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### Summary

- “Cannabis”, one name for a multitude of uses. An appropriate name for each use would help avoid confusion and conflation, which often lead to incorrect assessment of the plant’s properties.
- The effects of cannabis on health - in particular, the positive effects - are the subject of debate within the scientific community. Meta-analyses of the literature are required in order to reach conclusions concerning the level of evidence associated with each effect, but there is a lack of studies and their quality is often deficient.
- Cannabis is useful for the relief of symptoms such as pain but, as our knowledge currently stands, it has no curative virtues, and, in particular, no anticancer properties as is sometimes wrongly claimed.
- Cannabis use among young people is a source of concern since the health risks are real, at a time when its use has increased substantially in France.

### Ms. Huguette Tiegna, MP (National Assembly), Vice-Chairwoman

Depending on the variety, the *Cannabis sativa* plant has numerous properties, from the use of its fibres for paper or rope through to substances with biological - and, in particular, psychoactive - effects, earning its classification as a narcotic by the Single Convention on Narcotic Drugs of 1961.<sup>1</sup>

While many countries, including France, have authorised medicines containing cannabis compounds, a smaller number have introduced regulated access to cannabis (raw or processed) for medical purposes<sup>2</sup> and a few countries have legalised all uses.<sup>3</sup> Against this backdrop, France appears to be rather conservative, despite French people being the leading cannabis users in Europe.<sup>4</sup>

In view of these developments in other countries,<sup>5</sup> accompanied, in France, by demand among patients and health professionals,<sup>6</sup> the *Agence nationale de sécurité du médicament* (ANSM - French Agency for the Safety of Medicines) set up a specific temporary scientific committee to assess the relevance and feasibility of making cannabis available for medical use.<sup>7</sup> The positive opinion of this committee recently led to the creation of a second working group concerning the implementation of this trial, scheduled for the start of 2020.

The purpose of the present briefing is to conduct a review of the health benefits and risks of cannabis,

based on current scientific knowledge.

#### ■ Usages and methods of use

- A plant consumed in many different ways...

A single species of *Cannabis sativa* hemp, devoid of the psychotropic substance THC,<sup>8</sup> is cultivated in France today.<sup>9</sup> This species is called “industrial hemp” because fibres from the plant’s stalks are used for industrial applications; it can also be consumed in the form of oil, flour or seeds.<sup>10</sup>

For plant varieties containing THC, despite being illegal in France, cannabis is smoked mixed with tobacco, in the form of resin<sup>11</sup> (*hashish* or *hash*) or flower buds (*herbal cannabis*). The flowers can also be consumed in the form of an infusion and the resin can be incorporated in food preparations.<sup>12</sup>

- ... and for different purposes

Cannabis has long been used for its psychotropic properties, both for medicinal and ritual or religious purposes, since more than a millennium BC.<sup>13</sup> In Europe, the most common purpose is recreational or festive use for the euphoric properties, the “stoned” feeling or “high” that its use procures.<sup>14</sup> This type of use is practised in groups, by young people, and by more boys than girls.<sup>15</sup> The psychotropic effects are related to the THC: furthermore, the quest to maximise

these effects has led to the development of varieties with increasingly high THC concentrations.<sup>16</sup>

The medical use of cannabis has developed outside France, where patients can access raw flowers or cannabis preparations in pharmacies. The future trial in France aims to authorise and regulate this type of use.

The terms “medicinal” and “recreational” omit other uses: “wellness” cannabis corresponds to products without THC but with a high CBD content (cannabidiol, another cannabinoid). The wellness claims are primarily based on the muscle-relaxing properties of CBD, which is non-addictive<sup>17</sup> and has fewer psychoactive effects than THC.<sup>18</sup> Another use, often described as recreational, actually corresponds to a self-medicating use: for example to reduce anxiety and stress and make it easier to sleep.

### ■ Biological basis of the effects of cannabis

- The existence of an endogenous system receptive to cannabinoids

The cannabinoids in cannabis – or phytocannabinoids – have a biological effect because the human body has cannabinoid receptors; binding of THC or CBD to these receptors triggers cell processes resulting in a biological or behavioural effect. THC receptors CB1 and CB2 were identified and described in the 1990s.<sup>19</sup>

Scientists discovered that endogenous molecules exist that are capable of binding to these: endocannabinoids (eCB).<sup>20</sup> CB1 and CB2 receptors,<sup>21</sup> their natural ligands – eCB – and the enzymes that enable the synthesis and degradation of the latter<sup>22</sup> form the endocannabinoid system.

CB1 is predominantly present in the central nervous system,<sup>23</sup> but also in the peripheral nervous system,<sup>24</sup> whereas CB2 is mainly present in the cells of the immune system.<sup>25</sup> The amount of CB1 is higher in developing brains (from embryos to around 25 years of age) than in mature brains.

- Endocannabinoid system functions

The endocannabinoid system is essential on a local level, with eCBs ensuring modulation of synaptic activity,<sup>26</sup> but also on larger scales, such as in the growth of axons, these extensions of neurons that enable interneuronal communication.<sup>27</sup> The initiation of connections between neuron groups, sometimes distant from the brain, is necessary to increase brain connectivity, one of the processes of brain maturation.<sup>28</sup>

Disruptions in the endocannabinoid system have been identified in psychiatric disorders such as depression, autism, schizophrenia, addiction, stress and anxiety. While therapeutic projects using substances that interact with CB1, such as Rimonabant, have had to be

halted due to serious adverse effects, the strategies currently under development consist in modulating the degradation or synthesis of eCBs by inhibiting enzymes of the eCB system.<sup>29</sup> The eCB system is also involved in pain management.<sup>30</sup>

- Interaction between cannabis and the eCB system

Since phytocannabinoids can interact with cannabinoid receptors, the effects caused by using cannabis are the result of this interaction. In the brain, THC and CBD have antagonistic effects: THC activates CB1, resulting in psychotropic effects, which are partially diminished by CBD, without this mechanism being fully understood.<sup>31</sup>

Although they have the same biological target, phytocannabinoids do not work in the same way as eCBs: their action is much slower over time<sup>32</sup> and is global, whereas eCBs have a local action. These differences in temporality and degree of stimulation disrupt the neuromodulating role of the eCB system.

### ■ Positive health effects

A very large number of scientific studies have aimed to assess the health benefits and risks of cannabis. However, the lack of clinical trials of adequate quality in humans sometimes makes it impossible to reach a conclusion with respect to the accuracy of a claim.<sup>33</sup>

- Scientifically recognised positive effects

Literature reviews such as the one carried out by the American National Academies of Sciences, Engineering and Medicine<sup>34</sup> make it possible to associate a level of evidence with each suspected effect. This reveals positive effects of cannabis or cannabinoids to treat chronic pain in adults,<sup>35</sup> nausea and vomiting in subjects receiving chemotherapy to treat cancer<sup>36</sup> or with AIDS, appetite loss in patients at the end of life, muscular spasticity<sup>37</sup> in multiple sclerosis, and in rare types of epilepsy. They also appear to be potentially useful to improve symptoms associated with psychiatric disorders: anxiety, post-traumatic stress disorder and Tourette syndrome.<sup>38</sup> The use of cannabis may also have an anti-inflammatory action.

- From medicines containing phytocannabinoids to cannabis for medical use

The regulations were changed in France in 2013 to pave the way for the possibility of treatments using cannabis derivatives.<sup>39</sup> Two medicines containing phytocannabinoids currently have a marketing authorisation (MA). Sativex® was authorised in 2014 as a treatment for spasticity due to multiple sclerosis (MS).<sup>40</sup> Epidyolex® was granted an MA in 2019 for use in the treatment of rare and serious types of epilepsy.<sup>41</sup>

The ANSM (French Agency for the Safety of Medicines) plans to make cannabis for medical use available to 3,000 patients for a two-year trial period.<sup>42</sup> In line with the abovementioned scientific knowledge, the indications are pain refractory to currently accessible therapies, rare types of epilepsy,<sup>43</sup> as a supportive treatment in oncology (chemotherapy-related nausea and pain), palliative care and painful spasticity in multiple sclerosis.<sup>44</sup> The trial will consist in providing raw or slightly processed cannabis<sup>45</sup> to patients: use by smoking will be prohibited. The treatment will be initiated by a doctor, joining the trial on a voluntary basis, practising in a specialised hospital facility<sup>46</sup> and having undergone specific training.<sup>47</sup> The patients will be followed up in order to assess the prescribing and dispensing channels put in place and to monitor the safety and efficacy of the treatment.<sup>48</sup> A report will be submitted to Parliament at the end of the trial for examination of the mechanism prior to its continuation.

When growing medical cannabis, particular care along with stable, controllable conditions (temperature, humidity, sunshine, etc.) are required so that the cannabinoid contents of the plants are uniform. Pesticides cannot be used. It is therefore grown indoors. A relatively small surface area would be required if medical use were to be continued in the longer term in France: less than 100 ha would cover the needs of 300,000 people.

- The status of medical cannabis

Medical cannabis addresses a strong demand on the part of patients, who perceive a genuine benefit from it, in view of which it does not appear ethical to deny them access to it, as the ethics and cancer committee concluded. Furthermore, medicines containing cannabis will only be accessible for very limited indications in which they have been granted a marketing authorisation. However, in contrast with medicinal products that have been through the marketing authorisation process, medical cannabis has not demonstrated its efficacy by the usual means (placebo-controlled demonstration in randomised trials), nor has it demonstrated a superior efficacy to existing therapies; this would pose a problem if the issue of its reimbursement by the social security system were to be raised, in the event that the trial is continued in the longer term.<sup>49</sup>

Although the curative properties of the plant are currently being studied, particularly in the treatment of addictions<sup>50</sup> and pancreatic cancer,<sup>51</sup> current knowledge does not justify such uses for cannabis at present.

- Minor components of cannabis

Cannabis contains more than 100 cannabinoids and more than 200 terpenoids<sup>52</sup> but their effects on health have been the subject of very few studies. A few

researchers support the hypothesis that these minor compounds may act in synergy with THC and/or CBD, hence a better efficacy of cannabis (complete extract) compared to a medicinal product (purified substance): this is the *entourage*<sup>53</sup> effect, which is still the subject of debate.

#### ■ Negative health effects

The health risks associated with cannabis use result from the psychoactive effects of THC and disruption of the function of the endocannabinoid system, particularly during brain development phases; these depend on the amount used and the method of use.

- Scientifically recognised negative effects

In a non-medical context, cannabis use is associated, in particular, with a type of testicular cancer,<sup>54</sup> cardiovascular events, chronic bronchitis, death from poisoning in children, pregnancy complications or low birth weights of offspring. Driving under the influence of cannabis is also dangerous since vigilance is impaired for several hours.<sup>55</sup>

While the psychoactive effects of CBD are less than those of THC, the substance is not innocuous: in particular, it inhibits the hepatic enzyme that breaks down medicines; which can result in interactions between medicinal products.<sup>56</sup>

- Addiction and cannabis

THC can cause addiction to cannabis, with a lower risk of developing dependence, however, than with other substances.<sup>57</sup> Recent studies suggest that a susceptibility to addiction may be inherited epigenetically when parents are users.<sup>58</sup>

The higher the THC concentration in cannabis, the higher the risk of causing dependence, this effect being limited by the antagonistic action of CBD. However, the varieties developed for recreational use present increasingly high THC contents without any rise in CBD content and are therefore more dangerous.

- Cognitive and psychiatric effects of cannabis

In the developing brain, exposure to cannabis causes structural changes and disrupts the eCB system.<sup>59</sup> Exposure of young rats to THC causes disturbances in higher cognitive functions that persist in adult rats, even after exposure is stopped.<sup>60</sup>

Clinically, cannabis use is associated with cognitive problems (impaired memory, attention and learning capacities) and psychiatric problems (anxiety,<sup>61</sup> increased manic symptoms in bipolar disorders, increased suicide risk, etc.).<sup>62</sup>

There is a risk of developing psychotic symptoms, or even accelerating the development of schizophrenia, associated with cannabis use. This risk is higher if the person has a pre-existing susceptibility.<sup>63</sup> Moreover,

certain genetic factors appear to potentiate the influence of cannabis.<sup>64</sup> These effects vary substantially from one person to another, but the idea of not everyone being equal when it comes to addiction and disease is not one that is properly taken on board by adolescents.<sup>65</sup>

The cognitive problems caused by cannabis use during adolescence have repercussions on the individual's life: this use is associated with poor school results,<sup>66</sup> a dark professional future<sup>67</sup> and job loss.<sup>68</sup> In France, consumption has fallen slightly but problem use has increased.<sup>69</sup>

- Dangers associated with synthetic cannabinoids

Synthetic cannabinoids have stronger psychotropic effects than those of THC, since they have a higher affinity for the CB1 receptor. In 2017, these substances had already been responsible for 43 deaths due to acute poisoning in Europe.<sup>70</sup>

- Access to medical cannabis in France

Numerous patients already illegally self-medicate by using cannabis, either by growing it themselves or by buying the product in the street. This practice is dangerous since it is not medically supervised; products with THC and CBD concentrations that are not fully known are used, or they may be "cut" by dealers with substances that are not intended for consumption.

The issue of the influence of authorising medical cannabis, or even overall legalisation, on use among at-risk populations is raised. US states that have authorised medical use have not observed any increase in use among young people.<sup>71</sup> However, use in adults has increased in states that have authorised all uses.<sup>72</sup>

## ■ Recommendations

- Academic and industrial research players should be encouraged to organise rigorous clinical trials in order to better determine the relevance of medical cannabis use, identifying its mechanisms of

action. The biological and behavioural consequences resulting from non-medical use also need to be studied. A first measure could consist in facilitating scientists' access to cannabinoids and allowing them to work on complete-spectrum extracts with THC concentrations representative of those of the products bought in the street,<sup>73</sup> to enable a better assessment of the health effects of this use.

- The smooth implementation of the medical cannabis trial scheduled in France requires that the ANSM ensure the quality of the products supplied to patients and carry out active pharmacovigilance. Monitoring of research would make it possible to modify the therapeutic indications selected if so justified by evolving knowledge.

- If the trial is continued in the longer term, the ANSM could, in addition to its current functions, be tasked with controlling medical cannabis, from growing of the plant to processing of the flowers, in the same way as the "cannabis agencies" created in other countries, Germany in particular.

- Concurrently with this trial, prevention among pregnant women and young people must be intensified and rethought in order to counter the phenomenon of normalisation of this use. Early prevention<sup>74</sup> is necessary and the health risks of non-medical cannabis need to be explained. Biology teaching and an introduction to brain function would be the ideal supports.

- Better information for young people concerning psychiatric risks (in general) would help them better identify suppressed problems for which cannabis use is the wrong solution.

OPECST website:

<http://www.assemblee-nationale.fr/commissions/opecest-index.asp>  
<http://www.senat.fr/opecest/>

Health effects	Level of evidence of the effect
<b>Positive</b>	
<b>1) To treat the symptoms of a disease</b>	
<b>* biological symptoms</b>	
chronic pain	cannabis
spasticity (multiple sclerosis), assessed by the patient	cannabinoids
spasticity (multiple sclerosis), assessed by the clinician	cannabinoids
spasticity (paralysis, spinal cord injury)	cannabinoids
chemotherapy-induced nausea and vomiting	cannabinoids
appetite and weight loss (HIV/AIDS)	cannabis and cannabinoids
cancers	cannabinoids
anorexia et cachexia (cancer)	cannabinoids
epilepsy	cannabinoids ⚠
irritable bowel disease	cannabinoids (THC)
intraocular pressure (glaucoma)	cannabinoids
amyotrophic lateral sclerosis	cannabinoids
motor system symptoms (Parkinson's disease)	cannabinoids
dystonia (involuntary muscle contractions)	cannabinoids (THC)
<b>* behavioral symptoms</b>	
sleep disturbances (sleep apnoea, fibromyalgia, chronic pain, multiple sclerosis, etc.)	cannabinoids (THC + CBD)
anxiety	cannabinoids (CBD)
symptoms of Tourette syndrome	cannabinoids (THC)
symptoms of post-traumatic stress disorder	cannabinoids (THC)
symptoms of dementia	cannabinoids
depressive symptoms (chronic pain and dementia)	cannabinoids (THC + CBD)
behavioural symptoms (schizophrenic disorders)	cannabinoids (CBD)
behavioural symptoms (Huntington's disease)	cannabinoids
addictions	cannabinoids
<b>2) Positive effects without a therapeutic effect being sought</b>	
decreased risk of metabolic syndrome and diabetes	cannabis
increased pulmonary capacity	cannabis
<b>Negative</b>	
<b>3) On the development of cancers</b>	
lung cancers	cannabis
head and neck cancers	cannabis
testicular cancers (non-seminoma-type germ cell tumours)	cannabis
oesopharyngeal cancers)	cannabis
non-Hodgkin lymphoma, malignant gliomas, prostate cancer, cervical cancer, anal cancer	cannabis
leukaemias and brain cancers, in offspring	cannabis (parents)
<b>4) On cardiometabolic and respiratory risks</b>	
myocardial infarction (chronic use)	cannabis
myocardial infarction (occasional use)	cannabis
stroke	cannabis
risk of prediabetes	cannabis
chronic bronchitis symptoms	cannabis
improvements in respiratory symptoms	cannabis (cessation)
chronic obstructive pulmonary dis. if combined with tobacco use	cannabis
asthma	cannabis

Adapted from: The National Academies of Sciences, Engineering and Medicine. (2017). The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. ⚠ : Since this document was published at the start of 2017, the level of evidence may have changed for some effects. In particular, this is the case for epilepsy, with Epidyolex having been granted a European marketing authorisation for Dravet syndrome and Lennox-Gastaut syndrome.

<b>5) On the immune system</b>		
decrease in inflammatory markers		cannabis
liver fibrosis (hepatitis C)		cannabis
immune status in individuals with HIV		cannabis
<b>6) On accidents</b>		
motor vehicle accidents		cannabis
overdoses in children		cannabis
occupational accidents		cannabis
mortality - cannabis overdose		cannabis
mortality - all causes		cannabis
<b>7) For prenatal, perinatal and neonatal exposure</b>		
low birth weight		cannabis
pregnancy complications		cannabis
admission of the infant to the neonatal intensive care unit		cannabis
long-term outcomes in the offspring (sudden infant death syndrome, academic achievement, cannabis use, etc.)		cannabis
<b>8) On psychosocial risks</b>		
cognitive impairment (memory, attention, learning)		cannabis
impaired academic achievement		cannabis
increased rates of unemployment and low income		cannabis
impaired social and relational capacities		cannabis
<b>9) On mental health</b>		
schizophrenia and other psychoses		cannabis
better cognitive performance (individuals with psychotic disorders using cannabis)		cannabis
worsening of negative symptoms of schizophrenia		cannabis
worsening of positive symptoms of schizophrenia		cannabis
development of depressive disorders		cannabis
improvement/worsening of depression		cannabis
suicide attempts		cannabis
development of social anxiety disorder		cannabis
development of other anxiety disorders		cannabis
development of bipolar disorders		cannabis
worsening of bipolar disorders		cannabis
development of post-traumatic stress disorder		cannabis
worsening of symptoms of post-traumatic stress disorder		cannabis

Efficacy OR Association	Inefficacy OR No association	Level of evidence
		Substantial or conclusive evidence
		Moderate evidence
		Limited evidence
		No or insufficient evidence

cannabinoids : cannabidiol (CBD) or tetrahydrocannabinol (THC),  
synthesised or extracted, oral consumption

*Adapted from: The National Academies of Sciences, Engineering and Medicine. (2017). The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. □ : Since this document was published at the start of 2017, the level of evidence may have changed for some effects. In particular, this is the case for epilepsy, with Epidyolex having been granted a European marketing authorisation for Dravet syndrome and Lennox-Gastaut syndrome.*

## Individuals consulted\*

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- Prof. **Jean-Claude Alvarez**, toxicologist and pharmacologist, Department Head of the Pharmacology and Toxicology Laboratory, Garches University Hospital, member of the French National Academy of Pharmacy, Prof. **Jean Costentin**, pharmacologist, member of the French National Academy of Medicine and the French National Academy of Pharmacy, and Prof. **Jean-Pierre Goullé**, toxicologist, member of the French National Academy of Medicine and the French National Academy of Pharmacy
- Prof. **Nicolas Authier**, psychiatrist and pharmacologist, Head of the Medical Pharmacology Department and Department Head at the Centre for Pain Assessment and Treatment, Clermont-Ferrand University Hospital, Chairman of the temporary scientific committee (CST) dedicated to the implementation of the medical cannabis trial
- Prof. **Amine Benyamina**, psychiatrist and addiction specialist, Head of the Department of Psychiatry and Addictology at Paul Brousse Hospital, Villejuif and Chairperson of the French Addictology Federation
- Mr. **François Bruneaux**, Assistant to the Deputy Director, Subdirector of health products policy and practice and care quality at the General Directorate for Health
- Mr. **Yves Christol**, General Manager of InVivo Food&Tech and Ms. **Carole Hernandez-Zakine**, Director of Public Affairs for Bioline (InVivo)
- Mr. **Aurélien Delecroix**, Chairman of the French Hemp Union and Founding Chairman of the company Greenleaf
- Prof. **Marie-Odile Krebs**, psychiatrist, Department Head at Sainte-Anne Hospital, responsible for the Pathophysiology of Psychiatric Diseases team at the Paris Institute of Psychiatry and Neurosciences
- Ms. **Fabienne Lopez**, Chairperson of the “Principes actifs” (Active substances) Association, Messrs. **Christian D. Muller**, pharmacologist, Senior Research Officer at the CNRS, Hubert Curien Multidisciplinary Institute, and **Bertrand Rambaud**, respectively responsible for the Scientific Division and the Patient Division of the French-speaking Union for Cannabinoids in Medicine
- Mr. **Olivier Manzoni**, Inserm Research Director, Joint Manager of the Adolescence and Developmental Vulnerability to Neuropsychiatric Diseases team at the Mediterranean Institute of Neurobiology
- Ms. **Maria Melchior**, Inserm Research Director, Manager of the Social Epidemiology research team at Pierre Louis Institute of Epidemiology and Public Health
- Ms **Hélène Moore**, General Manager of Aurora France
- Mr. **Giles Moss**, General Manager Europe at GW Pharmaceuticals, Mr. **Jean-Luc Gaunel**, Manager France and Mr. **Ben Whalley**, Research Manager at GW Pharmaceuticals
- Ms. **Ivana Obradovic**, sociologist, Deputy Director of the French Monitoring Centre for Drugs and Drug Addiction (OFDT) and Associate Researcher at the Centre for Sociological Research in Law and Penal Institutions (CESDIP)
- Ms. **Nathalie Richard**, Deputy Director of the Division for Neurological Medicines at the ANSM and Ms. **Carole le Saulnier**, Director of Legal and Regulatory Affairs at the ANSM
- The Department of Science and Technology and the Department of Social Affairs at the French Embassy in Germany
- The Department of Science and Technology and the Department of Social Affairs at the French Embassy in the USA
- The Department of Internal Security at the French Embassy in Canada

\* NB: The individuals consulted in some cases expressed divergent opinions concerning one or more aspects of the briefing. Scientific coordination by Ms. Mathilde Lecompte, Scientific Advisor

## References

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- (1) Single Convention on Narcotic Drugs of 1961, adopted by the United Nations, as modified by the 1972 Protocol amending the Single Convention on Narcotic Drugs of 1961: [https://www.unodc.org/pdf/convention\\_1961\\_fr.pdf](https://www.unodc.org/pdf/convention_1961_fr.pdf).
- (2) This is the case for Germany, Australia, several states in the USA, Israel, the Netherlands, Portugal, the United Kingdom and Switzerland, etc. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2018). Medical use of cannabis and cannabinoids: questions and answers for policymaking.
- (3) This is the case for Uruguay, Canada and some states of the USA. See the executive summaries of the Observatoire français des drogues et toxicomanies (French Monitoring Centre for Drugs and Drug Addiction); “La légalisation du cannabis au Canada : genèse et enjeux de la réforme” (“Cannabis legalisation and regulations in Canada: background and challenges”) (<https://www.ofdt.fr/BDD/publications/docs/eisxioya.pdf>), “La légalisation du cannabis aux États-Unis, vers une régulation du marché ?” (“Cannabis legalisation in the USA: towards market regulation?”) (<https://www.ofdt.fr/BDD/publications/docs/eisxiouz6.pdf>) and “Une analyse comparée des expériences de régulation du cannabis :

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Colorado, État de Washington, Uruguay” (“A comparative analysis of cannabis regulation experiences: Colorado, Washington State, Uruguay” (<https://www.ofdt.fr/BDD/publications/docs/CannalexRFS.pdf>).

(4) There is little correlation between legal status and use. France has the highest use prevalence in Europe in the “recent use” (< 30 days), in 15-16 year-olds” category (ESPAD 2015 – The European school survey project on alcohol and other drugs) and in the “use in the last 12 months in 15-34 year-olds” category (report on illicit drugs in France 2017 – OFDT and European monitoring centre for drugs and drug addiction) ([http://www.emcdda.europa.eu/system/files/publications/3074/ESPAD\\_report\\_2015.pdf](http://www.emcdda.europa.eu/system/files/publications/3074/ESPAD_report_2015.pdf) and <http://www.emcdda.europa.eu/system/files/publications/4523/TD0416916ENN.pdf>).

(5) The European Parliament has adopted a resolution aimed at promoting research concerning the therapeutic potential of cannabis and its derivatives and their medical use where justified. European Parliament resolution of 13 February 2019 on the use of cannabis for medicinal purposes: ([http://www.europarl.europa.eu/doceo/document/TA-8-2019-0113\\_FR.html](http://www.europarl.europa.eu/doceo/document/TA-8-2019-0113_FR.html)), website consulted on 4.11.19.

(6) The demand on the part of patients was reflected in the case of an individual having taken the ethics and cancer committee and the French cancer league to court for what this individual perceived as a treatment refusal. ([https://www.ethique-cancer.fr/files/file\\_fields/2018/11/26/cec-2018-avis35-cannabis-texte-final.pdf](https://www.ethique-cancer.fr/files/file_fields/2018/11/26/cec-2018-avis35-cannabis-texte-final.pdf)).

(7) The specific temporary scientific committee began its work in September 2018 and completed it in June 2019. (<https://ansm.sante.fr/L-ANSM/Comites-scientifiques-specialises-temporaires/Comites-scientifiques-temporaires/Comites-scientifiques-temporaires/CSST-Evaluation-de-la-pertinence-et-de-la-faisabilite-de-la-mise-a-disposition-du-cannabis-therapeutique-en-France>), website consulted on 4.11.19.

(8) THC, or  $\Delta^9$ -tetrahydrocannabinol, is one of the main two cannabinoids in cannabis.

(9) The industrial hemp varieties that are allowed to be grown in France are varieties listed in a variety catalogue managed by the Ministry of Agriculture; these varieties contain less than 0.2% THC. Their cultivation is highly regulated and subject to controls, to check that the THC concentration does not exceed the legal limit. The industrial use of hemp flowers is prohibited in France. (<https://www.drogues.gouv.fr/actualites/cannabidiol-cbd-point-legislation>), consulted on 28.10.19.

Hemp varieties contain different cannabinoid concentrations depending on the species: the Cannabis indica species contains more THC than Cannabis sativa. Within each species, there is a very broad variety of strains due to the plant's considerable hybridisation capacities.

(10) France is the biggest producer of industrial hemp in Europe. Hemp can be used for numerous industrial applications: building, packaging, motor vehicle industry, pulp for paper, food (human and animal), etc. Institut technique du chanvre (2007). Le chanvre industriel. Guide technique. Edition Institut technique du chanvre and Chanebeau A. (2013). Le chanvre, du rêve aux milles utilisations ! Editions Platinium.

(11) In Europe, cannabis is most widely used in the form of blocks of resin. These blocks are composed of the resin naturally present in the plant's flowers, which has a higher cannabinoid concentration than the rest of the plant.

(12) As a more marginal use, cannabis can be consumed in the form of an oil extract, containing cannabinoids in higher concentrations since they are lipophilic. The method of use changes the kinetics of THC and CBD distribution in the blood: smoking is the fastest route, via the air/blood interface constituted by the alveoli of the lungs, while the ingested route is the slowest, particularly if other foods are eaten at the same time (there is therefore a risk of overdose with the ingested route due to the effects that appear to be limited in the short term). Mouth sprays are relatively rapid as a result of the high number of blood vessels in the mucous membranes.

(13) Written records describing the plant and its medicinal use in India and China date back to more than a millennium BC. Mechoulam, R. (2019). Cannabinoids As Therapeutic Agents (CRC Press). ISBN: 978-0-429-53626-7.

(14) In particular, this type of use existed in literary circles: in the 19<sup>th</sup> century, the poets Théophile Gautier and Charles Beaudelaire, for example, were members of the “Club des Haschischins” or “Hashish-smokers' club”. This use was also popular during the hippie movement. Mechoulam, R. (2019). Cannabinoids As Therapeutic Agents (CRC Press). ISBN: 978-0-429-53626-7.

(15) Spilka et al. (2018) Les drogues à 17 ans : analyse de l'enquête ESCAPAD 2017. Tendances. Observatoire français des drogues et toxicomanies. (<https://www.ofdt.fr/BDD/publications/docs/efxssy2.pdf>).

(16) The average THC content of cannabis increased from 5% in 2006 to more than 10% in 2016 and 11% in 2018 for herbal cannabis and from 8% to 17% and 26.5% for resin, i.e. a trebling of the THC concentration in resin in 12 years. European monitoring centre for drugs and drug addiction. (2019). Developments in the European cannabis market. EMCDDA Papers. (<http://www.emcdda.europa.eu/system/files/publications/11391/TDAU19001ENN.pdf>) and “Drogues, chiffres clés”, 8th edition, OFDT, 2019 (<https://www.ofdt.fr/BDD/publications/docs/DCC2019.pdf>).

(17) World Health Organisation Expert Committee on Drug Dependence. (2018). Cannabidiol, critical review report. (<https://www.who.int/medicines/access/controlled-substances/CannabidiolCriticalReview.pdf>).

(18) Since cannabidiol is not classed as a narcotic, the sale of products containing it is possible as long as these products do not claim any therapeutic benefits – which only medicinal products may claim – if there is no reference made to cannabis and if the products contain no traces of THC. (<https://www.drogues.gouv.fr/actualites/cannabidiol-cbd-point-legislation>), consulted on 28.10.19. However, the total absence of THC in products is limited by the fact that THC and CBD share common precursors in their biosynthesis.

It should be noted that the use of CBD in large quantities, as scheduled in the medical cannabis trial, falls within the scope of medicinal use. “Wellness” cannabis players estimate that this type of use could be characterised by a limited dose of 20 mg of CBD per day, whereas a medical effect could be achieved from doses of 60 mg/day. For example, Epidyolex® may be prescribed at doses ranging from 5 to 20 mg/kg/day, i.e., 50 to 200 mg/day for a child weighing 10 kg.

(19) Pertwee, R.G. (2006). Cannabinoid pharmacology: the first 66 years. Br J Pharmacol 147, S163–S171.

(20) The first endocannabinoids discovered were 2-arachidonylglycerol and anandamide. These are lipids, synthesised in the cell membrane. Other endocannabinoids have been discovered since, such as noladin ether, virodhamine and N-Arachidonoyl dopamine.

(21) Other receptors are also involved in the endocannabinoid system; this is the case for TRPV1. Unlike CB1 and CB2, which are “protein G-coupled” receptors, i.e., which have a relatively slow action mechanism since they are subject to a cascade of activations in the cell, the TRPV1 (transient receptor potential vanilloid 1) receptor is a channel receptor, the activation of which has an immediate effect on neuronal activity.

(22) There are no endocannabinoid reserves (lipids therefore hydrophobic) in the neurons, in contrast with hydrophilic neurotransmitters, stored in the form of vesicles. Hence, regulation of their synthesis and degradation by the enzymes performing these functions is a way of controlling their quantity and therefore their effects. These enzymes are pharmacological targets that could enable future treatments to act on the endocannabinoid system. Russo, E.B. (2016). Beyond Cannabis: Plants and the Endocannabinoid System. Trends Pharmacol. Sci. 37, 594–605 and Patel, S., Hill, M.N., Cheer, J.F.,

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Wotjak, C.T., and Holmes, A. (2017). The endocannabinoid system as a target for novel anxiolytic drugs. *Neuroscience & Biobehavioral Reviews* 76, 56–66.

23 The central nervous system consists of the brain and spinal cord. CB1 is present in most of the brain's structures: it is found in the cerebellum, the amygdala, the hippocampus and the prefrontal cortex, these structures being respectively associated with coordination of thoughts and actions, control of emotions, memory and higher cognitive functions (reasoning and executive functions). The CB1 receptor is almost absent from the brain stem, the structure that controls vital functions such as breathing and heart rate. The almost complete absence of cannabinoid receptors in this structure is the explanation widely given for the absence of cases of overdose due to cannabis, whereas opioid receptors, for example, are present in this part of the brain. Krebs M.O. et Jay T. (2018). Maturation cérébrale à l'adolescence et consommation de cannabis. *Addictions et comorbidités psychiatriques. La revue du praticien* 68, 7.

24 The peripheral nervous system includes all the nerves that convey motor activity of the central nervous system to the muscles and sensory information from the peripheral to the central nervous system. CB1 is more expressed in the brain than in other tissues, but it is also found in the muscles, therefore also in the heart, the liver, the bowel, adipose tissue, etc. Bouquie, R., Deslandes, G., Mazaré, H., Cogné, M., Mahé, J., Grégoire, M., and Jolliet, P. (2018). Cannabis and anticancer drugs: societal usage and expected pharmacological interactions – a review. *Fundamental & Clinical Pharmacology* 32, 462–484.

25 Via the microglia, immune system cells in the brain, the CB2 receptor is also found in the central nervous system. The action of THC via CB2, which is anti-inflammatory, also takes place in the brain, therefore.

26 eCBs have a retrograde action, in contrast with the prevailing paradigm for neurotransmitters (carrying information from an upstream neuron to a downstream neuron): at synapse level, eCBs are synthesised by the downstream neuron and bind to the receptors of the upstream neuron, reducing the latter's activity. This method of parallel regulation (or modulation) of neuronal activity on a local level (synapse) is one of the mechanisms enabling synaptic plasticity. This phenomenon consists of mechanisms that influence the transmission of information from one neuron to another, leading to the strengthening or weakening of certain synapses. In concrete terms, these mechanisms can modulate the amount of information transmitted by the upstream neuron and the way the information is received by the downstream neuron. Synaptic plasticity and the reinforcement of certain synapses - and hence certain connections - compared to others is the basis of learning processes.

27 Roland, A.B., Ricobaraza, A., Carrel, D., Jordan, B.M., Rico, F., Simon, A., Humbert-Claude, M., Ferrier, J., McFadden, M.H., Scheuring, S., et al. (2014). Cannabinoid-induced actomyosin contractility shapes neuronal morphology and growth. *Elife* 3, e03159.

28 An increase in structural connectivity (via axon bundles) and functional connectivity (the simultaneous activation of brain areas) is, along with synaptic refinement, during which some of the connections between neurons are eliminated, one of the phenomena characterising brain maturation. These phenomena are accompanied by cognitive changes. Office scientific briefing on "Neurosciences et responsabilité de l'enfant" ("Neurosciences and responsibility in children"), Michel Amiel, Senator, November 2019.

29 Patel, S., Hill, M.N., Cheer, J.F., Wotjak, C.T., and Holmes, A. (2017). The endocannabinoid system as a target for novel anxiolytic drugs. *Neuroscience & Biobehavioral Reviews* 76, 56–66.

30 Animals used as pain models present both a higher number of central and peripheral CB1 receptors and higher eCB levels. In addition, the injection of endocannabinoids in animals has an analgesic effect. Zogopoulos, P., Vasileiou, I., Patsouris, E., and Theocharis, S.E. (2013). The role of endocannabinoids in pain modulation. *Fundamental & Clinical Pharmacology* 27, 64–80 and Richardson, J.D., Kilo, S., and Hargreaves, K.M. (1998). Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 75, 111–119.

31 The action mechanism(s) of CBD is/are not fully understood; the biological targets of CBD are very varied. In vitro, CBD has an antagonistic effect on the CB1 receptor (it reduces the likelihood of THC activating the receptor), but at very high concentrations, not realistic with respect to recreational or medicinal use (McPartland et al, 2015). A recent study suggests that this antagonistic effect may occur at lower concentrations, but it needs to be repeated by other research teams to be confirmed (Tham et al, 2019). The effects of CBD, and in particular the anti-epileptic effects, probably come from other targets; the interactions between CBD and receptors such as TRPV1 or serotonin receptors are being studied.

McPartland, J.M., Duncan, M., Marzo, V.D., and Pertwee, R.G. (2015). Are cannabidiol and Δ9-tetrahydrocannabinol negative modulators of the endocannabinoid system? A systematic review. *British Journal of Pharmacology* 172, 737–753.

Tham, M., Yilmaz, O., Alaverdashvili, M., Kelly, M.E.M., Denovan-Wright, E.M., and Laprairie, R.B. (2019). Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. *British Journal of Pharmacology* 176, 1455–1469.

32 eCBs work on a time scale in the range of a second, since they are quickly degraded, whereas phytocannabinoids persist in the brain for up to several hours. In addition, the prolonged activation of CB1 by phytocannabinoids results in cascades of cell events, which are the source of the durability of the effects of cannabis use – lasting from one hour to around ten hours.

33 The multiple different ways of using cannabis (smoked, with or without tobacco, by spraying, by ingestion, etc.) and the difficulty of knowing the patient's exact consumption history (cannabis, tobacco, alcohol, etc.) are additional complications when it comes to collating studies and reaching conclusions. The National Academies of Sciences, Engineering and Medicine. (2017) *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*.

34 The National Academies of Sciences, Engineering and Medicine. (2017) *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*.

35 Mücke, M., Phillips, T., Radbruch, L., Petzke, F., and Häuser, W. (2018). Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews*.

36 Smith, L.A., Azariah, F., Lavender, V.T., Stoner, N.S., and Bettiol, S. (2015). Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database of Systematic Reviews*.

37 These are painful, uncontrolled muscle contractions, causing pain and spasms.

38 However, conclusions vary greatly depending on the studies. A recent meta-analysis pointed to the lack of high-quality studies, particularly in this field, and concluded that there was insufficient evidence to support the use of cannabinoids in the treatment of psychiatric disorders. Black, N., Stockings, E., Campbell, G., Tran, L.T., Zagic, D., Hall, W.D., Farrell, M., and Degenhardt, L. (2019). Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *The Lancet Psychiatry* In Press.

39 Decree No. 2013-473 of 5 June 2013 lifted the ban on using cannabis derivatives in the case of medicinal products (article R. 5132-86 of the French Public Health Code).

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40 However Sativex® is still not available in France, due to the absence of an agreement concerning the price of the medicine. In 2014, the Haute Autorité de Santé (French National Authority for Health) awarded Sativex® a low actual clinical benefit and no clinical added value compared to existing medicinal products. Sativex® contains THC and CBD in a ratio of 1: 1.

41 Epidyolex® had been available in France since 2018 thanks to a "Temporary Authorisation for Use" (ATU) early access programme. It was granted a European MA in 2019. Epidyolex® contains only CBD. Another medicine containing cannabinoids, Marinol®, is available on an ATU early access programme basis. The active substance – dronabinol – of this product is synthetic THC, not THC extracted from the plant, as is the case in Sativex®. Marinol® is indicated for cases of central and peripheral neuropathic pain following the failure of currently available treatments.

42 France's Assemblée nationale (National Assembly) adopted an amendment made by the general rapporteur for the draft social security funding law (PLFSS) for 2020, Olivier Véran, upon the first reading of this PLFSS (amendment No. AS721), which notably schedules that the conditions for implementation of the trial will be set using a regulatory process. The PLFSS 2020 will be examined in the Senate in early November, then submitted to a joint committee. Text of the adopted amendment:

"I. – On an experimental basis, for a period of two years, the State may authorise the medical use of cannabis in the form of products meeting pharmaceutical standards, in certain indications or clinical situations refractory to accessible indicated treatments.

II. – The conditions for implementation of the trial are defined by the regulations. In particular, these specify the treatment conditions, the number of patients concerned, arrangements for importing, production, procurement, prescribing and dispensing by hospital and community pharmacies, along with conditions for patient information and follow-up and health professional training.

III. – Within a period of six months following the end of the trial, the Government shall submit to Parliament a report concerning, in particular, the medical use of cannabis for patients, their follow-up, organisation of prescribing and dispensing channels, as well as the associated spending. This report shall specifically examine the relevance of extending the recourse to medical use of cannabis at the end of the trial and, if applicable, the conditions for its funding by the national health insurance system."

43 These concern Lennox-Gastaut syndrome and Dravet syndrome.

44 Estimates made by players in the field suggest that these indications could concern 300,000 to 600,000 people in France. An extension of the indications could increase the number of potential users to 1 to 2 million.

45 Cannabis extracts will probably be proposed in the form of oil, capsules or a mouth spray. Several types of cannabis will be available, with THC: CBD ratios capable of covering the spectrum of conditions to be alleviated. The THC: CBD ratios (expressing active substance concentration ratios) of 1: 1 and 5: 20 could be intended for neuropathic pain, including spasticity in multiple sclerosis, the high THC ratio (20: 1) for palliative care and the high CBD ratios (1: 20 and 1: 50) for rare epilepsy cases.

46 Pain management centres, specialised multiple sclerosis centres, etc.

47 A general practitioner, who has also taken the training, will then be able to take over management of the treatment. It is scheduled that training of doctors and the registry that will be used for patient follow-up and analysis of trial efficacy will be funded by the national health insurance system, while the products distributed to patients will be supplied free of charge by foreign companies who already have expertise in medical cannabis, the list of which has not been unveiled (however, it may be assumed that these could be Aurora, Canopy Growth, Bedrocan, etc.). The products will be dispensed by hospital and community pharmacies and pharmacists will have received specific training for this purpose.

48 A proper assessment of patient needs, as well as their rigorous follow-up, appear to be important in view of the fact that a third of patients having used medical cannabis in Germany stopped it following the development of adverse reactions and/or due to a lack of treatment efficacy (non-exhaustive preliminary data supplied by the scientific department of the French Embassy in Germany). This high level of adverse reactions is consistent with what is observed in clinical studies testing cannabis or cannabinoids in the treatment of diseases. The adverse reactions observed include dizziness, dry mouth, disorientation, nausea, euphoria, confusion or drowsiness. Hallucinations, paranoia and psychotic disorders can also occur.

49 Évaluation des médicaments en vue de leur remboursement – Haute Autorité de santé (Assessment of medicinal products with a view to their reimbursement – Haute Autorité de santé). [https://webzine.has-sante.fr/upload/docs/application/pdf/2017-03/dir4/v13ok-circuit\\_medicament\\_ct\\_ceesp-160317.pdf](https://webzine.has-sante.fr/upload/docs/application/pdf/2017-03/dir4/v13ok-circuit_medicament_ct_ceesp-160317.pdf).

50 In particular, the potential of CBD as a treatment for alcohol addiction is being explored. De Ternay, J., Naassila, M., Nourredine, M., Louvet, A., Bailly, F., Sescousse, G., Maurage, P., Cottencin, O., Carrieri, P.M., and Rolland, B. (2019). Therapeutic Prospects of Cannabidiol for Alcohol Use Disorder and Alcohol-Related Damages on the Liver and the Brain. *Front Pharmacol* 10, 627.

51 Research work is currently under way to study the potential therapeutic virtues of cannabis, particularly in the treatment of cancer. Relatively positive results have been obtained in vitro on pancreatic tumour cell cultures, but these cannot justify use in humans for curative purposes at present. Moreau, M., Ibeh, U., Decosmo, K., Bih, N., Yasmin-Karim, S., Toyang, N., Lowe, H., and Ngwa, W. (2019). Flavonoid Derivative of Cannabis Demonstrates Therapeutic Potential in Preclinical Models of Metastatic Pancreatic Cancer. *Front. Oncol.* 9.

52 This wealth of compounds - some of which are psychoactive and others simply aromatic - explains the large number of uses of cannabis, in contrast with other drugs. Russo, E.B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology* 163, 1344–1364.

53 The entourage effect is thought to concern both other cannabinoids (such as cannabinal or tetrahydrocannabivarin) and other compounds in the plant, like terpenes. There is no scientific consensus on this subject. In France, scientists do not have access to complete cannabis extracts; they may only work with THC, CBD or analogues of these molecules. So it is impossible for them to verify the entourage effect hypothesis. Pamplona, F.A., da Silva, L.R., and Coan, A.C. (2018). Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis. *Front Neurol* 9, 759 et Russo, E.B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br. J. Pharmacol.* 163, 1344–1364.

54 The testicular cancers associated with cannabis use are non-seminoma-type germ cell tumours. The National Academies of Sciences, Engineering and Medicine. (2017) *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*.

55 This effect being accentuated in occasional users compared to regular users. Hartley, S., Simon, N., Larabi, A., Vaugier, I., Barbot, F., Quera-Salva, M.-A., and Alvarez, J.C. (2019). Effect of Smoked Cannabis on Vigilance and Accident Risk Using Simulated Driving in Occasional and Chronic Users and the Pharmacokinetic-Pharmacodynamic Relationship. *Clinical Chemistry* 65, 684–693. However, driving under the influence of alcohol is associated with a 20 times higher risk of causing a road traffic accident, whereas this risk is only three times higher in the case of cannabis use. Martin, J.-L., Gadegbeku, B., Wu, D., Viallon, V., and Laumon, B. (2017). Cannabis, alcohol and fatal road accidents. *PLOS ONE* 12, e0187320.

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56 CBD can inhibit the action of cytochrome P450, a liver enzyme that breaks down medicines. Ewing, L.E., Skinner, C.M., Quick, C.M., Kennon-McGill, S., McGill, M.R., Walker, L.A., ElSohly, M.A., Gurley, B.J., and Koturbash, I. (2019). Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model. *Molecules* 24, 1694.

57 The risk is 9% for cannabis, compared to 32% for nicotine, 15% for alcohol or 23% for heroin. EMCDDA. (2018). Medical use of cannabis and cannabinoids: questions and answers for policymaking.

58 These studies show that exposure of parental gametes (spermatozoa and eggs) to THC causes epigenetic changes (which modify gene expression via the proteins that control their expression, without changing the DNA sequence). These changes may pass on a strong appetite for all drugs during adolescence to the offspring of such subjects. In fact, THC suppresses the expression of dopamine receptors in the nucleus accumbens (a region of the brain involved in reward and dependence mechanisms), exerting an addictogenic effect. Szutorisz, H., and Hurd, Y.L. (2016). Epigenetic Effects of Cannabis Exposure. *Biol. Psychiatry* 79, 586–594. Szutorisz, H., and Hurd, Y.L. (2018). High times for cannabis: Epigenetic imprint and its legacy on brain and behavior. *Neuroscience & Biobehavioral Reviews* 85, 93–101 and Goullé J.-P., Morel F. on behalf of the addictions sub-committee. (2019). Consommation de drogues licites et illicites chez l'adolescent: une situation alarmante qui impose une prévention précoce. Académie nationale de médecine report.

59 Lower connectivity of brain areas is observed and these structural changes are potentially irreversible. Disruption of the endocannabinoid system is observed in the prefrontal cortex, the site of higher cognitive functions. Hurd, Y.L., Manzoni, O.J., Pletnikov, M.V., Lee, F.S., Bhattacharyya, S., and Melis, M. (2019). Cannabis and the Developing Brain: Insights into Its Long-Lasting Effects. *J. Neurosci.* 39, 8250–8258.

60 Scheyer, A.F., Melis, M., Trezza, V., and Manzoni, O.J.J. (2019). Consequences of Perinatal Cannabis Exposure. *Trends Neurosci. In Press.* [10.1016/j.tins.2019.08.010](https://doi.org/10.1016/j.tins.2019.08.010).

61 Depending on the dose, THC can have anxiolytic or anxiogenic effects.

62 The National Academies of Sciences, Engineering and Medicine. (2017) *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*.

63 The risk of developing psychotic disorders was identified in 1987 in Sweden (Andréasson, S., Engström, A., Allebeck, P., and Rydberg, U. (1987). Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *The Lancet* 330, 1483–1486. In humans, this observation stems from a statistical association: an association has been solidly established, on a large panel of subjects, between cannabis use and the existence of psychotic disorders, or even schizophrenia, depending on the studies. These studies do not allow a causal link to be determined between cannabis and psychotic disorders – i.e., it is impossible to determine whether it is the cannabis use that has caused the disorders or whether individuals susceptible to the development of psychotic disorders may be more tempted to use cannabis. Studies in animals avoid the issue of genetic and environmental risk factors and show that, in rats, cannabis does indeed lead to the development of psychiatric disorders. Krebs, M.-O., Kebir, O., and Jay, T.M. (2019). Exposure to cannabinoids can lead to persistent cognitive and psychiatric disorders. *European Journal of Pain* 23, 1225–1233.

64 It has been shown that an allele of the COMT gene was associated with the development of psychotic disorders, but only when the individuals presented cannabis use. Caspi, A., and Moffitt, T.E. (2006). Gene–environment interactions in psychiatry: joining forces with neuroscience. *Nat Rev Neurosci* 7, 583–590.

65 Statement of Prof. Marie-Odile Krebs during hearings conducted to prepare the briefing.

66 Clergue-Duval, V., Mary-Krause, M., Bolze, C., Fombonne, E., and Melchior, M. (2019). Early Predictors of Trajectories of Tobacco Use Level from Adolescence to Young Adulthood: A 16-Year Follow-Up of the TEMPO Cohort Study (1999–2015). *Eur Addict Res* 25, 2–9.

67 Silins, E., Horwood, L.J., Patton, G.C., Fergusson, D.M., Olsson, C.A., Hutchinson, D.M., Spry, E., Toumbourou, J.W., Degenhardt, L., Swift, W., et al. (2014). Young adult sequelae of adolescent cannabis use: an integrative analysis. *The Lancet Psychiatry* 1, 286–293.

68 Airagnes, G., Lemogne, C., Meneton, P., Plessz, M., Goldberg, M., Hoertel, N., Roquelaure, Y., Limosin, F., and Zins, M. (2019). Alcohol, tobacco and cannabis use are associated with job loss at follow-up: Findings from the CONSTANCES cohort. *PLoS ONE* 14, e0222361.

69 In 2001, at 18 years of age, 45% of girls and 55% of boys had already tried cannabis, compared to 92 and 93% respectively for alcohol, 81 and 79% for tobacco, 3 and 5% for ecstasy. In the past few years, a slight decrease in use has been observed in young people (in 2017, however, only 39% of young people, on average, had already used cannabis), in parallel with an increase in use among older age groups. Problem use, on the other hand, is on the rise: 25% of users in 2017, compared to 22% in 2014 and 18% in 2011. Beck F. et al. (2000). "Consommations de substances psychoactives chez les 14-18 ans scolarisés : premiers résultats de l'enquête ESPAD 1999, évolution 1993-1999", *Tendances n° 6*; Spilka et al. (2018) Les drogues à 17 ans: analyse de l'enquête ESCAPAD 2017. *Tendances. Observatoire français des drogues et toxicomanies*, (<https://www.ofdt.fr/BDD/publications/docs/eftxssy2.pdf>) and Spilka et al. (2013) *Détection des usages problématiques de cannabis : le Cannabis abuse screening test (CAST)*. OFDT (<https://www.ofdt.fr/BDD/publications/docs/eisxst9.pdf>).

70 4% of young people have already tried these substances. EMCDDA. (2017). *European drug report: trends and developments*. [http://www.emcdda.europa.eu/system/files/publications/11364/20191724\\_TDAT19001FRN\\_PDF.pdf](http://www.emcdda.europa.eu/system/files/publications/11364/20191724_TDAT19001FRN_PDF.pdf) and Lafaye, G., Karila, L., Blecha, L., and Benyamina, A. (2017). Cannabis, cannabinoids, and health. *Dialogues Clin Neurosci* 19, 309–316 and Nouveaux produits de synthèse : dix ans de recul sur la situation française. (2018). OFDT (<https://www.ofdt.fr/BDD/publications/docs/eftxmya.pdf>).

71 However, there is a risk of seeing an increase in this use in the event of total liberalisation of access to cannabis. Melchior, M., Nakamura, A., Bolze, C., Hausfater, F., El Khoury, F., Mary-Krause, M., and Azevedo Da Silva, M. (2019). Does liberalisation of cannabis policy influence levels of use in adolescents and young adults? A systematic review and meta-analysis. *BMJ Open* 9, e025880.

72 Carliner, H., Brown, Q.L., Sarvet, A.L., and Hasin, D.S. (2017). Cannabis use, attitudes, and legal status in the U.S.: A review. *Prev Med* 104, 13–23 et Mauro, C.M., Newswanger, P., Santaella-Tenorio, J., Mauro, P.M., Carliner, H., and Martins, S.S. (2019). Impact of Medical Marijuana Laws on State-Level Marijuana Use by Age and Gender, 2004–2013. *Prev Sci* 20, 205–214.

73 In terms of both THC contents and genetic characteristics, since the contents in terms of other cannabinoids can vary considerably from one strain to another. Reardon, S. (2019). Cannabis used in US research differs genetically to the varieties people smoke. *Nature* <https://www.nature.com/articles/d41586-019-01415-z>.

74 In line with the recommendations of the Académie nationale de médecine (French National Academy of Medicine): Goullé J.-P., Morel F. on behalf of the addictions sub-committee. (2019). Consommation de drogues licites et illicites chez l'adolescent: une situation alarmante qui impose une prévention précoce. Académie nationale de médecine report.