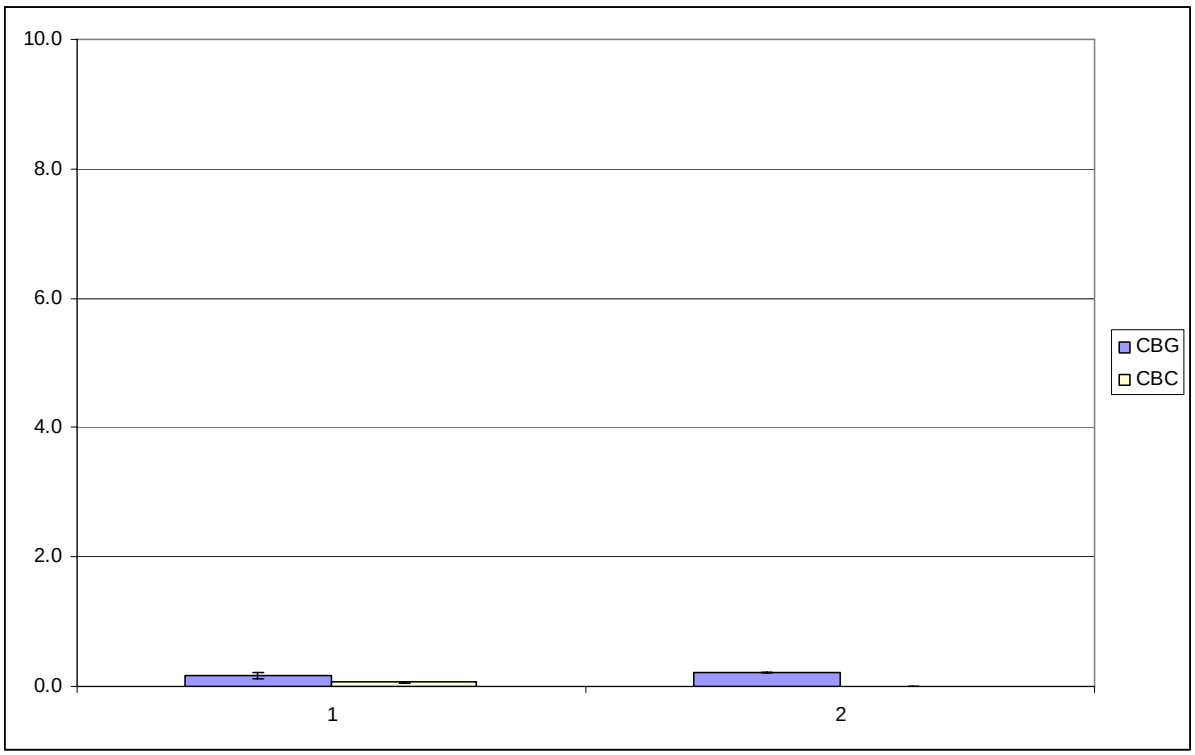


Bedrocan: 50 mg load (2 balloons filled)

THC, THCA and CBN



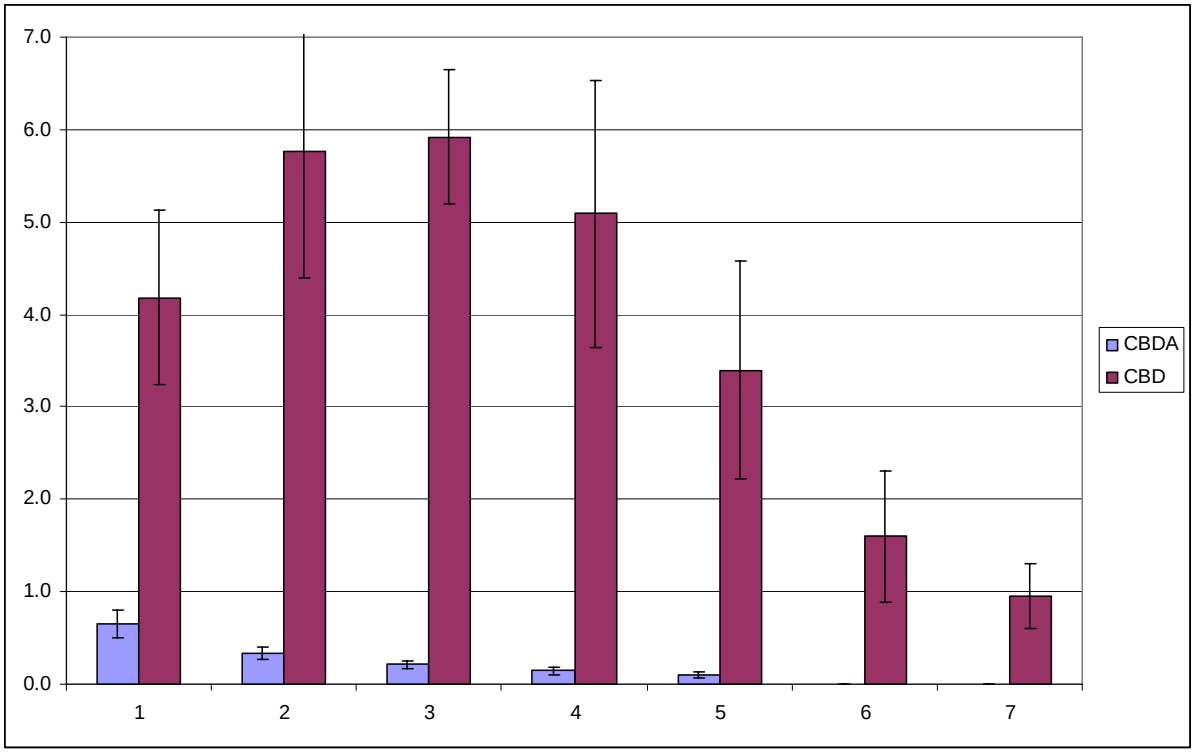
CBG and CBC



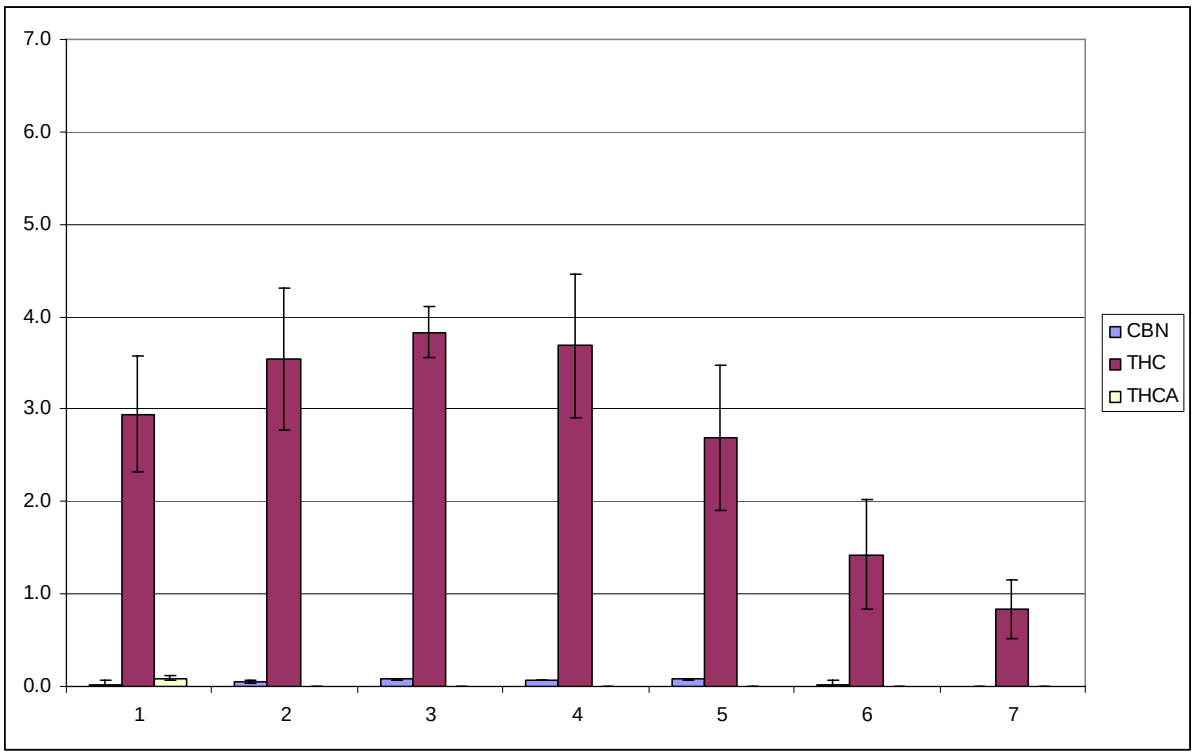
APPENDIX 2: results obtained with Bediol plant material. Bars show milligrams of cannabinoids detected in the balloon after vaporizing the indicated load.

Bediol: 500 mg load (7 balloons filled)

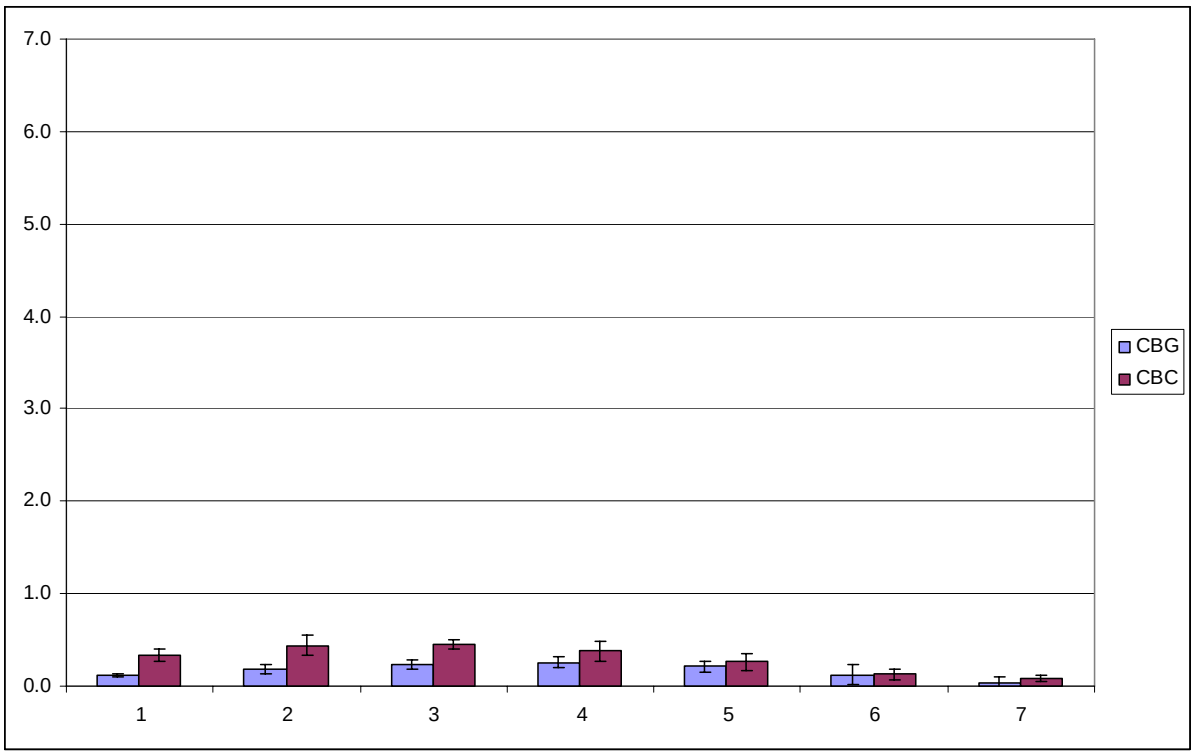
CBD and CBDA



THC, THCA and CBN

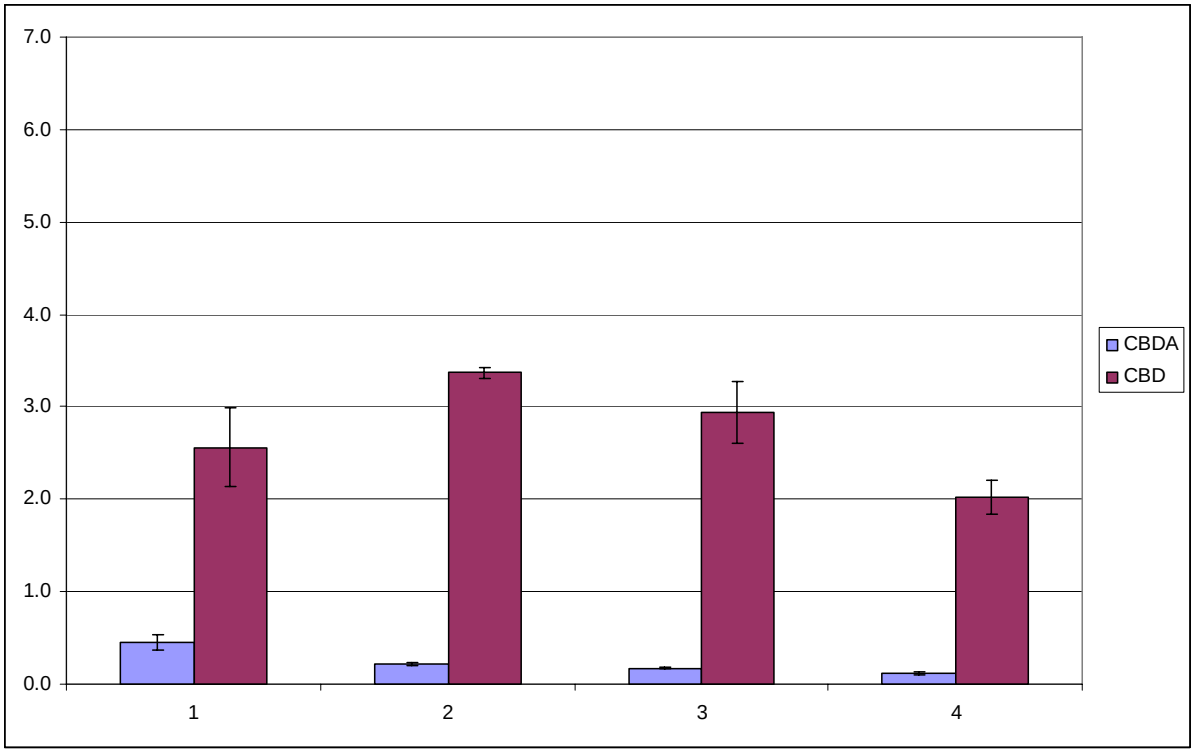


CBG and CBC

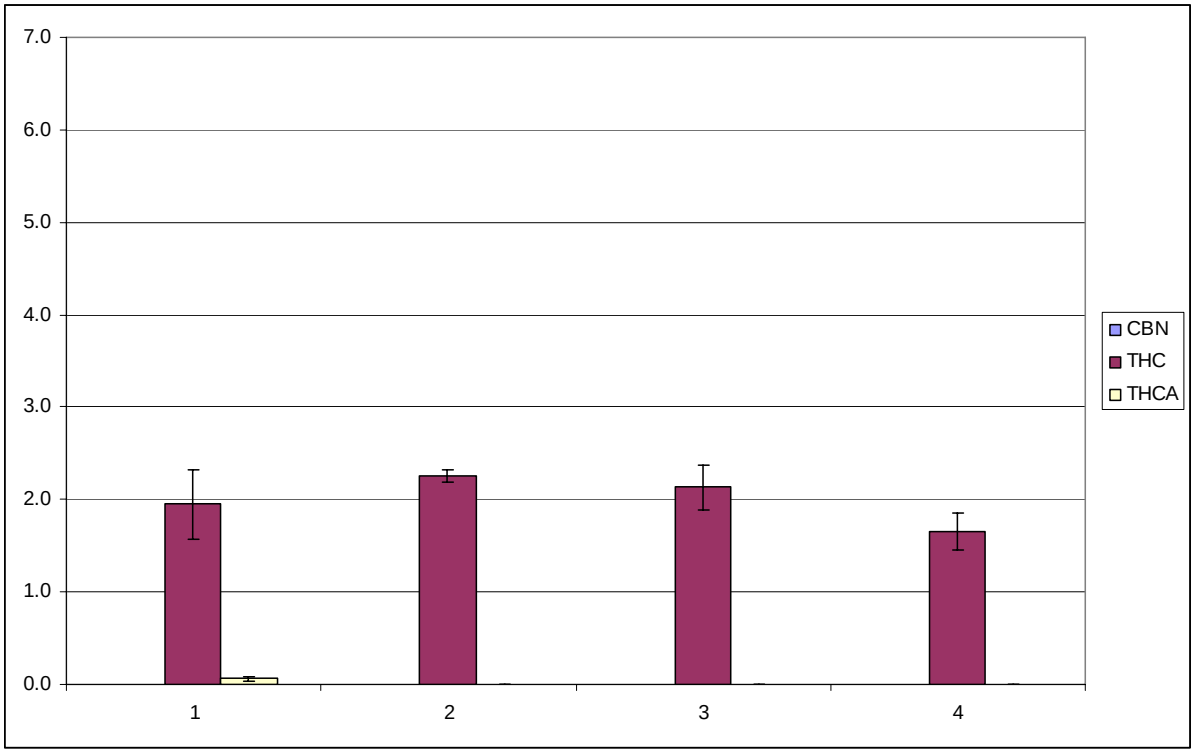


Bediol: 250 mg load (4 balloons filled)

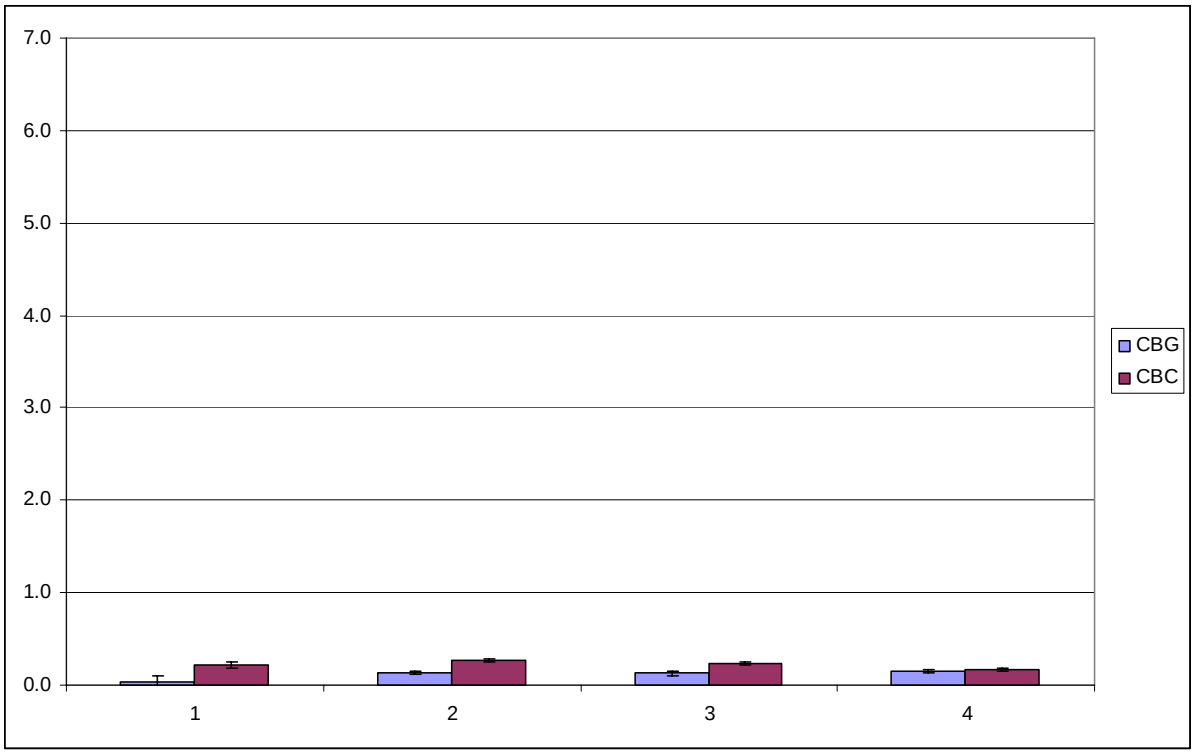
CBD and CBDA



THC, THCA and CBN

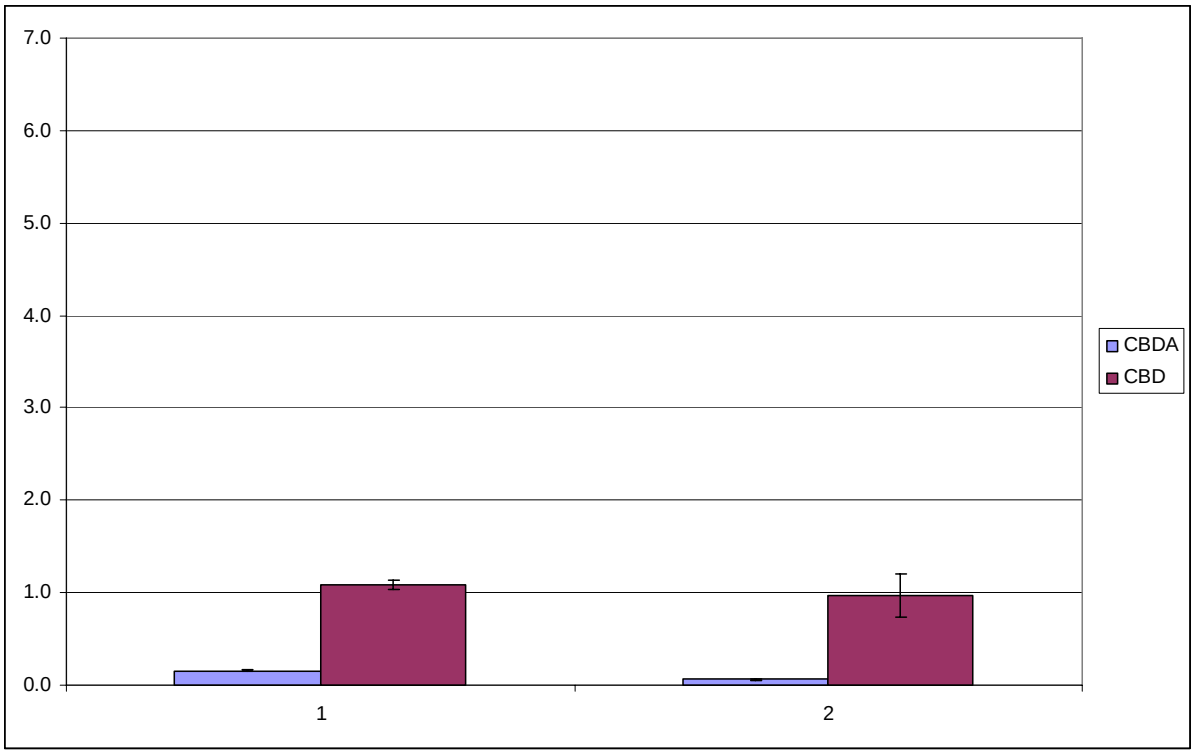


CBG and CBC

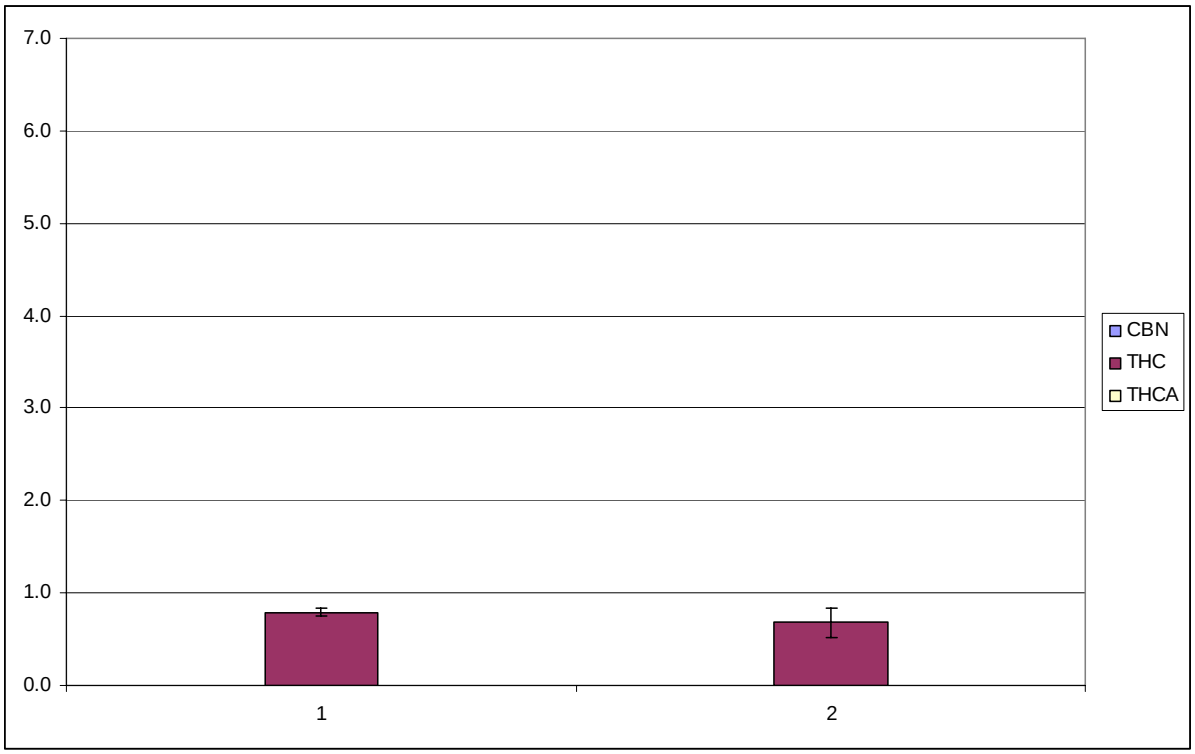


Bediol: 50 mg load (2 balloons filled)

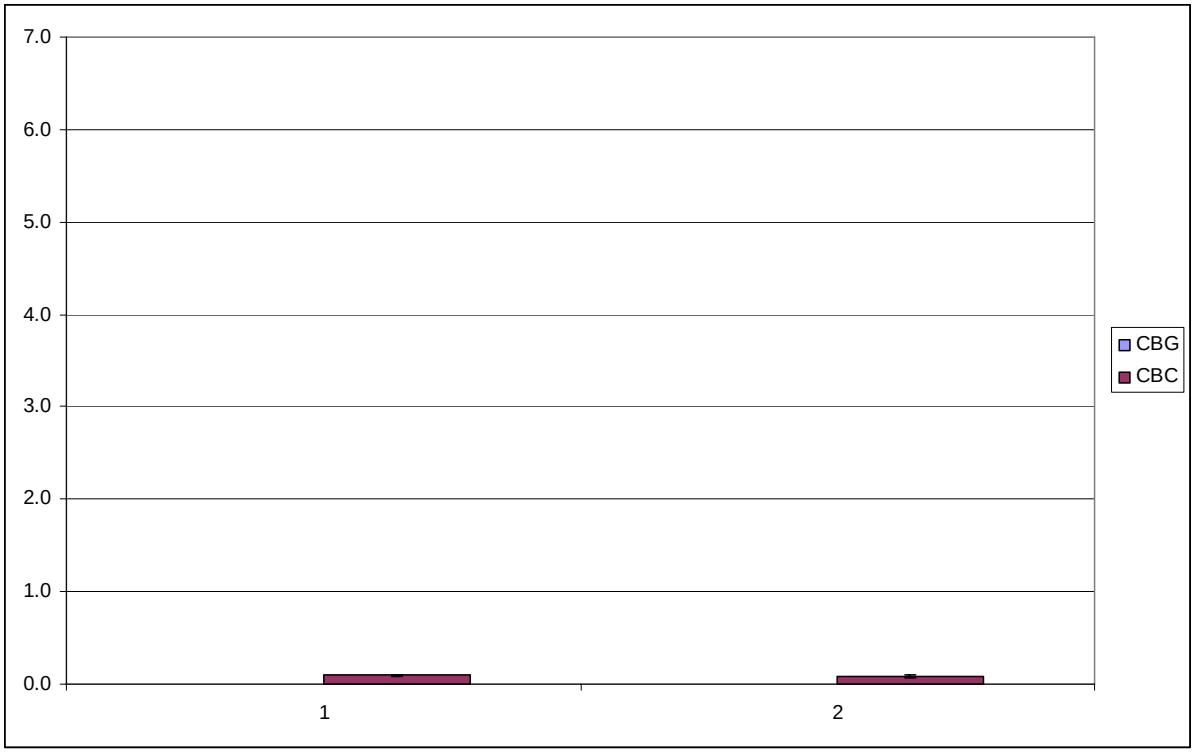
CBD and CBDA



THC, THCA and CBN

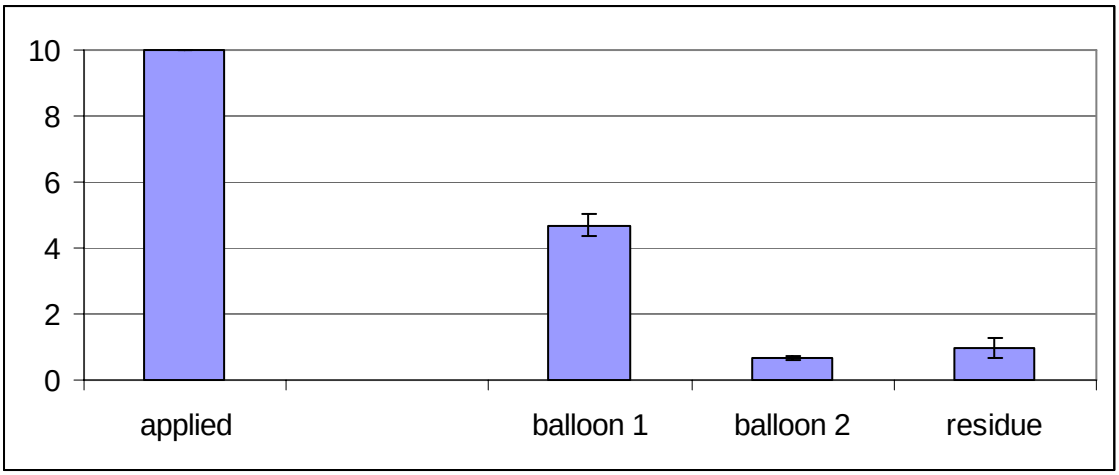


CBG and CBC

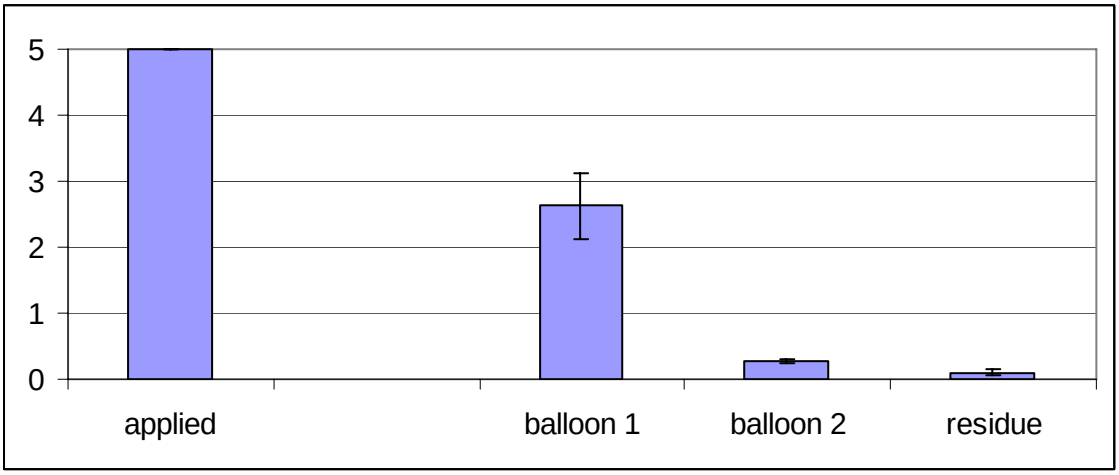


APPENDIX 3: results obtained with Dronabinol (THC) solution. Bars show milligrams of cannabinoids detected in the balloon after vaporizing the indicated load. Residue of THC on the liquid pad was determined in order to calculate total recovery of THC.

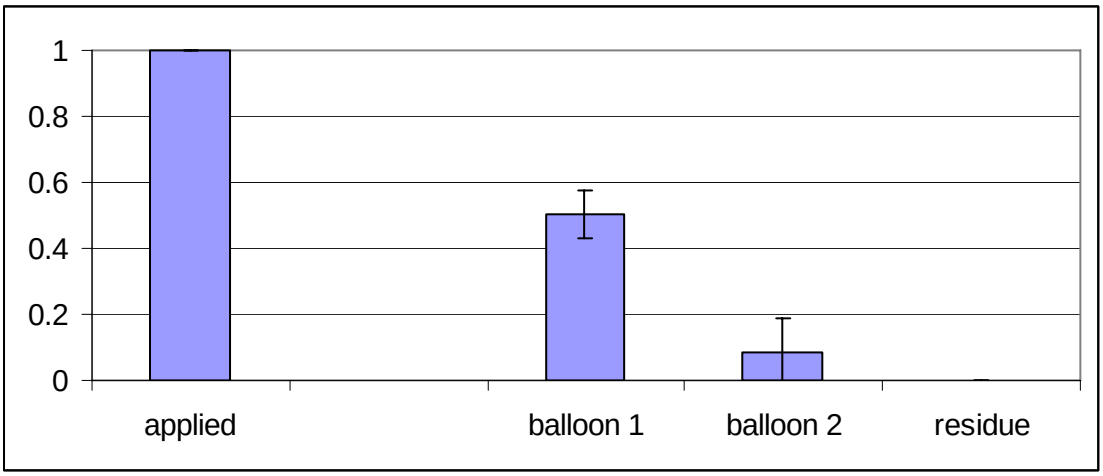
THC: 10 mg load (2 balloons filled)



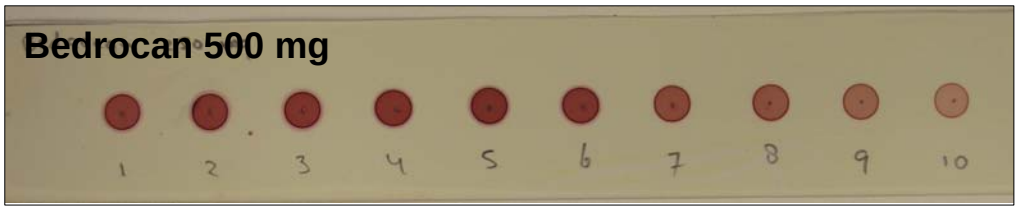
THC: 5 mg load (2 balloons filled)



THC: 1 mg load (2 balloons filled)



APPENDIX 4: TLC analysis of vapor extracts after filling 10 balloons with the same load (500 mg Bedrocan). The color intensity of the spots is roughly equivalent to total amount of cannabinoids present. Balloon # 3-6 contain the highest concentrations of cannabinoids, which correlates to UPLC results.



APPENDIX 5: Excerpt of the draft of the operating manual of the Volcano Medic.

7. Use of dronabinol (THC) dissolved in alcohol

Use only approved dronabinol (THC) as produced in Germany by THC-Pharm and Bionorica

Ethics and sold by prescription to pharmacies. The pharmacy produces an alcohol solution according to your physician's prescription (generally 2.5% THC) for inhalation with the Volcano Medic vaporizer.

[Sicherheitshinweis]
Observe the hygiene instructions before every use and after long breaks between uses and ensure that the mouthpiece has been cleaned, disinfected, and if needed, sterilized before the first and after the last inhalation (see Chap. X)

Preparation

Turn the filling chamber cap counterclockwise in order to remove it from the filling chamber.

[Bildunterschrift]
Remove filling chamber cap

When using dronabinol (THC) dissolved in alcohol, the screens in the filling chamber are not needed and should be removed. The liquid pad is inserted in the filling chamber instead of the lower screen.

[Bildunterschrift]
Preparation to use the liquid pad

Dronabinol (THC) dissolved in oil is not suitable for vaporization and is intended for oral administration.

Application

Turn the filling chamber upside down and use a pipette to drop the dronabinol (THC) dissolved in alcohol onto the bottom of the liquid pad. The liquid pad can hold up to 20 drops. At the beginning of treatment, apply max. one drop and carefully increase to the appropriate dosage. Always follow the doctor's orders!

[Bildunterschrift]
Dropping drops with a pipette

Then screw on the filling chamber cap again.

[Bildunterschrift]
Screw on filling chamber cap

Dronabinol (THC) is available as an alcoholic solution. The advantage of this is the liquid is

distributed more equally around the stainless steel wire of the liquid pad, yielding a larger surface area that can be vaporized. However, the alcohol must first be separated from the dronabinol, as alcohol should not be inhaled.
Then switch 'HEAT' on, set temperature to 100°C, and allow the device to heat up. When the temperature has reached 100°C, place the filling chamber with cap and liquid pad onto the hot air generator and make sure it clicks into place. Then press the 'AIR' button to pump air through the liquid pad.
The dronabinol does not vaporize at this temperature, but the alcohol evaporates quickly (up to 30 sec.). Since alcohol has a characteristic odor, you can easily determine by sniffing whether the filling chamber is alcohol free. Dronabinol has neither odor nor taste.

[Bildunterschrift]
Separate alcohol
When the filling chamber is free of alcohol, switch off the (AIR) pump. The dronabinol, which evaporates only at higher temperatures (over 150°C), remains in the liquid pad. Then remove the filling chamber, set the temperature to 200°C and continue heating.

The dronabinol is mostly vaporized in the first few seconds of filling the balloon. But you should continue filling the balloon (approx. 55 sec.) as the additional air dilutes the aerosol, which makes inhalation easier, especially for higher dosages.
When the temperature reaches 200°C, place the filling chamber and then the valve balloon on and allow them to click in place. This opens the valve. Stretch the valve balloon tight before setting it onto the filling chamber so that when filling, the balloon sits upright on the vaporizer. Turn on the (AIR) pump. The balloon will now be filled with dronabinol aerosol.

[Bildunterschrift]
Before putting the valve balloon on the filling chamber, stretch it tight so that the balloon is upright on the vaporizer when it is filled.
When the balloon is filled, switch off the air pump and remove the valve balloon together with the filling chamber. To do so, hold the filling chamber cap at the textured grip.

[Bildunterschrift]

Remove valve balloon with filling chamber

[Sicherheitshinweis]
Beware of hot surface!
Do not touch the parts of the filling chamber (except on the textured grip) until they have cooled off after filling a balloon.
Detach the valve balloon from the filling chamber. When you do so, the valve is automatically closed so that the vapors in the balloon cannot escape.

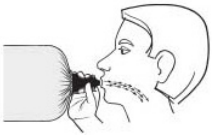
[Bildunterschrift]
Detach valve balloon from filling chamber

[Bildunterschrift]
Beware of hot surface!

Inhalation from the valve balloon

Attach the assembled mouthpiece to the valve and allow it to lock in place (Assembly of the mouthpiece page X)

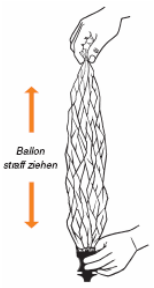
[Bildunterschrift]
Attach the mouthpiece to the valve balloon
To inhale, put the mouthpiece to your lips and lightly press against the mouthpiece with your lips. By doing so, the valve opens and the aerosol can be inhaled from the balloon.
As soon as you remove the pressure from the mouthpiece, the valve automatically closes.



[Bildunterschrift]
Press mouthpiece against lips to inhale

[Hinweis/Tipp]

When the contents of the balloon are almost used up, you can empty the balloon completely by pulling it tight.



[Bildlegende]
Stretch balloon tight

The balloon is not suitable for storing the aerosol for long periods, as it will condense on the skin of the balloon in time (a few hours). Inhale the contents of the balloon within 10 minutes.

Breathing technique

Inhale only half as much as possible. Hold your breath a few seconds and then breathe out slowly. We recommend concentrating on how you breathe. The cannabinoid aerosol is absorbed by the alveoli and then enters the bloodstream.

[Hinweis/Tipp]
The aerosol cannot take effect in the upper airways (mouth, throat, trachea) where there are no alveoli. It is thus especially efficient to inhale the aerosol from the balloon only for the first half of a breath and breathe ambient air for the second half.

End of inhalation

Pull out the plug when you have finished inhaling.

Then carry out the hygiene measures.

8. THE USE OF HEMP FLOWERS (CANNABIS FLOS)

Use only standardized, medicinal hemp flowers (cannabis flos) that have been tested for authenticity, purity, and pathogens according to the directives of the European Pharmacopeia (or comparable guidelines). In the Netherlands, the quality of products from Bedrocan BV is tested by the OMC (Office for Medical Cannabis) of the dutch health department and sold only in pharmacies.

[Sicherheitshinweis]
Do not use cannabis from the illegal black market. The same applies to products from "coffee shops", as this cannabis is not subject to any recognized quality control.
The amount of active ingredients in these products is generally unknown, may fluctuate considerably, and they often contain herbicides, fertilizers, bacteria, etc.

[Sicherheitshinweis]

Before every use and after long pauses between uses, observe the hygiene instructions and make sure that the mouthpiece is cleaned, disinfected, and if necessary, sterilized before the first and after the last inhalation (see Chap. X)

Preparation

Turn the filling chamber cap counterclockwise in order to remove it from the filling chamber.

[Bildunterschrift]
Remove filling chamber cap

Grind the hemp flowers with the enclosed herb grinder. Place a hazelnut-sized amount between the two grinders and rotate 4-5 times.

Depending on the amount of active ingredients and the recommended dosage, fill the filling chamber with at least 0.05 to max. 0.5 g of ground hemp flowers.

[Hinweis/Tipp]
For a reproducible dosis, use each filling chamber portion only once to fill a valve balloon. Other conditions for a reproducible dosis are: using standardized cannabis, the same amount, same temperature, same balloon size, and same breathing technique when inhaling.

Application

[Bildunterschrift]
Fill filling chamber

Then screw on the filling chamber cap again.

[Bildunterschrift]
Screw on filling chamber cap

[Hinweis/Tipp]
Take care that the screens are not obstructed with plant material. To guarantee optimal results, we recommend cleaning the screens after each vaporization process with the brush supplied with the device.

Switch on the heater (HEAT), set temperature to 185°C (365°F). When actual temperature is reached, put the filling chamber with cap on the hot air generator and allow it to lock in place. Put the valve balloon on the filling chamber and allow it to lock in place. This will open the valve.

Before putting the valve balloon on the filling chamber, stretch it tight so that the balloon is placed vertically on the vaporizer when it is filled. The balloon will now be filled with the cannabis aerosol.

[Hinweis/Tipp]
Before putting the valve balloon on the filling chamber, stretch it tight so that the balloon is placed vertically on the vaporizer when it is filled.
When the balloon is filled, switch off the air pump and remove the valve balloon together with the filling chamber. To do so, hold the filling chamber cap at the textured grip.

[Bildunterschrift]
Remove valve balloon with filling chamber
Do not touch the filling chamber (except at the textured grip) until it has cooled off after the balloon has been filled.

[Sicherheitshinweis]
Beware of hot surface!
Separate the valve balloon from the filling chamber. The valve closes automatically after separation and the aerosol in the balloon cannot escape.

[Bildunterschrift]
Separate valve balloon from filling chamber.

[Bildunterschrift]
Beware of hot surface!
When the heater is switched on, do not keep the filling chamber on the exhaust vent of the

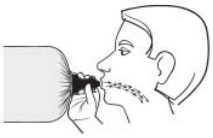
VOLCANO except to separate the alcohol and to fill the balloon. Otherwise the filling chamber can heat up so much that your fingers can be burned.

Inhalation from the valve balloon

Attach the assembled mouthpiece to the valve and allow it to lock in place (Assembly of the mouthpiece page X)

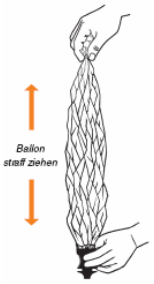
[Bildunterschrift]
Attach the mouthpiece to the valve balloon

To inhale, put the mouthpiece to your lips and press them lightly against the mouthpiece. By doing so, the valve opens and the aerosol can be inhaled from the balloon. As soon as you remove the pressure from the mouthpiece, the valve automatically closes.



[Bildunterschrift]
Press mouthpiece against lips to inhale

[Hinweis/Tipp]
When the content of the balloon is almost used up, you can empty the balloon completely by pulling it tight.



[Bildlegende]
Stretch balloon tight

The balloon is not suitable for storing the aerosol for long periods, as it will condense on the skin of the balloon in time (a few hours). Inhale the contents of the balloon within 10 minutes.

Breathing technique

Inhale only half as much air as possible. Hold your breath for a few seconds and exhale slowly. We recommend consciously concentrating on your respiration. The cannabinoid aerosol is absorbed by the alveoli and into the bloodstream.

[Hinweis/Tipp]
The aerosol cannot take effect in the upper airways (mouth, throat, trachea) where there are no alveoli. It is thus especially efficient to inhale the aerosol from the balloon only for the first half of a breath and breathe ambient air for the second half.

End of inhalation

Pull the plug after inhalation.

Open the cap of the filling chamber by turning it counterclockwise and discard the used plant material.

Then complete the hygiene measures.